Universitat Oberta de Catalunya

Estudis de Ciències de la Salut

Transcranial direct current stimulation intervention for smoking cessation: research protocol

Master's Thesis in Neuropsychology

Author: Núria Serradell i Ribé

Director: Raquel Viejo Sobera

25.01.2019

Acknowledgements

Aquest TFM no hagués estat possible sense la inestimable ajuda de la meva tutora, Raquel Viejo Sobera, que m'ha ajudat a entendre cada pas i concepte del treball, m'ha recolzat en totes les iniciatives que he tingut i m'ha donat suport i ànims en tot moment (fins i tot camí de l'aeroport!). Moltes gràcies per haver sigut tan generosa amb el teu temps.

També voldria donar les gràcies a l'Elena Muñoz Marrón i a tot l'equip del Cognitive NeuroLab, per haver-me permés col·laborar amb el laboratori i haver-me acceptat com un membre més.

A la meva família, per haver estat sempre al meu costat encoratjant-me i per haver-me ajudat a arribar fins a aquest punt.

Ao Rodrigo, por ter aguentado os meus nervos e mau humor, e ter sempre me apoiado. Pelas noites que me fez companhia enquanto eu trabalhava. E por todas as massagens que me fez para tentar me relaxar. Sem você o caminho teria sido muito mais duro.

Resum

El consum de tabac és una de les causes de mortalitat evitables més comunes al món, ocasionant més de set milions de morts cada any. Tot i que hi ha molts tractaments enfocats a la deshabituació al tabac, la majoria tenen taxes d'èxit baixes. Per tant, el tabac és considerat un dels problemes de salut més importants de l'actualitat. En aquest context, l'estimulació transcranial per corrent directa (tDCS) apareix com un tractament innovador per les conductes addictives. La tDCS és una tècnica no invasiva de neuromodulació en la qual s'apliquen corrents elèctriques lleus sobre el cuir cabellut per tal d'incrementar o disminuir l'excitibilitat cortical. És una eina segura, econòmica i fàcil d'administrar.

En els darrers 10 anys, alguns estudis centrats en el tractament de l'addicció al tabac amb tDCS han obtingut resultats prometedors, majoritàriament demostrant que l'ús d'aquesta tècnica pot provocar una reducció significativa del *craving* a la nicotina i/o del consum de tabac. Tanmateix, molts estudis enfocat a les addiccions, i executats fins al moment, estan basats en una sola sessió de tDCS, mentre que només uns quants tenen un grup control *sham* i estan basats en diverses sessions d'estimulació activa. Aquestes limitacions només permeten recomanar un nivell d'evidència B pel que a l'eficàcia de la tDCS per reduir el *craving* en pacients amb diversos tipus d'addiccions.

Aquest estudi planteja un protocol d'intervenció utilitzant tDCS per a reduir el consum de tabac. Presenta importants innovacions, com la utilització d'una estimulació més focalitzada, la grandària de la mostra i el nombre de sessions d'estimulació. L'obtenció de resultats que recolzin les nostres hipòtesis tindria impacte a nivell científic, econòmic, social i clínic.

Paraules clau

Conducta addictiva, craving, estimulació cerebral no invasiva, fumar, tDCS, tractaments d'addiccions, deshabituació al tabac, consum de tabac.

Abstract

Tobacco use is one of the biggest preventable cause of death in the world, causing more than seven million deaths every year. Although there are many treatments focused on smoking cessation, most of them have low success rates. So, it is considered one of the most serious public health threats of our time. In this context, transcranial direct current stimulation (tDCS) appears as an innovative treatment for addictive behaviors. tDCS is a non-invasive neuromodulation technique that uses weak electrical currents applied to

the scalp to increase or decrease the cortical excitability. This tool is safe, inexpensive and easy to administer.

In the last 10 years, some studies using tDCS to treat tobacco addiction have obtained promising results, mostly demonstrating a significant reduction of nicotine cravings and/or consumption. However, many of the studies focused on addictions and conducted until now are based on a single tDCS session, while only a few of them are sham-controlled and based in repeated daily sessions with active tDCS. These limitations only allow to recommend a level of evidence B regarding the efficacy of tDCS to reduce craving in patients with various types of addiction.

This study raises an intervention protocol using tDCS for the reduction of tobacco use. It presents important innovations, such as the use of a more focused stimulation, the size of the sample and the number of sessions. Positive results would have an impact in a scientific, economic, social and clinical levels.

Keywords

Addictive behavior, addiction treatments, craving, non-invasive brain stimulation, smoking, tDCS, tobacco cessation, tobacco consumption.

Index

1. Introduction

According to the World Health Organization (2017) tobacco use is one of the biggest preventable cause of death in the world and kills more than seven million people every year. These deaths are a consequence of diseases appeared because of the continued exposure to toxins in tobacco smoke (Benowitz, 2010). Some of the most common health problems related to tobacco addiction include chronic obstructive pulmonary disease or lung cancer. Besides, it increases the risk of having a stroke, rheumatoid arthritis, macular degeneration or many other kinds of cancer, among other illnesses (WHO, 2017).

In the last decades tobacco consume has been progressively reduced in developed countries, mostly because of the health policies developed and implemented by the governments themselves. Nevertheless, 80% of tobacco users live in developing countries, where this kind of actions do not exist or have been applied more recently (WHO, 2017). However, even with the trend towards reducing consumption, in many rich countries a large percentage of the population still smokes. For instance, in 2015, 32.4% of the population in Germany were smokers, 31.3% in Spain, 29.8% in France and 28.3% in Italy (WHO, 2016). For all this, smoking is considered one of the most serious public health threats of our time (Men, Liu, Yu, & Ma, 2014).

