The Use of tDCS Combined with CET Training for the Treatment of Pathological Dependence

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Abstract Studies on pathological addictions have shown how the need and the search for the substance are stimulated by environmental situations linked to the substance (trigger). This condition is determinant for the state of craving (Bonfiglio et al., Addict Behav Rep 9:100172, 2019). Craving is considered as a conditioning response linked to the search for the substance and determined by the subject's impulsiveness and inability to control himself. Several studies have shown how it is possible to reduce the need for craving and impulsivity through neurostimulation with tDCS (Transcranial direct-current stimulation). Other studies have obtained promising results in this area through the cue exposure paradigm (CET), which consists of presenting the subject with a series of trigger stimuli, which recall the substance, desensitizing its effect and increasing self-control. This work presents an example of a treatment that uses neurostimulation with tDCS together with the cue exposure paradigm on 10 subjects with sham tDCS and 10 with active tDCS, compared with 20 control subjects. After 10 sessions of neurostimulation with active tDCS and sham and cue exposure, the results seem to confirm the hypothesis of a reduction in craving levels and ability to resist for the condition with active tDCS and partially for the condition with sham tDCS. There were no improvements in impulsivity levels. The proposed treatment, despite the partial results, shows many potential, above all due to the possibility of a certain autonomy of use—in the absence of an operator—which goes against the current progress in the field of telemedicine and treatment through a remotely planned and supervised program.

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1 Introduction

Pathological dependence is a challenge for the World Health Organisation as it tends to become a chronic problem for addicted people and results in high costs for society. Pathological addiction is difficult to treat, especially because it very often involves chronic relapse, despite acute detox and withdrawal.

Many treatments are based on managing the patient's craving (which is chiefly to blame for relapse) and impulsivity by focusing on the direct effect that gratification has in this sense (Johnson, 2008; Addolorato et al., 2006; De Mulder & Dom, 2012).

Impulsivity is directly linked to a craving response and it is one of the main factors responsible for relapse (Wrase et al., 2008; Koob & Volkow, 2010); additionally, being aware of their own craving and the other causes that lead to relapse do not deter addicts from maintaining abstinence (Tiffany et al., 2000). This is likely to happen because the process leading to relapse is essentially automatic and uncontrollable in each individual, as explained by George and Koob (2011) via his three-stage cycle of addiction. As a matter of fact, pathological dependence refers to the final stage of a process that starts with an (often recreational) usage of a substance leading to dependant behaviour that is driven by impulsivity and obsessive compulsivity towards that substance (e.g. alcohol, cocaine, etc.) or the object of addiction (e.g. gambling, work, etc.). Usage becomes pathological when a person "loses control" over their drug-seeking and intake (Koob & Le Moal, 2008). From this standpoint, addiction is characterised by (a) compulsive drug-seeking and drug-taking; (b) loss of control over drug-taking leading to (c) negative emotional state (e.g. dysphoria, anxiety, irritability, etc.) because obtaining drugs becomes difficult or it is impaired (Koob & Le Moal, 2008).

An important aspect of experimental research is that it attempts to understand how individuals move from controlled drug use to the compulsive uncontrolled state that characterises addiction (Koob & Le Moal, 2008), which also includes neural and neurobiological mechanisms connected to dependence itself. The hypothesis that has been exhaustively verified suggests addiction results from a process that activates natural motivational systems and their related neural circuitry, such as the reward/gratification system (Koob & Le Moal, 2008); also, the dopamine system seems to be responsible for addiction (Kienast et al., 2013). Individuals suffering from pathological dependence display a dysregulation of the dopamine system, which leads to an increasing loss of motivation for natural rewards (such as food) and an increased interest in the drug as a the main and most important source of strength (Heinz et al., 2009).

Many brain regions are involved in the gratification/reward system and dopamine circuit, such as the dorsolateral-pre-frontal-cortex (DLPCF), the nucleus accumbens and the ventral tegmental area (VTA) (Bechara, 2005). Besides, compulsivity seems

to be a type of behaviour deriving from the dysregulation of the dopamine system caused by the activation of the hypothalamic-pituitary-adrenal (HPA) axis as a stress response.

