ISTITUTO DI
NEUROSCIENZE
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Brief description of the project

- **Title of the project**:

Neuromodulation techniques for the treatment of nicotine addiction

- **Description of the scientific and educational objective**

The severe health and economic consequences of the global tobacco use made tobacco control an essential public health priority. Cigarettes smoking has been responsible for more than 200 million deaths over the past 30 years, since it is one of the most important risk factors for premature mortality and morbidity globally. Smoking is a major cause of cardiovascular morbidity and mortality worldwide and it is the cause of many other diseases such as COPD and lung cancer. Therefore, reducing the prevalence of smoking is probably the most effective and cost-effective form of prevention of disease, disability and death, as well as a key public health priority. Moreover, tobacco smoking itself is the most common substance-use disorder, characterized by craving, withdrawal, and compulsive use despite negative consequences. Numerous lines of research have highlighted the addictive nature of cigarette smoking through the nicotine action on reward systems. The rewarding properties of nicotine that promote drug intake involve the mesolimbic projection of dopamine from the ventral tegmental area to the nucleus accumbens. In contrast, the aversive properties of nicotine, which limit drug intake and mitigate withdrawal symptoms, involve the projection of the retroflex fasciculus from the medial abenula to the interpeduncular nucleus. Additional brain regions have also been implicated in various aspects of nicotine dependence, such as prefrontal cortex (PFC), ventral pallidum, nucleus tractus solitarius and insula. All these brain regions are, directly or indirectly, interconnected as integrative circuits to drive drug-seeking and drug-taking behaviors.
Such mechanisms cause most people who attempt to quit smoking to experience craving symptoms, withdrawal symptoms, and fail the attempt, with only 3-10% having positive results after one year. Available treatments, such as behavioral support, varenicline, bupropione and nicotine replacement therapy (NRT) improve the chances of these attempts. However, long term outcomes are relatively low, therefore, there is a need to identify new, effective and safe alternatives to treat cigarette smoking addiction.
In this context, Non Invasive Brain Stimulation techniques (NIBS), as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have entered into the recognized and recommended guidelines therapies, due to the advantages related to safety, tolerability, cost-effectiveness and compatibility with other possible treatments.
Transcranial magnetic stimulation (TMS) is a tool that manipulates reward-related circuities during withdrawal correlates with levels of craving, relapse and continued nicotine consumption.
TMS exploits a high-intensity magnetic field, generated by a light electric current in a coil, which when applied to the scalp allows it to interfere with normal neural activity, modulating excitability and neuronal communication. The possibility of examining changes in cortical excitability after prolonged exposure to substances has given considerable impetus to the study of this technique in the field of addiction,

proposing it as a therapy also in nicotine addiction. In this field, TMS is a non-invasive therapeutic practice which appears to be effective in reducing nicotine craving.
According to two reviews of literature about the evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation, high-frequency (HF) rTMS of the dorsolateral prefrontal cortex (DLPFC) seems to attenuate nicotine consumption and craving. However, studies showed a significant heterogeneity in terms of methods and patients' profile and they did not show an increase in long-term abstinence rate, especially in patients in comorbidity with psychiatric conditions. To this day, only a Level C recommendation has been proposed for the possible efficacy of HF rTMS of the left DLPFC in reducing cigarette consumption.
Transcranial direct current stimulation (tDCS) is a neurostimulation technique based on the passage of a weak current (1–2mA) across the cortex using at least two electrodes.
Studies show that anodal stimulation that can depolarize the neurons is able to reduce craving originated in response to environmental/external stimuli, increasing the cortical excitability of the left DLPFC. Effects of tDCS is due to the modification of the conductivity of sodium and calcium' channels and to the shifting of electrical gradients that affect the ion balance inside and outside the neuronal membrane, modulating its activation threshold. According to a recent study, tDCS applied to the DLPFC is a possible treatment for smoking addiction because of its effectiveness in reducing craving.
The objective of this research is to evaluate if a new protocol of combined NIBS techniques administered in succession to the patient (tDCS + r-TMS) is more effective and lasting than conventional r-TMS protocol usually used in treating nicotine addiction.