Different treatments have been proposed to suppress tobacco dependence but most of them have had low success rates (Benowitz, 2010). Nowadays, one of the most common treatments for this addiction is the cognitive behavioral therapy. The first studies testing this therapy started around the 70s and 80s (e.g. Kazdin & Smith, 1979; Götestam & Melin, 1983); they have been evolving since then and are now focused on the design of smoking cessation programs based on this model (e.g. Hooten et al., 2014; Leiva et al. 2018) and the improvement of the existing programs. Although the cognitive behavioral treatment is a validated method, there are still many people for whom it does not work and would benefit from an alternative or a complementary treatment. In this context, transcranial direct current stimulation (tDCS) appears as an innovative treatment for addictive behaviors that has proven useful for the reduction of tobacco addiction (e.g. Falcone et al., 2016).

tDCS is a new treatment consistent in a non-invasive cerebral stimulation tool used for modulating the cortical excitability by the emission of a week electrical current to the brain via scalp electrodes. This technique is safe, painless and portable, so it can be used anywhere, even for patients who are not able to travel to a medical center or a research institution. Besides, it is very easy to train the researchers. Since 2008 have been performed around 70 studies applying this technique in tobacco. Although the technique is still in an experimental phase, most of these studies have obtained promising results, demonstrating a reduction of tobacco consumption and nicotine

craving (e.g. Fecteau et al., 2014; Falcone et al., 2016; Coles et al., 2018), suggesting that tDCS is effective as a treatment for smoking cessation.

In addictions, tDCS is usually applied over the dorsolateral prefrontal cortex of both hemispheres (with the anode over the right hemisphere and the cathode over the left). This stimulation protocol has very low spatial resolution and precision. New tDCS devices allow higher spatial resolution and better definition of the stimulated area which may allow a more focused stimulation. Considering this, here we propose a multisite stimulation protocol focused only on the right dorsolateral prefrontal cortex, with one anode in F4 and 5 cathodes around F4 (based on EEG 10-20 system).

Many of the studies conducted until now are based on a single tDCS session, while only a few of them are sham-controlled and based in repeated daily sessions with a specific active tDCS (Lefaucheur et al., 2017). These limitations only allowed Lefaucheur et al. (2017) to recommend “a level of evidence B regarding the efficacy of tDCS (...) to reduce craving in patients with various types of addiction”. Thus, the single session studies only confirm the efficacy of tDCS in the reduction of craving. To be able to confirm that tDCS treatment is also effective for smoking cessation is necessary to apply it for various sessions, so we can have a maintained long-term effect.

The main goal of the study is to evaluate the efficacy of multisite tDCS in the reduction of craving and tobacco consumption in smokers by performing 10 sessions of stimulation. Regarding the existing literature, we expect to observe a better success in the reduction of consumption of tobacco and nicotine craving in the experimental group compared to the sham group.

2. Methodology

2.1. Study design

A randomized controlled experimental study with a mixed design will be performed. The sample of the study will consist of 50 subjects, randomly distributed in the two experimental groups. The participants in the experimental group will receive active tDCS in 10 sessions during two consecutive weeks distributed in two blocks of 5 consecutive days while the control group will receive sham tDCS for the same period of time. We will perform a focal modulation of the right dorsolateral prefrontal cortex using anodal tDCS.

2.2. Sample

The sample will consist of 50 volunteer participants (25 per group), aged 18-55 years old. Participants will be recruited through advertisements at the UOC headquarters.

The inclusion criteria are being an active smoker (at least 5 cigarettes per day during a year) and being between 18 and 55 years old. The exclusion criteria are based on the tDCS application guidelines (Rossini et al., 2015). In particular, the exclusion criteria are: having a neurological disorder, suffering or having experienced a mood disorder in the last 6 months, taking medication that affects the nervous system, being pregnant, having dermatological problems in the scalp, having an implant or metal piece in the head, bringing pacemakers, medication pumps or aneurysm clips and having abused or having dependence of psychoactive substances currently or during the last 6 months.

To calculate the needed sample size we used G*Power software v3.1.9.3 (Buchner, Erdfelder, Faul & Lang, 2017), assuming a drop out risk of 15%, a type I error probability (α) of 0.05, and a type II error probability or statistical power ($1 - \beta$) of 0.9. To determinate the effect size, we used the data presented in a recent meta-analysis by Jansen et al. (2013). The total recommended sample size is 42, to which we added 8 more participants per group to cover the 15% dropout risk. The final sample size is then 50 participants, 25 per stimulation group.

2.3. Procedure

The study will have the following stages (see figure 1):

First, participants will be recruited through advertisements at the UOC headquarters between January and February 2019.

Then, the experimental phase and the data collection will start. The participants' enrollment in the study will last 6 months and 2 weeks and will have 10 experimental sessions. It will start with the first experiment session and will end 6 months after the last session, when we will collect the last data of the experiment.

Each session will last between 1 and 1.5 hours and will consist of three different stages. Participants will be instructed not to smoke during the 2 hours prior to each tDCS session.

Only in the first session, we will evaluate the participants level of nicotine dependence (see materials below). We will also measure the amount of CO2 in the lungs of each participant, explain the study and give an informed consent, which will have to be signed for the participant and the researcher. The rest of the session will be the same as in the following sessions.

In the first stage (before stimulation), we will collect the number of cigarettes consumed per day, and will evaluate the motivation for quitting smoking and the perceived self-efficacy, as well as the level of craving, the general state and the adverse effects questionnaire (see materials below).

In the second stage, we will conduct the tDCS stimulation (active or sham) for 20 minutes. Participants will be instructed not to close their eyes or speak during the stimulation since this would change the cerebral regions activated.

In the third stage (after stimulation), we will measure the craving immediately after the stimulation, the motivation and perceived self-efficacy, and the general state. We will also write down any adverse effect detected.

In the last session, in addition to following the usual protocol, we will measure the amount of CO2 in the lungs of each participant and evaluate the level of nicotine dependence.

Finally, 6 months after the last experimental session, we will collect the number of cigarettes consumed and measure the level of nicotine dependence and the amount of CO2 in the lungs.

	Study period				
	Enrollment	Interventions			Close-out
Timepoint	t_0	t_1	t_2 - t_9	t_{10}	t_{11} (6 months follow-up)
Enrollment	x				
Eligibility screening	x				
Informed consent		x			
Allocation	x				
Interventions					
tDCS active		←	—	→	
tDCS sham		←	—	→	
Assessments					
Nicotine Dependence		x		x	x
VAS Craving		x	x	x	
VAS General State		x	x	x	
VAS Motivation and Self-efficacy		x	x	x	
QSU-Brief		x	x	x	
Adverse effects questionnaire		x	x	x	
CO2 measurement		x		x	x
Number of cigarettes consumed		x	x	x	x

Figure 1. Study timeline following SPIRIT recommendations

2.4. Materials

To evaluate the level of nicotine dependence, in the first session participants will fill up an electronic version of The Fagerström Test (FNDT), (Heartherton, 1991); The Hooked

On Nicotine Checklist (HONC), (DiFranza, 2002); The Nicotine Dependence Syndrome Scale (NDSS), (Becoña et al., 2012); and The Glover Nilsson Test (Glover et al., 2002), (GN-SBQ). Although all these questionnaires measure the same variable, they provide complementary information. For example, the FNDT measures the level of physical dependence, the HONC measures the loss of control in front the substance, the NDSS includes the tobacco consume and, finally, the GN-SBQ includes three domains of dependence - psychological, social and gestural -. Participants will fill up the same questionnaires again in the last session and 6 months after.

