Placebo-controlled Randomized Clinical Trial: tDCS to Prevent Relapse in Alcohol Use Disorder

NCT ID: not yet assigned

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1. Background

Despite the available treatments in place, patients with alcohol use disorder (AUD) continue to relapse after treatment (Manning et al., 2016, 2020; Noël et al., 2021). For the past twenty years, neuromodulations techniques and their mechanisms, including transcranial direct current stimulation (tDCS), have been largely investigated in medical research (Ekhtiari et al., 2019; Fertonani & Miniussi, 2017; Nitsche et al., 2003; Philip et al., 2017). The tDCS is a neuromodulation tool acting by a current of maximum 2 mA delivered by two electrodes: the anode increases the cortical excitability (depolarizing the membrane potential on neurons) while the cathode inhibits the cortical excitability (hyperpolarizing the membrane potential) (Zhao et al., 2017).

The tDCS has shown interesting effects in patients with AUD when applied to the dorsolateral prefrontal cortex (dlPFC). The dlPFC is involved in decision-making, inhibitory control and working memory (Bechara 2005), as well as attentional bias (Bechara 2005), as well as attentional bias (Knight et al., 2020). The dlPFC appears to be hypoactivated in patients with AUD, which translates in impaired inhibition control and impaired attention to alcohol-related stimuli (Goldstein & Volkow, 2011).

Currently in the scientific literature we can find many studies focusing on craving but only few investigating relapse's mechanisms and treatment (Coles et al., 2018; Trojak et al., 2017). Nevertheless, two studies have shown that 10 sessions of tDCS on dlPFC (2mA, anode on the right, cathode on the left) allow a decrease in relapse's rate (3 and 6 months after the intervention) (Klauss et al., 2014, 2018). Among a sample of 33 hospitalized patients, eight patients in the active

tDCS condition were still abstinent after 6 months follow-up, compared to two in the sham tDCS condition (50% versus 11.8% of the respective samples).

Meta-analyses have shown a moderate effect of tDCS reducing craving (Chen et al., 2020; Hone-Blanchet et al., 2015; Jansen et al., 2013; Kang et al., 2019; Luigjes et al., 2018; Mostafavi et al., 2020; Sauvaget et al., 2015). The latest recommendations are to place the anode on the right CPFDL and the cathode on the left CPFDL, for a minimum of 5 sessions of 20 minutes at 2 mA (Fregni et al., 2020; Lefaucheur et al., 2017).

We conducted a first clinical trial at Unit 72 Addictology of CHU Brugmann between 2017 and 2020 (reference: CE 2017/117), which was funded by the King Baudouin Foundation (ref: 2016-J1130650-206500) and then by the Brugmann Foundation (fund 2020-2021) (article in writing, pre-registered: https://clinicaltrials.gov/ct2/show/NCT03447054). The study had a design with 2x2 conditions combining 5 sessions of (A) tDCS on the dlPFC (anode on the right and cathode on the left, active 2mA vs sham 0mA) simultaneously to (B) an inhibition cognitive training (ICT) type Go/Nogo (specific vs non-specific). The specific ICT consisted to associate the Nogo with alcohol images and Go with sports images. There were also neutral images associated with 50% of Go. While non-specific training had only neutral images. Results showed a decrease in relapse's rate two weeks after treatment due to real tDCS combined with ICT. Moreover, we found out that real tDCS combined with specific ICT was more effective than real tDCS combined nonspecific ICT. Nevertheless, we did not find any significant effect on other clinical variables [craving (visual analog scale), symptoms of depression (BDI-II), anxiety (STAI-A), work memory (OSPAN) and inhibition (Stop signal task)].

Following these results, one questions still remains: Should tDCS be combined with ICT in order to be effective? To answer this question, we are conducting a new clinical trial with 5 sessions of tDCS on CPFDL (20minutes, anode on the right, left cathode) without an ICT. This study follows the same tDCS configuration as the previous one and takes place within the same multidisciplinary framework of treatment in order to compare our data.

2. HYPOTHESES

For patients with AUD, the intervention of five sessions of tDCS during a detoxification:

- decreases the relapse rate 2 weeks after the treatment;
- decreases patient craving;
- improves depression and anxiety;
- strengthens inhibitory capacities.

3. PROTOCOL

3.1. Patients

This is a clinical trial that is part of an alcohol detoxification cure at Unit 72 Addictology of CHU Brugmann. The idea is to add a neuromodulation intervention to the initial management, multidisciplinary and psycho-bio-social. This will be a randomized, sham-controlled, single-blind study.