Recent neuroimaging studies have shown that the left dorsolateral-pre-frontal-cortex (DLPC) is where craving, as a pathology, is activated; this brain region also plays an essential role in craving regulation and its related resisting response (Hartwell et al., 2011), meaning the ability and willingness to resist the urge to use a substance. It has been hypothesised that this region is also responsible for desire regulation and the gratification deriving from pleasure (Hartwell et al., 2011).

Over the last few years, several studies have demonstrated that neurostimulation techniques such as transcranial direct current stimulation (tDCS), which target the dorsolateral prefrontal cortex, can reduce carving (Boggio et al., 2008) as well as its related dysfunctional behaviour (Rachid, 2016). Furthermore, such techniques appear to have long-term effects. This means that even if the treatment is normally concluded within a limited number of therapy sessions, it can still have long-term effects.

In particular, tDCS is a non-invasive and painless technique with only mild adverse effects, which, if they appear, are limited to a slight itchy sensation over the stimulation site. It is simple and easy to perform. It is a procedure that entails modulated brain excitability by placing electrodes over the scalp; these electrodes release a low-intensity current flow for a few minutes. It has also been shown that tDCS can modify cognitive processes by combining neural activity and impulsive behaviour (Fecteau et al., 2004).

As far as behaviour is concerned, several studies have proven the efficacy of cue-exposure therapy (CET) in reducing the stimulus reaction associated with the addictive substance and craving (Tiffany & Conklin, 2002).

For this study, the Pavlovian conditioning model has been used. Some contexts, situations and objects (e.g. a bottle, glass, the bar for an alcoholic) are repeatedly associated with the addictive substance (which is an unconditioned stimulus, US); the context, situations and objects are instead conditioned stimuli (CS). Consequently, these factors elicit an impulse to seek and take the substance (conditioned response, CR) as if it were an unconditioned response (UR). Due to this conditioned context, the addicted person feels the craving when they face a conditioned stimulus. Hence, the craving stimulus becomes a trigger for the dependent behaviour (Lee et al., 2007).

CET aims to completely erase the response associated with the stimulus connected to the addictive substance. In order to do this, it is necessary to repeatedly expose the dependent person to signals connected to the substance (i.e. conditioned response) that causes dependence (Lee et al., 2007); however, this is done by precluding consumption, which could otherwise be a unconditioned stimulus.

As a consequence, CET involves a conditioned response such as craving, physiological activation (e.g. heartbeat, skin conductance, etc.), attention and behaviour biases that are connected to seeking the substance and activated by stimuli that have been previously associated with that substance (Ferreri et al., 2018).

Research on the application of CET (using scripts, photographs, videos, and objects related to drug consumption) has also helped to better understand those situations that lead to continuous substance use, as well as those factors that produce relapse (Conklin and Tiffany, 2002).

In addition, many studies have focused on salient stimuli, meaning videos and images that are offered via tablets and computers to patients during a neurostimulation session. This approach has proven to significantly reduce the outcome connected to dependence among addicts (Li et al., 2020; Carl et al., 2020). It may be possible that combining training and cognitive-behavioural therapy with neural stimulation can boost the therapeutic effects; this approach can also result in significant improvement in maintaining abstinence and reducing craving.

In light of the above, the main objective of this study is to evaluate the efficacy of neural stimulation in subjects who agreed to undertake CET training. This CET training and neural stimulation is expected to reduce craving and impulsivity levels (Bonfiglio et al., 2020), thus also reducing the impulse to use substances and reinforcing coping mechanisms such as the ability to resist substance consumption. By doing so, it is hoped that this approach will prove that these two techniques have to be applied together in order to obtain significant behavioural and neural changes.

2 Methodology

2.1 Instruments

Barratt Impulsiveness Scale. BIS-11 is one of the most commonly used tests to measure impulsiveness (Patton et al., 1995). It comprises 30 items, which can yield total impulsivity as well as three related subscales: (a) attentive impulsiveness; (b) motor impulsiveness and (c) non-planning impulsiveness (Fossati et al., 2001). It has a four-point scale (0-not at all, 4-a lot).

Symptom Checklist-90. SCL-90 is a self-reporting instrument including 90 items where the subjects are asked to report on whether or not they have experienced specific symptoms in the 15 days prior to taking the test (Derogatis & Savitz, 1999). It consists of 9 primary symptoms dimensions: somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism. It has a four-point scale (0-not at all, 4-a lot).