In each session, we will collect a large amount of data. To collect most of these data we will use an app called Ethica (Hashemian, Staanley & Osgood, 2018). This app will allow us to have all the information in an online database.

To measure the level of craving we will use VAS and the QSU-brief (Cepeda-Benito et al., 2004). Each VAS applied during the sessions will consist of the same three questions related to the needed of smoking at that specific moment. QSU-Brief measures the needed of smoking. It has 10 items presented as a Likert scale with a range between 1 and 7, where 1 means "completely disagree" and 7 "completely agree". VAS will be applied to the participants by using Ethica, while the QSU-brief will be filled up using the lab computer.

Regarding the smoking intake, participants will report to the researcher the number of cigarettes consumed during the last 24 hours before the stimulation at the beginning of each session. In addition, participants will report the same data 6 months after the end of the experimental sessions.

To evaluate the motivation for smoking and perceived self-efficacy, participants will answer two VAS in each session. Each VAS will consist of the same four questions related to the interest in smoking cessation, the expectations of success, the expectations of avoiding relapses in 6 months and the expectations of avoiding relapses at long-term. Participants will use the app Ethica.

Participants will have to fill up a general state VAS and an adverse effects questionnaire. These questionnaires have been included as safety control tools. They have been designed to detect possible adverse symptomatology derived from the use of tDCS, so the questions are related to the physical, emotional and psychological state of the participant before and after the stimulation. In addition, suggested by some authors (e.g. Brunoni et al., 2011), the adverse effects questionnaire includes the most frequent symptomatology observed after stimulating with tDCS, such as tingle, itching and mild headache.

To perform the stimulation, we will use a tDCS 8-channel neuroestimulator system (Starstim, Neuroelectrics, 2018). The device includes a neoprene headcap, electrodes, an ear clip and a software called NIC.

The level of CO2 in the lungs will be evaluated with a carboximeter. Each participant will be evaluated the first and the last day of the experimental sessions and 6 months after the last session.

2.5. Stimulation

tDCS will be carried out using an 8 channels Starstim device (Neuroelectrics, 2018). Electrodes will be placed according to the international 10-20 EEG system. The anode will be placed in F4 (right DLPFC). The cathodes will be positioned in FC2, FC6, FZ, F8 and FP2 (see figure 2). Active tDCS will be applied with 30s ramp up to 2mA and maintained at this level for 20 minutes, followed by 30s ramp down. In sham, tDCS will be applied with 30s ramp up to 2 mA, followed by 30s ramp down and no stimulation for the remaining 20 minutes. Each participant will receive a total of 10 sessions during two consecutive weeks distributed in two blocks of 5 consecutive days.

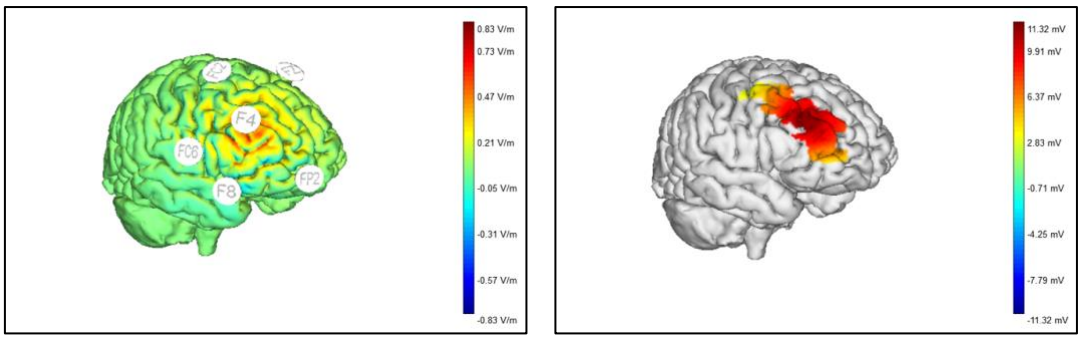

Fig. 2. Capture from NIC (Starstim software). The left image shows the different areas stimulated. The capture on the right shows the zone with the area excited.

2.6. Ethical aspects

The protocol of our study will be evaluated for the UOC Ethics Committee. All participants will receive an informed consent, which will have to read and sign before the study starts. In this document, we will inform them about the objectives, the inclusion criteria, the

conditions of the study and the procedure, the possible risks and side effects, the voluntariness of participation, their rights and the rights of the researchers regarding the study and the confidentiality and protection of personal data.

The personal data will be collected and analyzed to evaluate the efficacy of the tDCS treatment in smoke cessation. All the data will be treated with strict confidentiality, according to RGPB (EU) 2016/679. The personal data collected will not be distributed to third parties. The participants will be able to stop their participation at any time and request the deletion of the data provided and the data generated so far.

2.7. Statistical Analysis

All statistical analyses will be performed using SPSS software. The level of statistical significance will be placed at $p<0.05$.

We will perform analysis of variance (ANOVAS) to analyze the differences within participants across sessions and between stimulation groups.

One set of ANOVAS will compare each of the variables measured in each session throughout the ten sessions and between groups (10x2). These include the following variables: level of craving, level of motivation and perceived self-efficacy and number of cigarettes consumed.

Another set will compare the differences between the three main time points aimed to evaluate the long-term effects of the intervention: before, immediately after de intervention and 6 months later. We will perform one 3x2 (time x condition) ANOVA for each of the following variables: level of CO2 in the lungs, level of nicotine addiction, and the number of cigarettes consumed during the 24hrs before each session.

2.8. Workplan

We have estimated a total duration of 11 months to complete the study. Once we have analyzed the data, we will write the paper and start de diffusion between the specialized public, via congresses and scientific journals, and the general public, via dissemination days or informative magazines.

