

Abstract : Impact of tDCS on Cannabis Craving in patient with Schizophrenia and a comorbid cannabis use disorder : a randomized multicenter double-blind placebo-controlled study (tCCS)

Schizophrenia is a very comorbid condition with cannabis addiction. The prevalence of cannabis use in schizophrenia ranges from 13 to 45%, with a lifetime median of 27.1% (Sarrazin et al. 2015). This comorbidity is associated with a poor prognosis in these patients, exposing them to more severe symptoms, more relapses and re-hospitalizations, lower adherence to treatment and poorer quality remissions (Zammit et al. 2008). Therapeutics aimed at helping patients with schizophrenia to reduce or stop their cannabis use is of great importance because it could improve the overall prognosis of these patients (Machielsen et al. 2017).

Craving is considered to be an essential feature of drug addiction, prone to its chronicization and relapses after periods of abstinence (Franken 2003; Robinson and Berridge 1993).

Decreasing craving could then help patients with schizophrenia to reduce or even stop their cannabis use and thus improve the prognosis of their disease (Machielsen et al. 2017). There is currently no validated drug treatment for cannabis addiction. Non-invasive stimulation methods such as rTMS (repeated transcranial magnetic stimulation) or tDCS (direct current transcranial stimulation) targeting the dorsolateral prefrontal cortex (DLPFC) could induce an increase in mesolimbic dopamine secretion and thus "correct" the neurobiological disturbances of chronic dependence and impulsivity (Strafella et al., 2001; Diana et al. 2017). tDCS is a promising and well tolerated neuro-modulation tool. A low intensity current passes through the brain via two electrodes, the anode and the cathode, placed on the scalp. Anodal stimulation increases cortical excitability while cathodic stimulation decreases it (Nitsche et al. 2000).

several animal studies have shown the efficacy of tDCS in reducing craving and withdrawal states in animal models of addiction (cocaine, nicotine and food) (Pedron et al. 2014, 2016; Macedo et al. 2016). A meta-analysis of a RCT (Jansen et al. 2013) demonstrated a significant effect of tDCS on craving for several addictions. More recent meta-analyzes (Zhang et al. 2019; Song et al. 2019) have confirmed this anti craving effect. A pilot study evaluating the effect of tDCS (anode on the right DLPFC and cathode on the left DLPFC) on cannabis craving of habitual cannabis users revealed a significant decrease in craving (Boggio et al. 2010). Looking to schizophrenia pathology arecent clinical trial involving 100 patients with schizophrenia with predominantly negative symptomatology showed that tDCS (anode on the left DLPFC and cathode on the JTP) resulted in significant improvement in negative symptoms, with no significant adverse effects (Valiego et al. 2020).

Given this data we designed this study to assess the cumulative effect of repeated sessions of tDCS on cannabis craving in patients with schizophrenia. this study will be the first to evaluate repetitive sessions with a multicenter design