Self-efficacy and desire scale (SAD). SAD comprises 27 items that describe several situations. Each situation includes two sets of options presented in two columns on which the subjects have to respectively choose their craving for the substance and their perceived ability to resist its usage (Minervini et al., 2011). It is possible to generate the total score and three subtotals resulting from the three related subscales: positive emotions and social situations, negative emotions and potentially critical situations, habits and abstinence. It makes use of a 10-point scale (substance desire: × from 0 “minimal desire” to 10 “maximum desire”; resist

substance use perceived ability: from 0 "minimal ability to resist" to 10 "maximum ability to resist").

ASI (Addiction Severity Index). ASI is based on a semi-structured multidimensional interview that aims to rate the severity index of substance addiction. Its 55 questions were designed to establish the intensity and frequency of the problems connected to drug-use within the previous 30 days. Patients are also asked to provide a self-assessment of their physical and mental condition and their relationship with their family. In particular, ASI seeks to investigate these general areas: alcohol and drug abuse, emotional and physical health, employment, family relations and illegal activity. It is extensively employed and has been translated into more than 20 languages (McLellan et al., 1992).

2.2 Cue Eliciting Training

The training session involved presenting 30 stimulating visual prompts and 10 neutral visual prompts. The former had been previously agreed upon with the individual subject and selected from a database of images that recalled several addictive substances. The latter were the same for all subjects.

Each image appeared on the screen moving from left to right, right to left or toward the subject scrolling from the bottom up. Each image remained on screen for 5 s.

At the end of the training session, each subject was asked to relax for a while in order to allow them to decompress if viewing the stimulating visual prompts had caused them any physiological stress. During this phase, the subjects were shown a series of 20 relaxing photographs they had selected beforehand; these visual prompts did not recall any addictive substances and were in contrast with the stimulating visual prompts already reviewed. These relaxing prompts were shown twice for 5 s each, for a total of 40 sequences and were accompanied by background music or songs previously selected by the subject to help them to relax.

2.3 tDCS Neurostimulation

For this experiment, tDCS was applied by using BrainStim stimulation devices (EMS, Italy), with pairs of silicone-coated electrodes (35 cm^2) that were inserted into sponges soaked in saline solution for EEG.

The anode was placed on a stimulation site on the scalp corresponding to the left dorsolateral prefrontal cortex (F3 location in the EEG 10–20 international system). These brain placement sites were chosen because, according to the existing literature, the left prefrontal cortex is responsible for controlling craving, while the anterior cingulate cortex is responsible for impulsive reactions and craving control (Hayashi et al., 2013). A 2 mA current intensity was applied for 20 min.

The control group was subject to a sham tDCS wherein the electrodes were placed on the same sites on the scalp, but the current intensity of the stimulator was gradually reduced to zero after a 20-min treatment. By doing so, the subjects did not know which procedure they were undergoing, since the typical tactile sensation associated with tDCS was experienced only at the beginning of the stimulation process (Brunoni et al., 2014).

2.4 Subjects and Procedures

A total of 40 subjects were selected for this experiment and all were patients that had been hospitalised for their pathological dependence in a rehabilitation centre in Lombardy, Italy. The subjects were recruited on a voluntary basis and according to specific including and excluding criteria that were used during a preliminary interview. The including criteria were: (1) being 18 years old or older; (2) having been diagnosed with substance addiction according to the DSM 5; (3) stable clinical conditions; (4) having abstained from substances for at least 50 days. The excluding criteria were: (1) suffering from epilepsy; (2) displaying severe clinical symptoms connected to abstinence; (3) severe psychiatric comorbidity; (4) convulsions and delirium tremens during periods of abstinence; (5) being already involved in other training experiments or other neuromodulation treatments; (6) any other contraindication to non-invasive brain electric stimulation, e.g. patients with intracranial metallic implants. All subjects signed a form providing written consent to the processing of their personal data for research purposes. This research project was approved by the Ethics Committee of the Department of Brain and Behavioural Science at the University of Pavia.

The treatment programme comprised 10 sessions. Each subject underwent two treatment sessions every week. Each session lasted 20–30 min. Each session included: (a) tDCS (active or sham); (b) cue eliciting; (c) cue relaxing.

This trial was designed with three experimental conditions:

(a) condition 1: the subjects were trained using an active tDCS;
(b) condition 2: the subjects were trained using a sham tDCS;
(c) condition 3: the subjects did not have any treatment.