A total of 60 subjects will be recruited according to the inclusion and exclusion criteria. They will be randomly divided into two groups: the 'active' group (A) that will benefit from tDCS stimulation and the 'sham' group (S).

Exclusion criteria:

- Personal history of epilepsy;
- Have metal head implants that counter-indicate electrical stimulation;
- Diagnosis of chronic psychotic disorder, schizophrenia or bipolar type 1 disorder;
- Use of alcohol or other illicit substances during the experiment;
- Hair incompatible with neuromodulation.

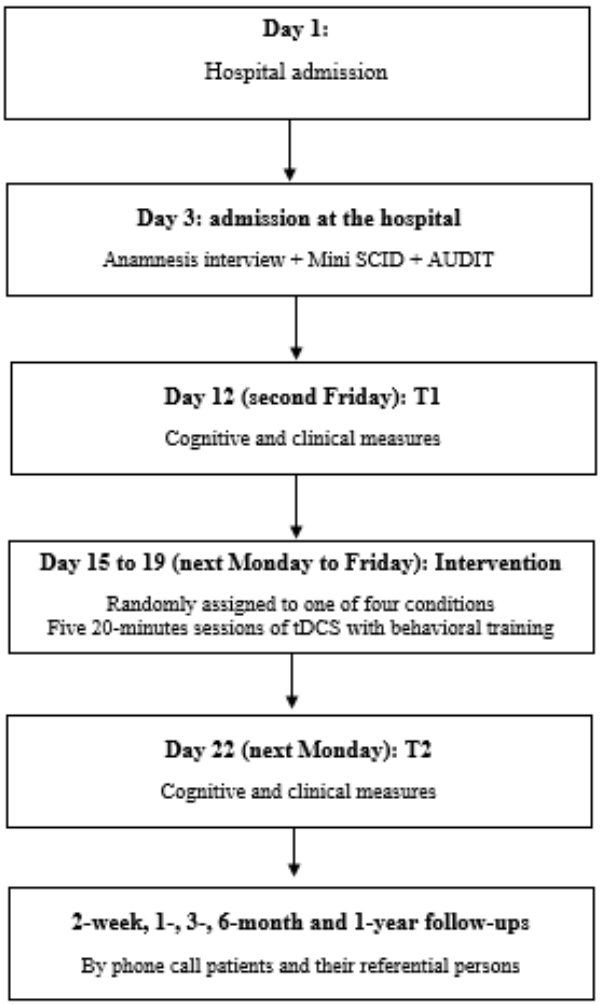
3.2. Procedure

During the first two weeks of hospitalization, the study will be offered to patients. If they accept, a first semi-structured interview will be organized to explain the study, sign the informed consent, collect more information and verify the inclusion and exclusion criteria. During this interview, the demographic characteristics (age, sex and level of education), history with alcohol (number of years of dependence, number of previous treatment, etc.), frequency and amount of alcohol consumed before treatment, psychiatric history, etc. The DSM 5 criteria will be verified, and patients will complete these questionnaires in French version: *Alcohol Use Disorder Identification Test* (AUDIT), *Impulsivity Behavior Scale* (UPPS-P) and *Trait Anxiety Inventory* (STAI-B).

From Monday to Friday of the third week of hospitalization, patients will receive the procedure. Five consecutive 20 minute days of tDCS, either active or sham. Before and after each session, the tie will be measured using analog visual scales. To measure the effects of tDCS, on the Friday preceding (T1) and the Monday following (T2) the intervention week,

patients will respond to a battery of questionnaires and cognitive tasks during the recording of evoked potentials (via an electroencephalogram). T1 and T2 will each last approximately one hour.

Figure 1: *Study plan. Day 1 is theoretically the first day of hospitalization and the procedure takes place between Day 15 and 19.*



In order to observe whether specific neural changes underlie relapse and abstinence, evoked potentials will be acquired for each participant at two points, before the start of the stimulation by tDCS and once the five sessions have been completed.

Once hospitalization is complete, patients will be followed by telephone call to find out the status of their abstinence and/or alcohol consumption. The call will be made via Unit 72 personnel.

Recruitment would start if possible at the end of March 2021 for a period of 12 months. Based on our estimates based on the performance of the previous study, five patients will be recruited per month.