Timeline proposed:

	Oct. 2018	Nov. 2018	Dec. 2018	Jan. 2019	Feb. 2019	Mar. 2019	Apr. 2019	May 2019	Jun. 2019	Jul. 2019	Aug. 2019	Sep. 2019	Oct. 2019	Nov. 2019	2019, 2020, ...
Review of existent literature															
Study design															
Institutional review board (IRB)															
Sample recruitment															
Training															
Data collection															
Data analysis															
Diffusion of the results															

3. Expected results

We will do a global analysis of data in order to obtain the short-term effects and the long-term effects.

First, we will perform the analyses to compare the short-term changes occurred during the 10 sessions. We expect that the within-group analyses will show that the craving in the participants of the active group will decrease progressively after each session, showing a significant reduction when comparing the data between the first and the last session (Boggio et al., 2009). Besides, we expect that the craving will decrease after the stimulation. We will also expect that the use of tobacco will decrease session after session. Regarding the sham group, and considering Boggio et al. (2009) and Fecteau et al. (2014) studies, we will expect the same tendency towards reduction of tobacco consumption and craving observed in the control group, but not statistically significant.

So, in the short-term effects, we expect to find a progressive reduction in the consumption in both groups, although greater in the experimental group. We expect to obtain a global and significant time effect, a significant group effect and an interaction effect, significant and greater in the experimental group. We cannot predict if the results will show a significant interaction effect in the control group.

Regarding the long-term effects, we will expect to obtain results corroborating our hypotheses. The comparisons between groups will show that the experimental group will have less craving, will consume fewer cigarettes and will have a smaller volume of monoxide of carbon than the control group after the treatment and at the end of the study. Doing predictions about the same variables after 6 months seem too risky since we will be stimulating only for 10 days. Taking into account the hypotheses, we will expect a reduction of the consumption after 6 months. However, since it is the first time that this procedure will be performed, does not exist any previous literature to support it. These expectations are consistent with previous studies (Boggio et al., 2009) that found that in the active group the participants reduced a 30% the consumption of tobacco, while the sham group only reduced it a 10%. Fecteau et al. (2014) found similar results in their study. In any case, both groups reduced the tobacco use.

Thus, in the long-term analysis, we will expect to find a cessation of smoking in the experimental group and a similar smoking use than before the treatment in the control group. We expect to find similar effects than in the short-term effects, although if the control group does not stop smoking, it is possible that the time effect will not be significant.

Pilot

Here we present the most relevant results obtained in a 5-session pilot study conducted between November and December 2018. The pilot study included some relevant differences compared to the project presented here, it included a positive control group receiving cognitive behavioral therapy, we used a video of people smoking to elicit the craving (Dunbar et al., 2014; Tong, Bovbjerg & Ervlich, 2007) and we did not include the measurement of the CO2 in the lungs.

Since we only had 2 participants (one in the active group and the other in the sham group), we could not perform any statistical analyses over the data collected. Thus, we compared within-subject differences. In addition, we did a qualitative analysis of the data comparing both participants and we were able to test the procedure and the characteristics of the assessment tools. Some of the results obtained in the pilot study can be seen in Annex 6.1.

As we can see in figure 4 (presented in Annex 6.1), the active participant did not consume tobacco throughout the study, while the sham participant did an irregular consume showing a subtle tendency to reduction.

Regarding the craving (figures 5 and 6), the data shows that the sham participant had a greater reduction than the active participant, although the results presented in figures 7 and 8 (QSU-Brief) show contradictory data.

Figure 3 shows the level of nicotine dependence of both participants before starting the intervention.

4. Discussion

This project has been developed with a focus on the impact in people's life but also its viability. The possible difficulties that the project faces, mainly related to the sample, the material and the human resources needed, have been taken into consideration. We will discuss all of them in the following sections.

4.1. Viability

First, the sample size required to achieve enough statistical power to draw solid conclusions is one of the major factors that can compromise the project's viability. The recruitment of 50 participants is challenging mostly because the experiment consists of 10 sessions in 10 days over 2 consecutive weeks, always at the same time of the day, making the risk of drop out very high. Also, the exclusion criteria are very extensive, which will imply that many volunteers may be discarded. To minimize the impact of these possible problems, we will have the support of the human resources department from UOC. The department will help us design a campaign to recruit volunteers. We expect that this campaign will have enough impact between the workers and students of the UOC institution to provide us the 50 participants needed. Besides, since the workers are in the same building than our lab it will be easy for them to attend the sessions. Regarding the students, we expect them to have some free hours during the day. However, as mentioned in the methods section, we already took into account the drop out risk, so we included 8 extra participants to the 42 calculated initially.

Regarding the material resources, the Cognitive NeuroLab, where the experiment will be conducted has a fully equipped laboratory, with a tDCS device (Neuroelectrics Starstim 8 channels) and computers that can be used to answer the surveys. The questionnaires and applications used for collecting the data are open source (e.g. The Fagerstörm Test; Ethica App). The only material that we do not have is the carboximeter but we will get it from another research group from the UOC. On the other hand, we need to consider the human resources. In this aspect, the lab has 3 part-time researchers and 4 part-time external collaborators. Although more human resources would be helpful to conduct the study, the research staff is enough to collect and process the data. Finally, considering the amount of time required to conduct the study, we established a period of 6 months to collect the data. This means that we will have to perform more than one session per day, each lasting 1-1.5 hours.

4.2. Impact

Regarding the impact of the study, some authors (Lefaucheur et al., 2017) classified the tDCS with a level B of evidence in the treatment of addictions. So, in case that we can

confirm our hypothesis, it will be a great contribution in the process to increase the level of evidence of the tDCS in this pathology. Achieving the highest evidence would have an important impact mostly in the scientific field, but also from a social, economic and clinical point of view.

In a scientific level, if we are able to confirm that tDCS is effective as smoking cessation therapy, we may be able to expand these results to treat addiction to other substances, since the principal brain regions affected for different kinds of addictions (such as prefrontal cortex, hippocampus or amygdala) are similar in many cases (Goldstein & Volkow, 2011; Herman & Roberto, 2015). On the other hand, despite the study tries to verify the efficacy of this technique in smoking cessation treatment, negative results could lead us to rethink about the best brain region to deliver the stimulation. For example, Falcone et al. (2019) found a lack of effect of tDCS on short-term smoking cessation when applying the stimulation on the left DLPFC, while Klauss et al. (2018) found the same results in crack-cocaine users when doing a bilateral stimulation of the DLPFC. However, in a previous study with the same intervention used by Klauss et al. (2018), Batista et al. (2015) found that tDCS was "clinically useful in the treatment of drug addictions". Thus, so far we have yet to confirm the efficacy of the tDCS and establish the exact target area to be stimulated.

