In collaboration with the Italian Academy of Advanced Studies, my research team has previously published five manuscripts examining the activation of the motor system during the observation of actions in works of art. We successfully characterized the networks responsible for these effects. Building upon this foundation, we recently investigated the impact of olfactory stimulation on the motor system, identifying a facilitatory effect. These findings prompted us to examine the activation of the motor system during the observation of drug-related cues in patients with substance use disorder (SUD) and comorbid depression.

We are currently performing experiments to examine the activation of the motor system in response to drug-related cues. We aim to utilize multisensory cue stimulation, drawing from our prior research, to assess motor system activation in craving as a potential biomarker in clinical trial settings.

First, we started experiments using transcranial magnetic stimulation to assess motor system activation in response to multisensory drug-related cues. Preliminary results confirm our research questions and indicate the use of electrophysiological parameters as a quantifiable biomarker for drug craving. In a subsequent experiment, we intend to administer transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) to lessen craving and improve mood in patients with co-occurring substance use disorder and depression. We hypothesize that the activation of the motor system during craving may serve as a predictor for the response to tDCS intervention. We are now recruiting patients. Co-occurring substance use disorder and depression often exacerbate each other’s symptoms and complicate treatment outcomes. By investigating interventions that target both conditions, such as tDCS, we aim to provide more effective therapeutic approaches that improve overall patient well-being and quality of life. Our research endeavors aim to advance the understanding of the neurobiological mechanisms underlying addiction and comorbid depression. By using innovative interventions like tDCS, we hope to contribute to the development of personalized treatment strategies that address the complex interplay between addiction and mental health disorders. We express our gratitude to the Italian Academy of Advanced Studies for their continued support and collaboration in this research endeavor.
Effects of transcranial direct current stimulation on mood, craving, and relapses in drug users with depression

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Summary
Studies have shown that there is a significant link between substance use disorder (SUD), depression, and suicide. These conditions can affect the prognosis and treatment outcomes of affected individuals. Almost one-third of patients with major depressive disorder also have SUD, which increases the risk of suicide and causes greater social and personal impairment. Antidepressant drugs, mainly selective serotonin (5-HT) reuptake inhibitors (SSRIs), are the primary psychopharmacological treatment for patients with depression. However, several systematic reviews and meta-analyses have demonstrated that SSRIs are not effective in these patients indicating the need to investigating new potential alternative to the pharmacological treatment. Since dorsolateral prefrontal cortex (dPFC) is hypoactive in both depression and SUD, we plan to increase the excitability of this brain area by using Transcranial direct current stimulation (tDCS), an innovative, noninvasive, and safe neuromodulation technique. We hypothesize that this treatment will be safe and it will be associated with a decrease in drug craving/use, and improvement in mood. Furthermore, we will investigate biomarkers as predictors of the therapeutic effects. We hope that the results of this pilot trial will pave the way for personalized, circuit-based brain stimulation treatment in patients with co-occurring disorders.

Neurobiology of addiction: a key role for brain's prefrontal cortex

Drug addiction is a multifaceted and severe chronic disorder characterized by a compulsion to seek and use drugs, loss of control over drug intake, and the emergence of a negative emotional state when access to drugs is prevented. It involves alterations in brain neurocircuitry and neurochemistry that affect motivation, reward, and executive functions. Dopamine plays a critical role in the rewarding effects of drugs and the initiation of addiction, while glutamatergic systems in the prefrontal cortex contribute to the compulsive nature of drug seeking and diminished cognitive control (1).

Drug addiction involves a cycle of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation stages, with neuroplastic changes in the mesolimbic dopamine system and various brain structures, including the ventral striatum, amygdala, and prefrontal cortex. Cellular adaptations in the prefrontal cortex reduce the value of natural rewards and enhance responsiveness to drug-associated stimuli, contributing to the overpowering motivational strength and decreased ability to control drug-seeking behavior. When the brain's prefrontal cortex, responsible for decision-making and impulse control, becomes less active there is a loss of control over drug intake and increased compulsive drug-seeking behavior. Molecular mechanisms and genes mediate aspects of tolerance, dependence, and sensitized responses to drugs (2).
Neurobiology of depression: a key role for brain's prefrontal cortex

The neurobiology of depression is a complex phenomenon, involving intricate interactions between various brain regions and neurotransmitter systems. The prefrontal cortex (PFC), a key area implicated in the regulation of mood and emotion, exhibits dysfunction associated with depressive symptoms. Depression is characterized by structural and functional abnormalities in the prefrontal cortex, anterior cingulate cortex, hippocampus, and amygdala, resulting from dysfunctions in these regions. These abnormalities contribute to depressive symptoms. Studies indicate that both the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) are involved in unipolar depression. The ventromedial and dorsolateral sectors of the prefrontal cortex have distinct functional contributions to depression, with the former associated with the experience and expression of emotion and the latter with affect regulation. Neurobiological research has identified neurotransmitter systems, including glutamate, GABA, serotonin, norepinephrine, and dopamine, as well as neurotrophic factors and signal transduction systems, as important in the etiology of depression. An imbalance in stress hormone receptors in the prefrontal cortex may contribute to the stress-systems hyperactivity and depression.