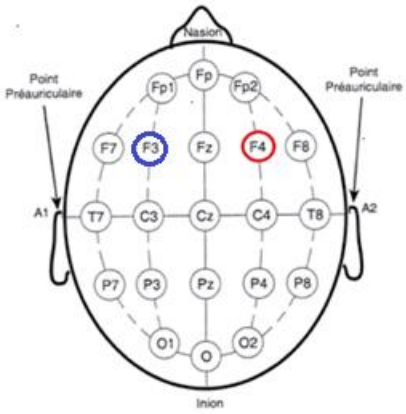
3.3. tDCS

During the neuromodulation session, the patient will watch nature documentaries, cut into 5 episodes of 20 minutes.

The configuration of tDCS is based on recommendations in the literature (Fregni et al., 2020; Lefaucheur et al., 2017).

- 5 sessions of bilateral stimulation of the dlPFC;
- Electrode setup: the anode right on F4 and cathode left on F3, according to international system 10-20 for EEG;
- Administration of 2mA of current for 20 min;
- Sham group: 0 mA for 20 min, 2 mA for the first 15 and last seconds.

Figure 2: *Localization of the anode (red) and the cathode (blue) over the dlPFC.*



3.4. Measures

Primary dependent variables :

Relapse and total abstinence measured at several defined times: two weeks, one month, three months, six months and one year after treatment..

Secondary dependent variables:

- Craving measured before and after each tDCS session via visual analog scales, such as Likert -100 to +100, as well as the *Alcohol Urge Questionnaire* (AUQ) with 8 items. Craving will also be measured in T1 and T2 through the *Craving Experience Questionnaire* (CEQ);

- Symptoms of depression with the *Beck Depression Inventory* (BDI-II) and positive and negative affectivity with the Positive and Negative Affect Schedule (PANAS) measured at T1 and T2;
- Anxiety trait in T1 and T2 with the *State Anxiety Inventory* (STAI-A).
- The working memory performance measured in T1 and T2 with the span reversed.
- Inhibitory control evaluated by performance at a Go/Nogo task and its event-related potential (Nogo N2 and Nogo P3). This measurement will be carried out as part of a clinical examination (cognitive and neurophysiological battery with an electroencephalogram) offered to patients during their hospitalization at Unit 72. This review will be conducted before and after the intervention (in T1 and T2).

All the questionnaires were in French version.

Metacognition items:

At the end of the experiment, patients will be asked orally (1) Do you think you are in the active tDCS group?, (2) Would you be interested in continuing this intervention over a longer period of time?

3.5. Statistical analyses

Primary measurement: In order to respond to our primary assumptions about relapse, we will perform logistic regressions with the independent variable conditions (tDCS active scored 1 and tDCS sham scored -1) and the variable dependent relapse at each measurement (2 weeks, 1 month, 3 months, 6 months and 1 year). A Kaplan-Meier survival analysis will be performed on the number of days prior to relapse to compare the curves up to one year of follow-up.
Finally, in order to compare our two conditions to the four conditions of the previous study, we will perform a logistic regression with linear polynomial contrasts (combined active tDCS with ICT > tDCS only > tDCS sham).

Secondary measures: In order to respond to our secondary assumptions about the variables before and after the intervention, we will perform mixed repeated measures ANOVAs [Time (T1 vs. T2) x Condition (tDCS active vs. tDCS sham)].

4. Benefices

At the individual level, stimulation by tDCS could on the one hand help patients to prolong alcohol abstinence time and on the other have positive effects on mood, especially an improvement in the level of anxiety and depression.

In a broader sense, this study will contribute to a better definition of the mechanisms involved in abstinence and in the phenomenon of relapse of alcohol use disorders. It will also compare whether tDCS is more effective alone or combined with cognitive training. The purpose of this study is to support medical research to improve management for people with alcohol dependence.

5. Safety and tolerability of tDCS

The tolerance of tDCS will be assessed during stimulation with an likert scale. A short questionnaire reporting possible side effects will be distributed to all participants to record the symptoms caused by stimulation.

The most common side effects include tingling, itching, and mild erythema. Although they are less frequent, the perception of a feeling of discomfort or burning, as well as the occurrence of a headache, are also possible events. These are side effects that are well tolerated, essentially limited to the time of stimulation and do not require medical treatment. Severe adverse effects or late onset were not identified.

6. Ethics

This study will be carried out in accordance with the ethical principles set out in the Declaration of Helsinki (1964) and the Belgian law of 7 May 2004 on experiments on the human person. The signature of a free and informed written consent will be requested from the selected participants prior to commencing the experiment.