- **Supervisor:**

Prof. Rocco A. Zoccali

- **Research design and methods**

All subjects will be consecutively recruited from general population. The study will be conduct at the Psychiatric Unit of the University Hospital Gaetano Martino (University of Messina, Italy), during a period of 15 months. A total sample of 72 subjects will be enrolled.
The inclusion criteria for recruitment will be:
a) Age between 18 and 65 years
b) Ability to read and sign the informed consent.
c) Addiction and craving for cigarettes smoking
The exclusion criteria for recruitment will be:
a) Concomitant severe, unstable, active neurological or physical disease
b) Patients with schizophrenia
c) Patients with intellectual disability
d) Patients with substance related disorders (other than tobacco/nicotine)
e) Patients with previous episodes of epilepsy or unexplained seizures
f) Patients who have implanted electronic devices and/or cochlear implants and/or vagus nerve stimulators
g) Patients with cardiac pacemakers
h) Patients with non-removable metal objects near the coil.

Each participant will undergo:
1. Medical examination
2. Prescription of any clinical and/or instrumental diagnostic investigations.
3. Psychodiagnostics assessment
4. Neurostimulation treatment.

The enrolled patients will be divided into two groups according to 1:1 randomization.
The A group will undergo a conventional TMS protocol
The specific method is explained below:

- stimulation will have a frequency of 10 Hz, with administration of 50 stimuli per train, divided into 20 trains for a total number of stimuli equal to 2000, and interval intertrain equal to 30 sec. Stimulation will be performed once a day for 21 days. The stimulation will be administrated on the area corresponding to the left DLPFC, with 110 percent of the motor threshold, i.e., the minimum energy required to elicit MEPs (Motor Evoked Potentials).

The B group will undergo an experimental short, intensive protocol of neuromodulation with the "double session" modality, which involved the application of tDCS and rTMS treatments in succession, twice per session for five consecutive days (for a total of 10 tDCS treatments and 10 rTMS treatments).
The specific protocols of each method are given below:

- tDCS protocol: electrodes (PiSTIM) with a diameter of 12 mm and surface area circular area of 3.14 cm2 approx will be used. The electrodes will be placed at DLPFC. Specifically, anodal stimulation will be performed with a voltage of 1500 μA, at the level of the left DLPFC and cathodic stimulation will be performed on the corresponding area on the right. A highly conductive saline gel will be applied to each electrode, and the protocol will last for 20 min.
- rTMS protocol: stimulation frequency of 15 Hz, with administration of 50 stimuli per train, divided into 48 trains for a total number of stimuli equal to 2400, and interval intertrain equal to 15 sec for a total protocol duration of 880 sec. The stimulation will be administered on the area corresponding to the left DLPFC, with 100 percent of the motor threshold, i.e., the minimum energy required to elicit MEPs (Motor Evoked Potentials).

The study will have a duration of 6 months. Patients will receive psychodiagnostics evaluation at baseline, at the end of treatment (after 21 days for the A group, and after 5 days for the B group) and at month 6 after the end of the study, with different timelines for each group.

- **Expected results with emphasis on promoting economic development:**

We hypothesize that subjects undergoing the combined NIBS technique protocol will have a better outcome in terms of nicotine abstinence maintenance in the longer-term follow-up than subjects treated with single NIBS protocol.

The company ISTITUTO DI NEUROSCIENZE "Prof. Rocco A. Zoccali" will host the PhD student beneficiary of the grant funded on the resources of DM 352/2022 for n. ___6_____months (min 6 max 18) during the course of the phD program.

Period abroad for no. ___6_____months (min 6 max 18) at the following institution:
Hackensack Meridian School of Medicine, Department of Medical Sciences and Department of Neurology 123 Metro Boulevard, Nutley, NJ 07110.