The social, economic and clinical aspects influence each other. Nowadays, there are millions of victims of health diseases associated to tobacco consumption, mostly affected for lung cancer, pulmonary diseases and cardiovascular diseases (WHO, 2017). But tobacco use also increases the risk of having other health pathologies, such as osteoporosis, reproductive disorders, duodenal and gastric ulcers or delayed wound healing, above others. Thus, this addiction increases in about a 50% the risk of dying prematurely from a complication of smoking (Benowitz, 2010). The confirmed efficacy of the tDCS would provide new therapeutic programs and increment the amount of people able to stop tobacco use. So, the clinical impact would affect both, the social and the economic domains. Since the addictive behaviors represent a very important expense for the public health system, fewer people smoking would mean that the public health system may have more economic resources to invest in other medical or social needs of the population.

4.3. Conclusions

Here we present a research proposal for an experimental study trying to improve smoking cessation through a non-invasive brain stimulation intervention. The sample of the study will consist of 50 subjects, randomly distributed in the two experimental groups. The participants in the experimental group will receive active tDCS for 10 days distributed in two blocks of 5 consecutive days along two weeks while the control group will receive

tDCS sham for the same period. We will measure the level of craving and nicotine dependence thorough the treatment and will do a 6 months follow-up.

After a thorough literature review, we propose some improvements compared to previous studies. First, we propose a new disposition of the electrodes that will allow us to stimulate a very specific region of the brain. Second, we will recruit a sample of 50 participants, which is much larger than the usual in previous studies using this technique (e.g. Fecteau et al., 2014). Finally, we will increase the length of the treatment to 10 sessions, which is the double of some other similar studies (e.g. Brangioni et al., 2018). Therefore, our study has four strong points: the innovative technique, the new disposition of the electrodes, the large sample size, and the increase in the number of sessions. These improvements are aimed to overcome weaknesses found in previous studies related to the lack of effects often related to insufficient statistical power.

We expect to observe a reduction in tobacco consumption and nicotine craving in the experimental group compared to the sham group. The confirmation of our hypotheses would contribute to increase the literature supporting the use of tDCS in tobacco addiction. Moreover, providing a new strategy to reduce tobacco addiction will have an important scientific, social, economic and clinical impact, such as the reduction of the number of patients suffering from tobacco-related diseases, thus lowering the public health system burden.

5. References

Abrams, D. B., Monti, P. M., Carey, K. B., Pinto, R. P. & Jacobus, I. (1988). Reactivity to smoking cues and relapse: two studies of discriminant validity. *Behaviour Research and Therapy,* 26(3), 225-233.

Becoña, E., Fernández del Río, E., López, A., Míguez, M. C., Castro, J., Nogueiras, L. ... Vázquez, D. (2012). La escala breve de evaluación del síndrome de dependencia de la nicotina (NDSS-S) en fumadores españoles. *Psicothema*, 23(1), 126-132.

Becoña, E., Martínez-Vispo, E., Senra, C., López-Durán, A., Rodríguez-Cano, R. & Fernández del Río, E. (2017). Cognitive-behavioral treatment with behavioral activation for smokers with depressive symptomatology: study protocol of a randomized controlled trial. *BMC Psychiatry*, 17(1), 134.

Benowitz, N. L. (2010). Nicotine Addiction. *New England Journal of Medicine*, 362(24), 2295-2303.

Brangioni, M.C., Pereira, D. A., Thibaut, A., Fregni, F., Brasil-Neto, J. P. & Boechat-Barros, R. (2018). Effects of Prefrontal Transcranial Direct Current Stimulation and Motivation to Quit in Tobacco Smokers: A Randomized, Sham Controlled, Double-Blind Trial. *Frontiers in Pharmacology*, 9(14).

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzeiro, B. G. & Fregni, F. (2011). A Systematic Review on Reporting and Assessment of Adverse Effects associated with Transcranial Direct Current Stimulation. *International Journal of Neuropsychopharmacology*, 14(8), 1133-1145.

Coles, A. S., Karolina, M. S. & George, T. P. (2018). A Review of Brain Stimulation Methods to Treat Substance Use Disorders. *The American Journal on Addictions*, 27, 71-91.

Conklin, C. A. & Tiffany, S. T. (2002). Applying extinction search and theory to cue-exposure addiction treatments. *Addiction*, 97(2), 155-167.

DiFranza, J.R., Savageau, J.A., Fletcher, K., Ockene, J.K., Rigotti, N.A., McNeill, A.D., Coleman, M., & Wood, C. (2002). Measuring the loss of autonomy over nicotine use in adolescents. *Archives of Pediatric and Adolescent Medicine*, 156, 397-403.

Dinur-Klein, L., Dannon, P., Hadar, A., Rosenberg, O., Roth, Y., Kotler, M., ... Zangen, A. (2014). Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial. *Biological Psychiatry*, 76(9), 742- 749.

Dunbar, M. S., Shiffman, S., Kirchner, T., Tindle, H. & Scholl, S. (2014). Nicotine Dependence, "Background" and Cue-Induced Craving and Smoking in the Laboratory. *Drug and Alcohol Dependence*, 1(142), 197-203.

Emmons, K., Emont, S., Collins, R. & Weidner, G. (1988). Relapse prevention versus broad spectrum treatment for smoking cessation: a comparison of efficacy. *Journal of Substance Abuse*, 1(1), 79-89.

Falcone, M., Bernardo, L., Ashare, R. L., Hamilton, R., Faseyitan, O., McKee, S. A., ... Lerman, C. (2016). Transcranial Direct Current Brain Stimulation Increases Ability to Resist Smoking. *Brain Stimulation*, 9(2), 191-196.

Faue, M., Folen, R. A., James, L. C. & Needels, T. (1996). The triple tobacco cessation program: Predictors for success and improved efficacy. *Military Medicine*, 162(7), 445-449.

Fecteau, S., Agosta, S., Hone-Blanchet, A., Fregni, F., Boggio, P., Ciraulo, D. & Pascual-Leone, A. (2014). Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: a preliminary study. *Drug and Alcohol Dependence*, 140, 78-84.

Fregni, F., Liguori, P., Fecteau, S., Nitsche, M. A., Pascual-Leone, A., & Boggio, P. S. (2008). Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: A randomized, sham-controlled study. *Journal of Clinical Psychiatry*, 69(1), 32-40.