7. References

Chen, J., Qin, J., He, Q., & Zou, Z. (2020). A Meta-Analysis of Transcranial Direct Current Stimulation on Substance and Food Craving : What Effect Do Modulators Have? *Frontiers in Psychiatry*, *11*. https://doi.org/10.3389/fpsyt.2020.00598

Coles, A. S., Kozak, K., & George, T. P. (2018). A review of brain stimulation methods to treat substance use disorders. *The American Journal on Addictions*, *27*(2), 71-91. https://doi.org/10.1111/ajad.12674

Ekhtiari, H., Tavakoli, H., Addolorato, G., Baeken, C., Bonci, A., Campanella, S., Castelo-Branco, L., Challet-Bouju, G., Clark, V. P., Claus, E., Dannon, P. N., Del Felice, A., den Uyl, T., Diana, M., di Giannantonio, M., Fedota, J. R., Fitzgerald, P., Gallimberti, L., Grall-Bronnec, M., … Hanlon, C. A. (2019). Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine : A consensus paper on the present state of the science and the road ahead. *Neuroscience & Biobehavioral Reviews*, *104*, 118-140. https://doi.org/10.1016/j.neubiorev.2019.06.007

Fertonani, A., & Miniussi, C. (2017). Transcranial Electrical Stimulation : What We Know and Do Not Know About Mechanisms. *The Neuroscientist*, *23*(2), 109-123. https://doi.org/10.1177/1073858416631966

Fregni, F., El-Hagrassy, M. M., Pacheco-Barrios, K., Carvalho, S., Leite, J., Simis, M., Brunelin, J., Nakamura-Palacios, E. M., Marangolo, P., Venkatasubramanian, G., San-Juan, D., Caumo, W., Bikson, M., Brunoni, A. R., & Neuromodulation Center Working Group. (2020). Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation (tDCS) in neurological and psychiatric disorders. *The International Journal of Neuropsychopharmacology*. https://doi.org/10.1093/ijnp/pyaa051

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction : Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience*, *12*(11), 652-669. https://doi.org/10.1038/nrn3119

Hone-Blanchet, A., Ciraulo, D. A., Pascual-Leone, A., & Fecteau, S. (2015). Noninvasive brain stimulation to suppress craving in substance use disorders : Review of human evidence and methodological considerations for future work. *Neuroscience and biobehavioral reviews*, *59*, 184-200. https://doi.org/10.1016/j.neubiorev.2015.10.001

Jansen, J. M., Daams, J. G., Koeter, M. W. J., Veltman, D. J., van den Brink, W., & Goudriaan, A. E. (2013). Effects of non-invasive neurostimulation on craving : A meta-analysis. *Neuroscience & Biobehavioral Reviews*, *37*(10), 2472-2480. https://doi.org/10.1016/j.neubiorev.2013.07.009

Kang, N., Kim, R. K., & Kim, H. J. (2019). Effects of transcranial direct current stimulation on symptoms of nicotine dependence : A systematic review and meta-analysis. *Addictive Behaviors*, *96*, 133-139. https://doi.org/10.1016/j.addbeh.2019.05.006

Klauss, J., Anders, Q. S., Felippe, L. V., Nitsche, M. A., & Nakamura-Palacios, E. M. (2018). Multiple Sessions of Transcranial Direct Current Stimulation (tDCS) Reduced Craving and Relapses for Alcohol Use : A Randomized Placebo-Controlled Trial in Alcohol Use Disorder. *Frontiers in Pharmacology*, *9*. https://doi.org/10.3389/fphar.2018.00716

Klauss, J., Penido Pinheiro, L. C., Silva Merlo, B. L., de Almeida Correia Santos, G., Fregni, F., Nitsche, M. A., & Miyuki Nakamura-Palacios, E. (2014). A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. *The International Journal of Neuropsychopharmacology*, *17*(11), 1793-1803. https://doi.org/10.1017/S1461145714000984

Knight, H. C., Smith, D. T., & Ellison, A. (2020). The role of the left dorsolateral prefrontal cortex in attentional bias. *Neuropsychologia*, *148*, 107631. https://doi.org/10.1016/j.neuropsychologia.2020.107631

Lefaucheur, J.-P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M. A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., … Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*, *128*(1), 56-92. https://doi.org/10.1016/j.clinph.2016.10.087

Luigjes, J., Segrave, R., de Joode, N., Figee, M., & Denys, D. (2018). Efficacy of Invasive and Non-Invasive Brain Modulation Interventions for Addiction. *Neuropsychology Review*. https://doi.org/10.1007/s11065-018-9393-5