Self-evaluation questionnaires were administered before starting the treatment programme (T0), after finishing the training programme (T1) and 1 month after the end of the treatment (T2). The experimental group was given the questionnaires the day after their interview during which their demographic data were collected and the stimuli were agreed upon. This was a blind trial for the experimental group, but not for the research team involved in administering the trial.

Table 1 reports on the frequency distribution, the mean values and standard deviation for the collected demographic data and diagnoses under scrutiny.

According to the Symptoms Checklist (SCL), the data shows no significant differences across the three groups in terms of their symptoms (all $p > 0.05$). This

Table 1 Frequency distribution, mean and standard deviation for demographic data

Variables		Subjects of condition 1 $n = 10$	Subjects of condition 2 $n = 10$	Subjects of condition 3 $n = 20$
Demographic data	Age	33	41.6	40.5
		± 11.6	± 16.6	± 9.1
	Education	10.9	11.7	11.5
		± 3.4	± 4.5	± 3.5
	Sex	7 M	6 M	17 M
		3 F	4 F	3 F
Therapy	Pharmacological	10	8	11
	Substitutive	5	3	1
Clinical data	Poly-substance abusers	4	7	12
	First cocaine	2	3	8
	First alcohol	4	4	4
	First heroin	4	3	8
	Age first use primary substance	22.7	28.1	22.2
		± 8.1	± 17.3	± 8.7
	Days of abstinence	95.4	121.9	121.5
		± 46.6	± 171.5	± 154.9

therefore shows that there was no difference between the three groups in psychiatric terms. Furthermore, no values above 1 were detected, which demonstrates that none of the subjects displayed severe psychiatric symptoms.

3 Data Analysis

The outcome measures were analysed using a Linear Generalised Model (ANOVA). For each outcome, the within-groups factor results from the three administration steps (Time: T0, T1 and T2; meaning pre, post e follow-up) and the between-groups factor results from the data obtained by analysing the three groups of subjects under the three conditions (Condition: condition 1, condition 2, condition 3). The mean-square error term was used to conduct Tukey's honestly significant difference (HSD) post-hoc tests to determine potential differences between conditions. Post-hoc tests were considered significant at $P \leq 0.05$, with Cohen's d effect sizes reported for all post-hoc comparisons.

4 Results

With regard to impulsiveness, a significant relation between condition vs. time ($F4,58 = 11.4$, $p < 0.001$, age-square $= 0.99$) was detected. Table 2 below presents the mean values of the "impulsiveness" variable under all three conditions (see Table 2).

As may be noticed, the level of impulsiveness tends to remain constant under all three conditions during T0, T1 and T2. The only exception is condition 2, where the level of impulsiveness increases during T1 and T2.

As for the desire to take the substance again, a significant effect in the relation condition vs. time was also detected ($F4,58 = 2.49$, $p < 0.05$, age-square $= 0.67$). Table 3 below includes the mean values regarding the "desire" variable under all three conditions (see Table 3).

The level of desire to use the substance tends to decrease between the pre- and post-treatment period under condition1. Conversely, it remains stable under

Table 2 Mean and standard deviation of impulsiveness for the three condition at time T0, T1 and T2

Time	Conditions	Means	Standard deviations	N
T0	Condition 1	68.89	12.966	9
	Condition 2	71.10	8.212	10
	Condition 3	65.54	11.370	13
	Total	68.22	10.901	32
T1	Condition 1	69.22	14.158	9
	Condition 2	71.10	8.212	10
	Condition 3	65.54	11.370	13
	Total	68.31	11.284	32
T2	Condition 1	67.33	14.586	9
	Condition 2	81.20	10.293	10
	Condition 3	62.85	7.777	13
	Total	69.84	13.154	32

Table 3 Mean and standard deviation of desire value for the three condition at time T0, T1 and T2

Time	Conditions	Means	Standard deviations	N
T0	Condition 1	171.11	26.521	9
	Condition 2	178.97	31.152	10
	Condition 3	171.97	19.906	13
	Total	173.92	25.075	32
T1	Condition 1	154.56	21.431	9
	Condition 2	178.97	31.152	10
	Condition 3	171.97	19.906	13
	Total	169.26	25.494	32
T2	Condition 1	165.27	36.830	9
	Condition 2	180.67	21.810	10
	Condition 3	189.54	9.588	13
	Total	179.94	25.001	32