Goldstein, R. Z. and Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience,* 12(11), 652-669.

Götestam, K. G. & Melin, L. (1983). An experimental study of covert extinction on smoking cessation. *Addictive Behaviors*, 8, 27-31.

Heatherton T.F., Kozlowski L.T., Frecker R.C. & Fagerstrom, K.O. (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addictions*, 86, 1119-1127.

Herman, M. A. and Roberto, M. (2015). The addicted brain: understanding the neurophysiological mechanisms of addictive disorders. *Frontiers in Integrative Neuroscience*, 9(18).

Hooten, W. M., Townsend, C. O., Hays, J. T., Ebnet, K. L., Gauvin, T. R., Gehin, J. M., ... Warner, D. O. (2014). A cognitive behavioral smoking abstinence intervention or adults with chronic pain: A randomized controlled pilot trial. *Addictive Behaviors*, 39(3), 593-599.

Jansen, J. M., Dams, J. G., Koeter, M. W., Veltman, D. J., Van den Brink, W. & Goudriaan, A. E. (2013). Effects of non-invasive neurostimulation on craving: a meta-analysis. *Neuroscience and Biobehavioral Reviews*, 37(10), 2472-2480

Kazdin, A. E. & Smith, G. A. (1979). Covert conditioning: a review and evaluation. *Advances in Behaviour Research and Therapy*, 2, 57-98.

Lefaucheur, J. P., Antal, A., Ayache, S., Benninger, D., Burnelin, J., Cogiamanin, F., ... Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*, 128, 56-92.

Lehmann, G. & Calin-Jageman R. (2017). Is Red Really Romantic? *Social Psychology*, 48, 174–183.

Leiva, A., Estela, A., Bennasar-Veny, M., Aguilo, A., Llobera, J. & Yanez, A. M. (2018). Effectiveness of a complex intervention on smoking in adolescents: A cluster-randomized controlled trial. *Preventive Medicine*, 114, 88-94.

Li, X. B., Sahlem, G. L., Badran, B. W., McTeague, L. M., Hanlon, C. A., Hartwell, K. J., … George, M. S. (2017). Transcranial magnetic stimulation of the dorsolateral prefrontal cortex inhibits medial orbitofrontal activity in smokers. *American Journal on Addictions*, 26(8), 788-794.

Liu, J., Gill, N., Teodorczuk, A., Li, Z. A. & Sun, J. (2018). The efficacy of cognitive behavioural therapy in somatoform disorders and medically unexplained physical symptoms: A meta-analysis of randomized controlled trials. *Journal of affective disorders*, 245, 98-112.

Meng, Z., Liu, C., Yu, C. & Ma, Y. (2014). Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates smoking behavior. *Journal of Psychiatric Research*, 54, 19-25.

Moery, E. & Calin-Jageman, R. (2016). Direct and conceptual replications of Eskine (2013): Organic food exposure has little to no effect on moral judgments and prosocial behavior. *Social Psychology and Personal Science*, 7, 312–319.

Pripfl, J., Tomova, L., Riecansky, I., & Lamm, C. (2014). Transcranial Magnetic Stimulation of the Dorsolateral Prefrontal Cortex Decreases Cue-induced Nicotine Craving and EEG Delta Power. *Brain Stimulation*, 7(2), 226-233.

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., … Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clinical Neurophysiology*, 126(6), 1071–1107

Sánchez, E., Llorente del Pozo, J. & Iraurgi, I. (2011). Terapia cognitivoconductual: prevención de recaídas en el tratamiento de las adicciones. In Pedrero, E. J., Ruíz, J. M., Verdejo, A., Llanero, M. & Ambrosio, E. (Ed.), *Neurociencia y adicción* (pp. 255-266). Sociedad Española de Toxicomanías.

Stevens, M., King, D. L., Dorstyn, D. & Delfabbro, P. H. (2018). Cognitive behavioral therapy for Internet gaming disorder: A systemic review and meta-analysis. *Clinical Psychology and Psychotherapy*.

Tang, N. K. (2018). Cognitive behavioural therapy in pain and psychological disorders: Towards a hybrid future. *Progress in Neuropsychopharmacology & Biological Psychiatry*, 87(B), 281-289.

Tong, C., Bovbjerg, D. H. & Erblich, J. (2007). Smoking-related videos for use in cue induced craving paradigms. *Addictive Behaviors*, 32(12), 3034-3044.

World Health Organization (2017). *WHO report on the global tobacco epidemic, 2017: monitoring tobacco use and prevention policies*. Genève: World Health Organization.

6. Annex

6.1. Pilot study: graphic view of the results

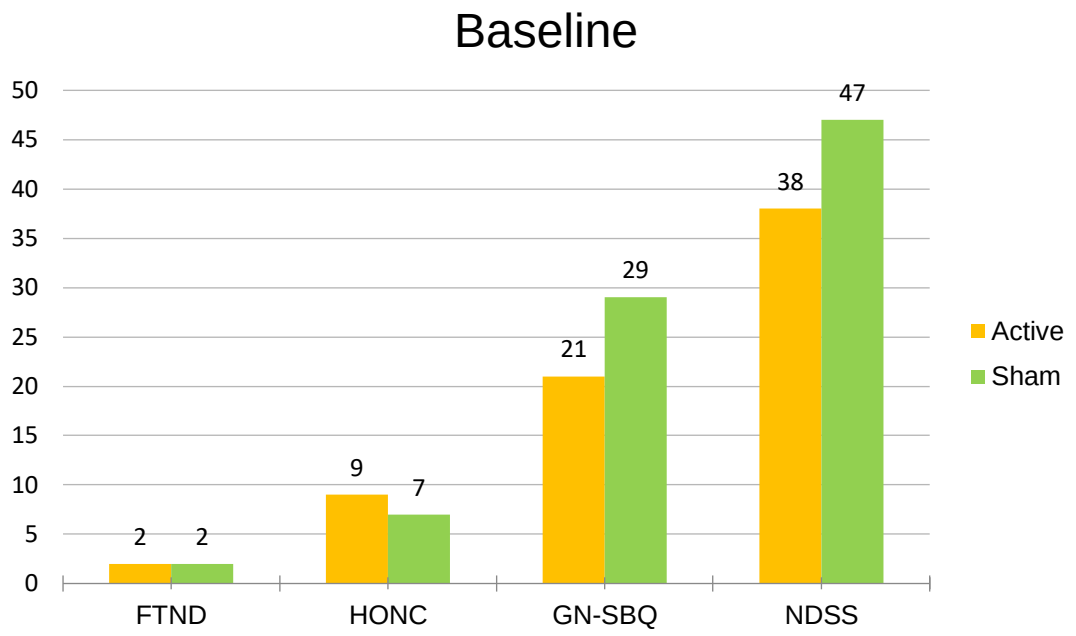

Figure 3. Comparison between the two participants in the baseline (FTND, HONC, GN-SBQ, NDSS) to measure the level of nicotine dependence