Manning, V., Garfield, J. B. B., Staiger, P. K., Lubman, D. I., Lum, J. A. G., Reynolds, J., Hall, K., Bonomo, Y., Lloyd-Jones, M., Wiers, R. W., Piercy, H., Jacka, D., & Verdejo-Garcia, A. (2020). Effect of Cognitive Bias Modification on Early Relapse Among Adults Undergoing Inpatient Alcohol Withdrawal Treatment : A Randomized Clinical Trial. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2020.3446

Manning, V., Staiger, P. K., Hall, K., Garfield, J. B. B., Flaks, G., Leung, D., Hughes, L. K., Lum, J. A. G., Lubman, D. I., & Verdejo-Garcia, A. (2016). Cognitive Bias Modification Training During Inpatient Alcohol Detoxification Reduces Early Relapse : A Randomized Controlled Trial. *Alcoholism: Clinical and Experimental Research*, *40*(9), 2011-2019. https://doi.org/10.1111/acer.1316

Mostafavi, S.-A., Khaleghi, A., & Mohammadi, M. R. (2020). Noninvasive brain stimulation in alcohol craving : A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *101*, 109938. https://doi.org/10.1016/j.pnpbp.2020.109938

Nitsche, M. A., Liebetanz, D., Lang, N., Antal, A., Tergau, F., & Paulus, W. (2003). Safety criteria for transcranial direct current stimulation (tDCS) in humans. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical*

Neurophysiology, *114*(11), 2220-2222; author reply 2222-2223. https://doi.org/10.1016/s1388-2457(03)00235-9

Noël, X., Dubuson, M., Rougier, M., Lelard, T., Mouras, H., Kornreich, C., Wyckmans, F., Pereira, M., Chatard, A., Jaafari, N., & Campanella, S. (2021). Distinct Whole-Body Movements in Response to Alcohol and Sexual Content in Alcohol Use Disorder. *Alcoholism, Clinical and Experimental Research*. https://doi.org/10.1111/acer.14557

Philip, N. S., Nelson, B. G., Frohlich, F., Lim, K. O., Widge, A. S., & Carpenter, L. L. (2017). Low-Intensity Transcranial Current Stimulation in Psychiatry. *American Journal of Psychiatry*, *174*(7), 628-639. https://doi.org/10.1176/appi.ajp.2017.16090996

Sauvaget, A., Trojak, B., Bulteau, S., Jiménez-Murcia, S., Fernández-Aranda, F., Wolz, I., Menchón, J. M., Achab, S., Vanelle, J.-M., & Grall-Bronnec, M. (2015). Transcranial direct current stimulation (tDCS) in behavioral and food addiction : A systematic review of efficacy, technical, and methodological issues. *Frontiers in Neuroscience*, *9*. https://doi.org/10.3389/fnins.2015.00349

Trojak, B., Sauvaget, A., Fecteau, S., Lalanne, L., Chauvet-Gelinier, J.-C., Koch, S., Bulteau, S., Zullino, D., & Achab, S. (2017). Outcome of Non-Invasive Brain Stimulation in Substance Use Disorders : A Review of Randomized Sham-Controlled Clinical Trials. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *29*(2), 105-118. https://doi.org/10.1176/appi.neuropsych.16080147

Zhao, H., Qiao, L., Fan, D., Zhang, S., Turel, O., Li, Y., Li, J., Xue, G., Chen, A., & He, Q. (2017). Modulation of Brain Activity with Noninvasive Transcranial Direct Current Stimulation (tDCS) : Clinical Applications and Safety Concerns. *Frontiers in Psychology*, *8*. https://doi.org/10.3389/fpsyg.2017.00685

Appendices:

Table 1: Lists of documents / questionnaires / tasks that will be collected

	Semi-structured interview Day 3-4	T1 Day 12	Sessions Day 15-19	T2 Day 22
Informative letter	X			
Informed consent	X			
Anamnesis	X			
AUDIT (AUD symptoms)	X			
Craving Experience Questionnaire	X			
UPPS-P (impulsivity)	X			
STAI-B (trait anxiety)	X			
STAI-A (state anxiety)		X		X
Visual analog scales on craving		X	X	X
Alcohol Urge Questionnaire		X		X
PANAS		X		X
BDI-II		X		X
Reverse memory span		X		X
Go/Nogo with ERPs		X		X
Questions on metacognition				X