Altered gene expression in the prefrontal cortex, particularly in ATP biosynthesis and GABAergic neurotransmission, is observed in suicides with and without major depression, indicating a role for these pathways in depressive psychopathology. Reduced expression of immediate early genes in the prefrontal cortex of depressed humans and mice suggests a deficit in neuronal activity. Conversely, brain stimulation of the prefrontal cortex has antidepressant effects in a mouse model of depression. Neuroimaging studies have highlighted the interaction between heightened limbic activity and reduced activation in dorsal cortical structures, which may underlie the dysregulation of affect in major depression.

In summary, the prefrontal cortex plays a vital role in the neurobiology of depression, with various regions and neurotransmitter systems contributing to the regulation of mood and emotion. Dysfunctions in these areas, including structural and functional abnormalities, altered gene expression, and imbalances in neurotransmitter and hormone receptor systems, are associated with depressive symptoms. The interaction between limbic and cortical regions, as well as the influence of the gut microbiota and the endocannabinoid system, are important areas of focus for understanding the pathophysiology of depression and developing targeted treatments (3).

Multisensory drug-cues reactivity and the prefrontal cortex: I see it, I like it, I’ll grab it!

The prefrontal cortex and multisensory cue reactivity are two important areas of study in the field of neuroscience. The prefrontal cortex is known to play a critical role in processing and integrating sensory cues, which can affect attention, cognition, and behavior. Research has shown that multisensory cues activate brain regions associated with motivation, craving awareness, and self-related processing to a greater extent than unisensory stimuli. Drug-related cues have been found to activate the dorsolateral prefrontal cortex more than natural reward-related cues, suggesting that there may be a distinct neural pathway for drug cue reactivity. The prefrontal cortex's response to multisensory integration is influenced by the reliability of cues. Thus, the prefrontal cortex is crucial for multisensory cue reactivity, with its various subregions contributing to the processing of sensory cues in different ways. Drug-related cues activate specific areas within the prefrontal cortex, which may differ from those activated by natural rewards. The prefrontal cortex's response to multisensory integration is influenced by the reliability of cues, with the prefrontal cortex adjusting its response based on the certainty of the information received.
These insights highlight the complex role of the prefrontal cortex in multisensory perception and its potential implications for understanding and treating addictive behaviors (4).

**Assessing brain changes induced by exposure to drug-cue by using TMS**

Transcranial Magnetic Stimulation (TMS) is a neurophysiological technique used to assess cortical excitability and motor function. When investigating the effect of visual cues on craving and its impact on motor evoked potential (MEP) amplitude assessed with TMS, researchers typically aim to understand how external stimuli, such as images, places, odor related to cravings (e.g., food, cigarettes, drugs), modulate cortical excitability and motor responses.

Cues associated with cravings can elicit heightened neural responses in regions associated with reward processing and motivation. For example, images of food can activate brain regions involved in food craving, such as the insula and striatum, while images of cigarettes can activate areas associated with nicotine craving. These cues can evoke subjective experiences of craving and trigger physiological responses. MEPs are neurophysiological responses recorded from muscles following TMS-induced cortical stimulation. Changes in MEP amplitude reflect alterations in cortical excitability, with larger MEP amplitudes indicating increased excitability and vice versa. Studies have shown that exposure to visual cues related to craving can modulate MEP amplitudes, suggesting a link between motivational states and movement preparation.

Attention and motivation play crucial roles in mediating the effects of visual cues on MEP amplitude. Studies have demonstrated that directing attention toward craving-related stimuli enhances the modulation of MEPs, suggesting that cognitive factors influence cortical excitability changes. Moreover, individual differences in motivation and craving intensity can further modulate the impact of visual cues on MEPs. Understanding the influence of drug cues on MEP amplitude in the context of craving has implications for both basic neuroscience research and clinical applications. In addiction research, TMS studies investigating craving-related MEP changes may provide insights into the neural mechanisms underlying addictive behaviors. Moreover, MEP facilitation during craving may be used as a biomarker associated with motivational states in clinical trials. We hypothesize that the exposure to multisensory drug cues will induce activation of motor cortex indicating facilitation of movement preparation (5), (6).