Table 4 Mean and standard deviation for ability to resist for the three condition at time T0, T1 and T2

Time	Conditions	Means	Standard deviations	N
T0	Condition 1	171.86	20.24	9
	Condition 2	178.48	34.95	10
	Condition 3	178.25	23.93	13
	Total	176.53	26.28	32
T1	Condition 1	176.20	16.85	9
	Condition 2	178.48	34.95	10
	Condition 3	178.25	23.93	13
	Total	177.74	25.51	32
T2	Condition 1	176.06	33.65	9
	Condition 2	184.18	20.20	10
	Condition 3	146.85	11.39	13
	Total	166.73	27.39	32

Table 5 Mean and standard deviation for severity of addiction for the three condition at time T0, T1 and T2

Time	Conditions	Means	Standard deviations	N
T0	Condition 1	1.49	.61	9
	Condition 2	1.25	.34	10
	Condition 3	1.33	.39	13
	Total	1.35	.44	32
T1	Condition 1	.94	.72	9
	Condition 2	1.25	.34	10
	Condition 3	1.33	.39	13
	Total	1.19	.50	32
T2	Condition 1	.98	.62	9
	Condition 2	.84	.56	10
	Condition 3	1.23	.45	13
	Total	1.04	.54	32

condition 2 and condition 3. The craving for the substance tends to increase under all three conditions.

As for the ability to resist substance-taking, a key role seems to be played by the condition vs. time interaction ($F4,58 = 6.30$, $p < 0.001$, age-square $= 0.98$). Table 4 below includes all the mean values of this variable under all three conditions (Table 4).

The ability to resist substance-taking tends to remain stable within the T0 and T1 period under all three conditions. Under condition 3, it decreases considerably between T1 and T2, while it remains stable under the other conditions.

As regards the severity of the subjects' addiction, a significant factor seems to be the condition vs. time interaction ($F4,58 = 4.75$, $p < 0.001$, age-square $= 0.93$). Table 5 below presents the mean values detected under all three conditions (see Table 5).

As may be noted, the level of severity of the subjects' dependence tends to decrease under condition 1 between T0 and T1, while it remains stable under the

other two conditions. This variable instead tends to decrease under condition 1 and condition 2 between T1 and T2, while it remains stable under condition 3.

5 Discussion

This experimental project has returned results that in part confirm the research hypotheses laid out here. Firstly, it appears clear that the increase in the impulsiveness level between T1 and T2 among subjects under condition 2 does not tend to decrease. This may depend on the fact that subjects under this condition did not undertake a tDCS procedure that, as demonstrated, can reduce impulsiveness and craving.

It may be noted that the level of craving decreases for all the subjects under condition1 while it remains stable for those under conditions 1 and 3 between T0 and T1. Conversely, craving tends to increase between T1 and T2 for the subjects under conditions 2 and 3, meaning during the period when none of the subjects were undergoing treatment; nevertheless, it remains stable for the subjects under condition 1. The latter result confirms the hypothesis that tDCS does have an effect on reducing craving and consequently, the desire and impulsiveness linked to seeking and taking a substance. This effect is due to the subjects' neurostimulation and continues even after the treatment is concluded, thus proving its long-term efficacy. The subjects under conditions 2 and 3 did not undertake any treatment that was directly targeting craving reduction between T1 and T2. Even if these subjects' craving level between T0 and T1 remained stable, it increased between T1 and T2, probably due to prolonged abstinence from the substance.

It is interesting to note that the ability to resist craving remains stable under all three conditions, despite the fact that under conditions 2 and 3 craving tends to increase progressively between one stage and another. It seems therefore safe to suggest that the CET training might have had an effect on subjects' ability to resist and find coping strategies to avoid relapse, even if it did not help reduce craving. Consequently, in the long-term and due to prolonged abstinence, only the subjects in group 3 experienced a decrease in their ability to resist craving.

What is more, the results obtained through ASI testing have shown that the treatment used for this project was successful in the subjects under conditions 1 and 2. The ASI test measures several aspects connected to addiction but craving and resistance to substance-taking are only two factors that have an indirect impact on the severity index. ASI testing yields data resulting from personal interviews that assess a wider range of variables, including legal aspects. The resulting data can therefore be considered as a reliable outcome in terms of the subject's general dependence condition, but it says very little about outcomes for specific symptoms such as craving and impulsiveness. That said, the results obtained regarding the group under scrutiny confirm the hypothesis that tDCS treatment in conjunction with CET training can effectively impact the severity of subjects' dependence, reducing it and contributing to progressive symptom remission.