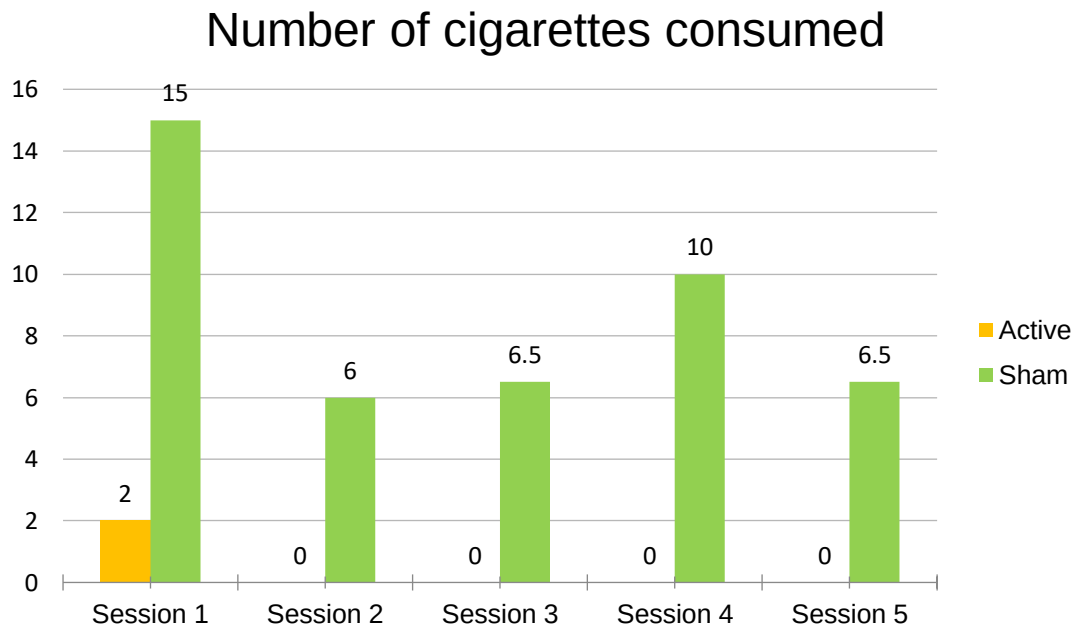

Figure 4. Comparison between the number of cigarettes smoked for each participant during the 24 hours before each session of stimulation

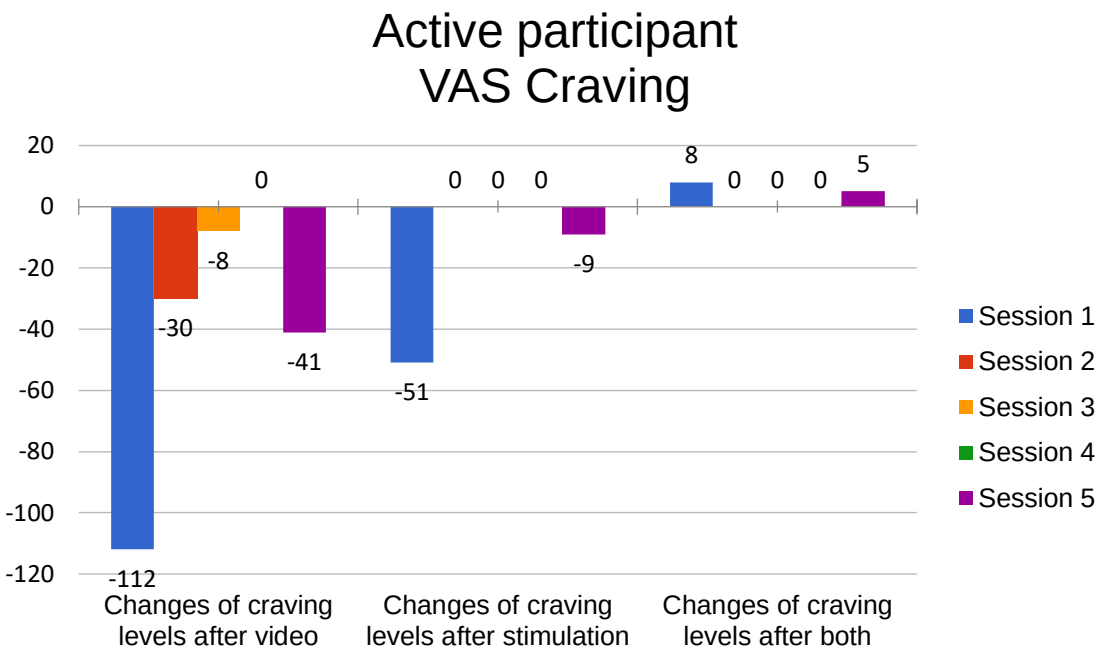

Figure 5. Craving changes from the active participant after the video exposure, after the stimulation and after both