**Increasing dLPFC activation using transcranial direct current stimulation**

Transcranial direct current stimulation (tDCS) induces long-lasting changes in cortical excitability via a weak constant electric current that flows between two electrodes: an anode (+) and a cathode (-). It is thought that the current under the anode causes membrane depolarization of the neurons, which brings their membrane potentials closer to the threshold of excitability, making it more likely to generate an action potential. On the other hand, the cathode induces hyperpolarization, which decreases neuronal excitability and therefore corresponds to inhibition of the neurons. In the context of craving, tDCS has been investigated as a potential therapeutic tool to modulate neural circuits associated with addictive behaviors.

High definition (HD)-tDCS with ring electrodes represents a specialized approach to tDCS that aims to target specific brain regions with enhanced spatial precision. Traditional tDCS typically involves the placement of large rectangular or circular electrodes over broad areas of the scalp, which can lead to
diffuse current distribution and nonspecific effects on underlying brain structures. By concentrating current flow within the central opening of the ring, this technique can potentially target smaller cortical regions with greater precision (focal tDCS). We hypothesize that treatment of DLPFC with focal tDCS will be associated with increased activation of this brain area and reduced craving (7) (8).

Clinical trial outline

Objective: To evaluate the efficacy of HD-tDCS over the left DLPFC in reducing craving and drug use, as well as improving mood symptoms in individuals with substance use disorder. We will first perform an experiment aimed at addressing the effect of multisensory drug cue experience on motor evoked potential. Results will be compared to the ones obtained during a multisensory non-drug-related exposure. (control condition) In this way, we plan to quantify the individual craving and use this neurophysiological parameter as a biomarker. After one week, the participant will enter a pilot clinical trial:

Study Design: Randomized, sham-controlled clinical trial.

Participants:

- Inclusion Criteria: Adults aged 18-65 diagnosed with substance use disorder (e.g., alcohol, cocaine, opioids) and depression based on DSM-5 criteria.
- Exclusion Criteria: History of severe psychiatric disorders (e.g., psychosis, bipolar disorder), neurological disorders, implanted metallic devices in the head, or contraindications to tDCS.

Intervention: Participants will receive HD-tDCS over the left DLPFC twice a day for 20 minutes each session for five consecutive days. The stimulation parameters will be as follows:

- Anode electrode centered over F3 (left DLPFC) and four cathode electrodes surrounding the anode.
- Stimulation intensity: 2 mA.
- Sham stimulation: Mimics the sensation of active stimulation but without delivering therapeutic current.

Outcome Measures:

1. Primary Outcome:
   - Craving severity assessed using validated clinical scales (e.g., Visual Analog Scale for Craving, Obsessive Compulsive Drug Use Scale).
   - Drug use frequency and quantity measured through self-report and corroborated with biological markers (e.g., urine toxicology).
   - MEP amplitude during multisensory drug-cues exposure

2. Secondary Outcomes:
• Depression severity evaluated using standardized clinical scales (e.g., Beck Depression Inventory).
• Anxiety symptoms assessed using validated measures (e.g., Beck Anxiety Inventory).

Assessment Time Points:
1. Baseline assessment prior to the first stimulation session.
2. Follow-up assessment immediately after the completion of the five-day stimulation period.
3. Follow-up assessments at one month and three months’ post-treatment to evaluate sustained effects.

Epigenetic Biomarker Analysis:
• DNA methylation profiling will be conducted using blood samples collected at baseline.
• Candidate genes associated with craving and addiction-related pathways (e.g., BDNF, OPRM1) will be assessed.
• Methylation levels will be quantified using epigenome-wide arrays or targeted methylation assays.

Statistical Analysis:
• Data will be analyzed using appropriate statistical methods, such as repeated-measures analysis of variance (ANOVA) or mixed-effects models.
• Intention-to-treat analysis will be employed to account for potential dropout rates.
• Linear regression and machine learning techniques will be employed for epigenetic biomarker analysis.

Ethical Considerations:
• The study protocol will be approved by the Institutional Review Board (IRB) or Ethics Committee.
• Informed consent will be obtained from all participants prior to enrollment.

Highlights and bullet points: This sham-controlled clinical trial aims to provide evidence regarding the efficacy of HD-tDCS over the left DLPFC as a potential treatment for substance use disorder and comorbid depression:
• Co-occurrence of SUD and depression is very common.
• In both patients with SUD and depression there is hypoactivity of DLPFC.
• We plan to increase DLPFC activation using HD-tDCS treatment. DLPFC is a crucial node in attention, motivation, reward, craving, and mood regulation.
• After treatment, we expect a reduction in subjective craving, and craving-related brain activation.
• Clinical, neurophysiological, and genetic biomarkers will be investigated in the attempt to identify predictors.
• The results of this pilot study will provide a pathway to personalization of integrated treatments in patients with SUD and depression.

References