All in all, this study has aimed to verify the efficacy of a neurostimulator tDCS treatment, coupled with CET training on a group of patients with addiction problems. This hypothesis appears to be partially confirmed. Neurostimulation has proved to be effective in reducing craving levels and dependence among the subjects under condition 1; it also contributes to reducing impulsiveness (monitored via a specific procedure) and increasing the ability to resist substance-taking. The CET training, on the other hand, does not seem to help reduce craving and impulsiveness levels, thus defying our expectations and hypotheses. However, it seems to help control the urge to take a substance. This data refers to the subjects under condition 2 and seems to be confirmed for the treatment period between T0 and T1, but it could not be confirmed for the following period between T1 and T2.

Interestingly, the subjects under condition 3, who can be defined as the control group, seem to confirm our hypothesis regarding the possible outcome in the treatment period between T0 and T1; however, they did not confirm our hypothesis for the T1 to T2 treatment period, when these subjects display the same outcome obtained by group 2. This is likely to depend on the fact that the CET training added a partial effect that was limited to the treatment period, while the tDCS treatment had long-term effects.

This study clearly has some limitations, which need to be taken into consideration. Firstly, the subjects who partook in this experiment were hospitalised in a rehabilitation centre where contingent factors can be very difficult to control. In addition, the criteria for choosing these subjects were that they be involved in similar group or individual activities (e.g. psychotherapy meetings), undergoing similar treatments and more or less experiencing similar conditions (e.g. being allowed out of the centre the same number of times or receiving an equal number of family visits). Nevertheless, it was impossible to control all these variables throughout the treatment period; therefore, the fact that such variables may have indirectly influenced the treatment outcome cannot be discounted.

In addition, the gender percentage is significantly unbalanced with a much higher number of male participants; also, the selection process was not random, and a double-blind experimental procedure could not be undertaken due to organization issues within the rehabilitation centre. That said, all the subjects were part of a rehabilitation programme and helped by a team of operators that actively collaborated on a daily basis with the research team involved in this experiment.

It is proposed that these limits be overcome to the extent possible in future research and that another condition be added with subjects solely treated using tDCS. In addition, we aim to conduct another experiment with subjects that will be solely treated with tDCS without training.

References

Addolorato, G., Leggio, L., Abenavoli, L., Agabio, R., Caputo, F., Capristo, E., Colombo, G., Gessa, G. L., & Gasbarrini, G. (2006). Baclofen in the treatment of alcohol withdrawal syndrome: A comparative study vs. diazepam. *The American Journal of Medicine, 119*(3), 276–e13.

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. *Nature Neuroscience, 8*(11), 1458–1463.

Boggio, P. S., Sultani, N., Fecteau, S., Merabet, L., Mecca, T., Pascual-Leone, A., Basaglia, A., & Fregni, F. (2008). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled study. *Drug and Alcohol Dependence, 92*(1–3), 55–60.

Bonfiglio, N. S., Parodi, D., Rollo, D., Renati, R., Pessa, E., & Penna, M. P. (2020, June). Use of training with BCI (brain computer Interface) in the management of impulsivity. In *2020 IEEE international symposium on medical measurements and applications (MeMeA)* (pp. 1–5). IEEE.

Bonfiglio, N. S., Renati, R., Agus, M., & Penna, M. P. (2019). Validation of a substance craving questionnaire (SCQ) in Italian population. *Addictive Behaviors Reports, 9*, 100172.

Brunoni, A. R., Boggio, P. S., De Raedt, R., Benseñor, I. M., Lotufo, P. A., Namur, V., et al. (2014). Cognitive control therapy and transcranial direct current stimulation for depression: A randomized, double-blinded, controlled trial. *Journal of Affective Disorders, 162*, 43–49.

Carl, E., Liskiewicz, A., Rivard, C., Alberico, R., Belal, A., Mahoney, M. C., Quisenberry, A. J., Bickel, W. K., & Sheffer, C. E. (2020). Dosing parameters for the effects of high-frequency transcranial magnetic stimulation on smoking cessation: Study protocol for a randomized factorial sham-controlled clinical trial. *BMC Psychology, 8*, 1–14.

