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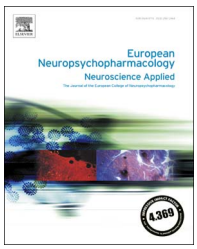

Deep Transcranial Magnetic Stimulation of the Dorsolateral Prefrontal Cortex in Alcohol Use Disorder Patients: Effects on Dopamine Transporter Availability and Alcohol Intake

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Abstract
Repetitive Transcranial Magnetic Stimulation (rTMS) of the dorsolateral prefrontal cortex may affect neuro-adaptations associated with alcohol use disorder (AUD), potentially influencing

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craving and alcohol intake. We investigated alcohol intake and dopamine transporter (DAT) availability by Single Photon Emission Computed Tomography (SPECT) in the striatum of AUD patients before and after deep rTMS. Fourteen patients underwent baseline clinical and SPECT assessment. Eleven out of fourteen patients were randomized into two groups for the REAL (n.5) or SHAM (n.6) treatment. Clinical and SPECT evaluations were then carried out after four weeks of rTMS sessions (T1). At baseline, AUD patients showed higher striatal DAT availability than healthy control subjects (HC). Patients receiving the REAL stimulation revealed a reduction in DAT availability at T1, whereas the SHAM-treated group did not. In addition, patients receiving the REAL stimulation had a decrease in alcohol intake. The results of this longitudinal pilot study may suggest a modulatory effect of deep rTMS on dopaminergic terminals and a potential clinical efficacy in reducing alcohol intake in AUD patients. Further investigations are required to confirm these preliminary data.

1. Introduction

Alcohol use disorder (AUD) is a major public health problem in the western world. In the last decade, lifetime prevalence rates have soared to unprecedented levels (Grant et al., 2015). A general consensus has emerged on drug addiction as a substance-induced, aberrant form of neural plasticity (Kalivas and Brady, 2012; Melis et al., 2005). Dopamine (DA) plays a key role in the acute reinforcing effects of alcohol (Boileau et al., 2003) and in the neurobiological mechanisms underlying chronic abuse and dependence (Martinez et al., 2005; Tupala et al., 2004).

Preclinical studies showed a reduction in DAergic activity in alcohol withdrawn rats (Diana et al., 1993) and a decrease of DA release in the nucleus accumbens (Diana et al., 1993; Weiss et al., 1996). Human studies demonstrated a reduction in D2 receptors in the ventral striatum and a blunted amphetamine-induced DA release in the limbic striatum of detoxified alcoholics (Martinez et al., 2005; Volkow et al., 2007). Furthermore, greater uptake kinetics in female rhesus monkeys have been described after chronic alcohol self-administration (Siciliano et al., 2016a, 2016b). Conversely, a higher number of D2 receptors in unaffected members of alcoholic families may protect against alcoholism (Volkow et al., 2006), whereas increasing the D2 receptor number in high alcohol preference selected rodents reduces alcohol consumption (Thanos et al., 2004) and further supports an inverse relationship between DA transmission and alcohol intake. Dopamine in the synaptic cleft is modulated by the Dopamine Transporter (DAT), a plasma membrane protein which translocates the released transmitter from the extracellular space into the presynaptic neuron (Vaughan and Foster, 2013). Transport capacity of DAT and DA binding properties are regulated by complex and overlapping mechanisms that provide neurons the ability to modulate DA clearance in response to physiological demands (Vaughan and Foster, 2013). Moreover, alterations in genes coding for DAT genes (Uhart and Wand, 2009) are a risk factor for developing AUD (Melis et al., 2005). The hypofunctioning of the DA system plays a key role in alcohol abuse and leads to hypothesize that 'boosting' the system may have therapeutic effects in reducing alcohol intake (Diana, 2011).

Despite the knowledge advancement in the neurobiology of AUD, therapeutic progress has been limited (Addolorato et al., 2012; Leggio et al., 2010). Among treatments, Repetitive Transcranial Magnetic Stimulation (rTMS) could represent a new valid and non-invasive tool (Feil and Zangen, 2010; Gorelick et al., 2014). It allows modulation (stimulation or inhibition) of the cortical mantle by projecting a fluctuating magnetic field through the skull into the brain to generate electrical currents which in turn modulate neuronal firing (Kluger and Triggs, 2007; Rossini and Rossi, 2007). Several studies showed the effect of rTMS on the excitability of mesolimbic and mesostriatal DAergic pathways (Cho and Strafella, 2009; Fitzgerald et al., 2006; Pascual-Leone et al., 1994; Strafella et al., 2001), thereby suggesting its use in psychiatric disorders associated with abnormal dopaminergic activity and altered cortical excitability (Zyss et al., 2015). rTMS of the dorsolateral prefrontal cortex (DLPFCx) increases DA release in the striatal pathway, in the cingulate and orbitofrontal cortices (Cho and Strafella, 2009; Strafella et al., 2001). The right-side stimulation may reduce spontaneous alcohol craving, while left-sided treatment has no effect (Höppner et al., 2011; Mishra et al., 2010). Although a reduction in alcohol intake has been reported after rTMS in AUD (Ceccanti et al., 2015), there are no studies investigating striatal DAT availability and alcohol intake in AUD patients submitted to rTMS.

The aim of this study was to explore the possible effect of deep rTMS of the DLPFCx on DAT availability and alcohol intake in AUD treatment-seeking patients.

2. Experimental procedures

This longitudinal pilot study included fourteen AUD patients, diagnosed with the DSM-5 criteria: 12 males, aged between 39 and 64 years (mean age: 48 ± 9), 9 tobacco smokers. Patients were enrolled by the AUD Unit of the Internal Medicine, Gastroenterology and Hepatology Department of the Catholic University in Rome, Italy, according to the following inclusion criteria: 1) at least two days a week of excessive alcohol consumption during the month prior to screening; 2) ability to provide informed consent; 3) a Clinical Institute of Withdrawal Assessment in Alcohol Withdrawal score ≤ 10; 4) willingness to abstain from or substantially reduce alcohol consumption; 5) permanent residence. Exclusion criteria included: 1) clinically significant psychiatric diseases; 2) past or