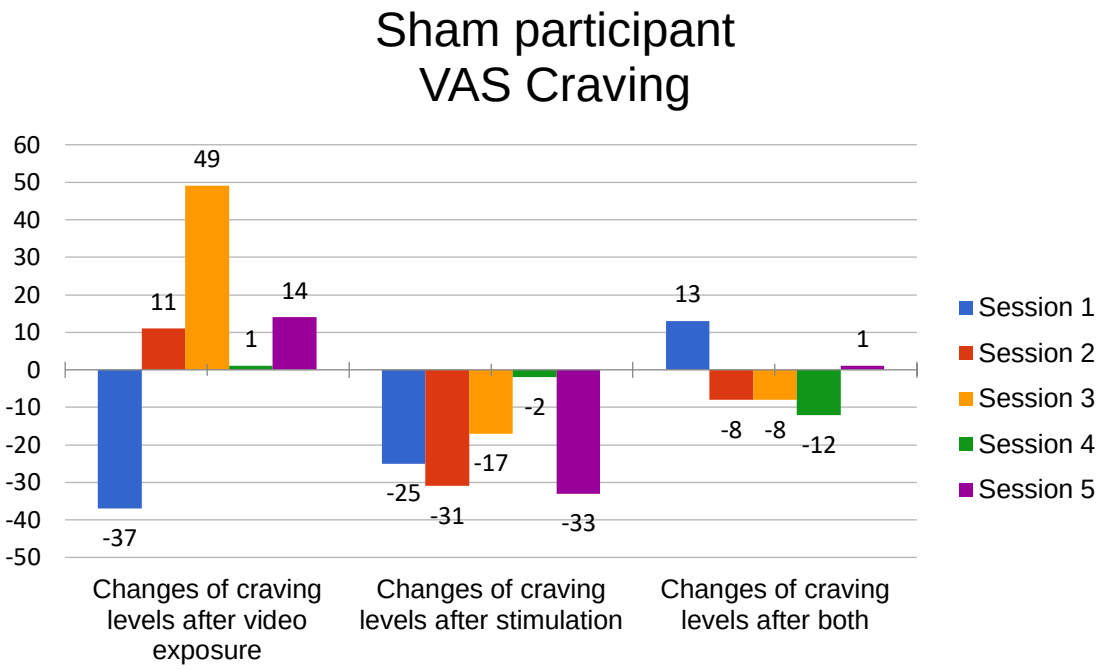

Figure 6. Craving changes from the sham participant after the video exposure, after the stimulation and after both

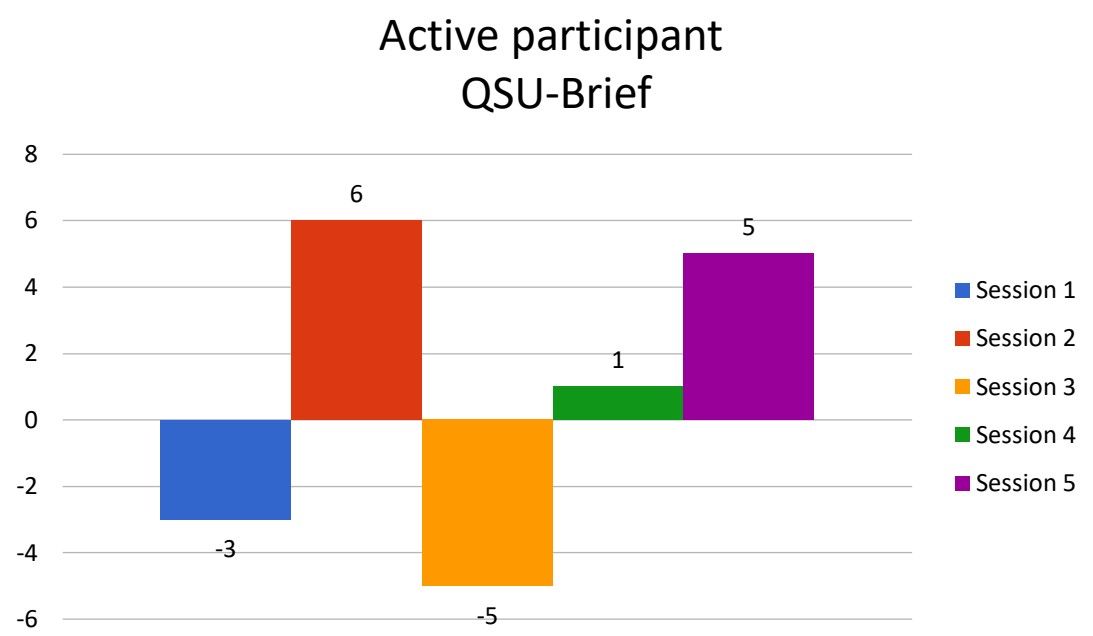

Figure 7. QSU-Brief results (evaluation of craving) showing differences pre-post per session from the active participant

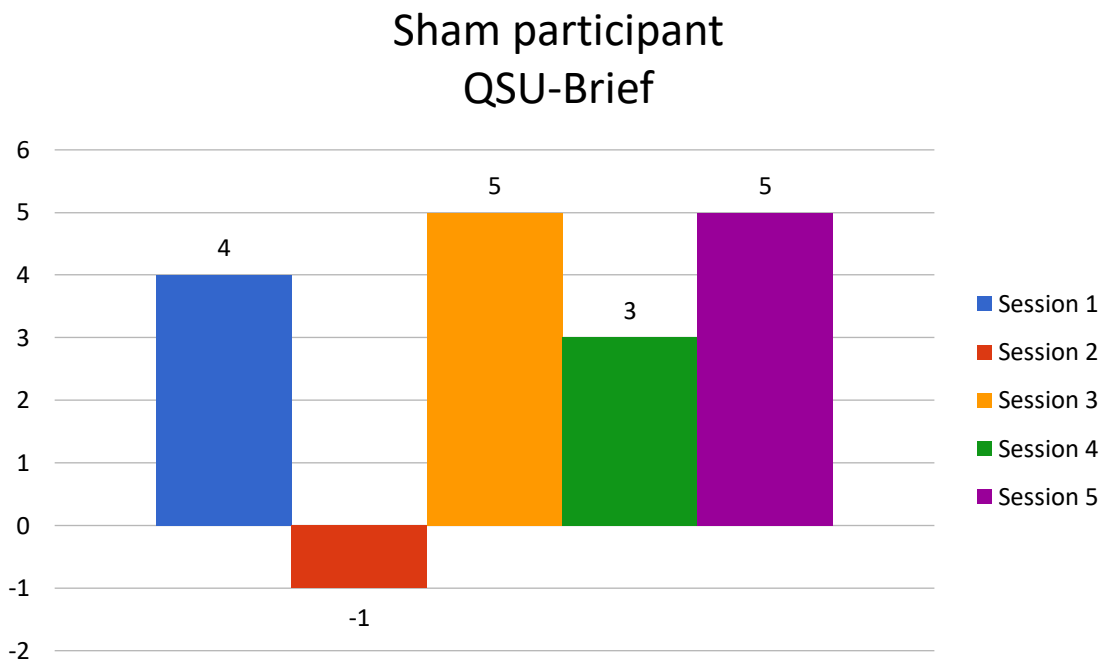

Figure 8. QSU-Brief results (evaluation of craving) showing differences pre-post per session from the sham participant