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

De Mulder, I., & Dom, G. (2012). Disulfiram as a treatment for cocaine dependency. *Tijdschrift voor Psychiatrie, 54*(1), 51.

Derogatis, L. R., & Savitz, K. L. (1999). *The SCL-90-R, brief symptom inventory, and matching clinical rating scales*.

Fecteau, J. H., Bell, A. H., & Munoz, D. P. (2004). Neural correlates of the automatic and goal-driven biases in orienting spatial attention. *Journal of Neurophysiology, 92*(3), 1728–1737.

Ferreri, F., Bourla, A., Mouchabac, S., & Karila, L. (2018). E-Addictology: An overview of new technologies for assessing and intervening in addictive behaviors. *Frontiers in Psychiatry, 9*, 51. https://doi.org/10.3389/fpsyt.2018.00051

Fossati, A., Di Ceglie, A., Acquarini, E., & Barratt, E. S. (2001). Psychometric properties of an Italian version of the Barratt impulsiveness Scale-11 (BIS-11) in nonclinical subjects. *Journal of Clinical Psychology, 57*(6), 815–828.

George, O., & Koob, G. F. (2011). Craving, context and the cortex. *Nature Neuroscience, 14*(4), 409–410.

Hartwell, K. J., Johnson, K. A., Li, X., Myrick, H., LeMatty, T., George, M. S., & Brady, K. T. (2011). Neural correlates of craving and resisting craving for tobacco in nicotine dependent smokers. *Addiction Biology, 16*(4), 654–666.

Hayashi, T., Ko, J. H., Strafella, A. P., & Dagher, A. (2013). Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proceedings of the National Academy of Sciences, 110*(11), 4422–4427.

Heinz, A., Beck, A., Wrase, J., Mohr, J., Obermayer, K., Gallinat, J., & Puls, I. (2009). Neurotransmitter systems in alcohol dependence. *Pharmacopsychiatry, 42*(S 01), S95–S101.

Johnson, B. A. (2008). Update on neuropharmacological treatments for alcoholism: Scientific basis and clinical findings. *Biochemical Pharmacology, 75*(1), 34–56.

Kienast, T., Schlagenhauf, F., Rapp, M. A., Wrase, J., Daig, I., Buchholz, H. G., et al. (2013). Dopamine-modulated aversive emotion processing fails in alcohol-dependent patients. *Pharmacopsychiatry, 2*(04), 130–136.

Koob, G. F., & Le Moal, M. (2008). Neurobiological mechanisms for opponent motivational processes in addiction. *Philosophical Transactions of the Royal Society, B: Biological Sciences, 363*(1507), 3113–3123.

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology, 35*(1), 217–238.

Lee, J. H., Kwon, H., Choi, J., & Yang, B. H. (2007). Cue-exposure therapy to decrease alcohol craving in virtual environment. *Cyberpsychology & Behavior, 10*(5), 617–623.

Li, X., Hartwell, K. J., Henderson, S., Badran, B. W., Brady, K. T., & George, M. S. (2020). Two weeks of image-guided left dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation improves smoking cessation: A double-blind, sham-controlled, Randomized Clinical Trial. *Brain Stimulation, 13*, 1271–1279.

McLellan, A. T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., et al. (1992). The fifth edition of the addiction severity index. *Journal of Substance Abuse Treatment, 9*(3), 199–213.

Minervini, I., Palandri, S., Bianchi, S., Bastiani, L., & Paffi, D. (2011). Desire and coping self-efficacy as craving measures in addiction: The self-efficacy and desire scale (SAD). *The Open Behavioral Science Journal, 5*(1), 1–7.

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of clinical psychology, 51*(6), 7681–774.

Rachid, F. (2016). Neurostimulation techniques in the treatment of nicotine dependence: A review. *The American Journal on Addictions, 25*(6), 436–451.

Tiffany, S. T., Carter, B. L., & Singleton, E. G. (2000). Challenges in the manipulation, assessment and interpretation of craving relevant variables. *Addiction, 95*(8s2), 177–187.

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

Wrase, J., Makris, N., Braus, D. F., Mann, K., Smolka, M. N., Kennedy, D. N., et al. (2008). Amygdala volume associated with alcohol abuse relapse and craving. *American Journal of Psychiatry, 165*(9), 1179–1184.