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Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study

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Abstract
Recent animal studies demonstrate that compulsive cocaine seeking strongly reduces prelimbic frontal cortex activity, while optogenetic stimulation of this brain area significantly inhibits compulsive cocaine seeking, providing a strong rationale for applying brain stimulation to reduce cocaine consumption. Thus, we employed repetitive transcranial magnetic stimulation (rTMS), to test if dorsolateral prefrontal cortex (DLPFC) stimulation might prevent cocaine use in humans. Thirty-two cocaine-addicted patients were randomly assigned to either the experimental group (rTMS) on the left DLPFC, or to a control group (pharmacological agents) during a 29-day study (Stage 1). This was followed by a 63-day follow-up (Stage 2), during which all participants were offered rTMS treatment. Amongst the patients who completed Stage 1, 16 were in the rTMS group (100%) and 13 in the control group (81%). No significant adverse events were noted. During Stage 1, there were a significantly higher number of cocaine-free urine drug tests in the rTMS group compared to control ($p=0.004$). Craving for cocaine was also significantly lower in the rTMS group compared to the controls ($p=0.038$). Out of 13 patients who completed Stage 1 in the control group, 10 patients received rTMS treatment during Stage 2 and showed significant improvement with favorable outcomes becoming comparable to those of the rTMS group. The present preliminary findings support the safety of rTMS in cocaine-addicted patients, and suggest its potential therapeutic role for rTMS-driven PFC stimulation in

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reducing cocaine use, providing a strong rationale for developing larger placebo-controlled studies.

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1. Introduction

Cocaine use disorder (CUD) represents a significant health problem and is very common worldwide, with about 14–21 million users in 2014 (European Monitoring Centre for Drugs and Drug Addiction, 2014). In spite of the significant morbidity associated with cocaine use, no unequivocally effective pharmacological or psychological therapies have been identified to date. Chronic cocaine use causes damage and changes in the prefrontal cortex (PFC) (Volkow et al., 2004a), including significant brain volume reduction (Moreno-López et al., 2012; Matochik et al., 2003), cortical hypoactivity (Goldstein and Volkow, 2002, 2011; Kaufman et al., 2003), impairment in executive functions, and dysregulation of neurotransmitters systems (Volkow et al., 2003; Licata and Renshaw, 2010; Ke et al., 2004).

Physiologically, the PFC is thought to play a critical role in the addictive cycle, including reinforcement learning, craving, and inhibitory control (Koob and Volkow, 2010). Importantly, preclinical studies have also shown that loss of inhibitory control, resulting from damage to the PFC, seems to be crucial in compulsive drug-seeking behaviors (Jasinska et al., 2014; Chen et al., 2013). In particular, recent research employed a rat model in which compulsive cocaine seeking persisted in a subgroup of rats despite delivery of mild foot shocks, and demonstrated that prolonged cocaine self-administration significantly decreased *in vivo* and *ex vivo* intrinsic excitability of deep layer pyramidal neurons in the prelimbic cortex (PLC), which was significantly more pronounced in compulsive drug-seeking animals. Furthermore, *in vivo* optogenetic prelimbic cortex stimulation significantly prevented compulsive cocaine seeking (Chen et al., 2013). These findings created a rationale, and additional data to test the hypothesis that stimulation of functionally equivalent brain regions in humans could reduce cocaine seeking and consumption.

Several studies indicate that the rodent PLC is the closest functional homolog of the dorsolateral PFC (DLPFC) in humans (Papaleo et al., 2012; Balleine and Dickinson, 1998), while others suggest a functional correspondence with the anterior cingulate cortex (ACC) (Gass and Chandler, 2013). Consensus on this matter is still lacking, due to the extraordinarily large anatomical diversity between the rodent and the human frontal/anterior cortices, but both DLPFC and ACC play a major role in top-down inhibitory control and reward mechanisms. They are also linked structurally and functionally (Holroyd and Coles, 2002), as it has been shown that neurostimulation of DLPFC has direct effects over ACC (Conti and Nakamura-Palacios, 2014).

Therefore, a direct clinical translation of the previous preclinical literature (Chen et al., 2013) could be attempted by testing the hypothesis that electrical stimulation of the DLPFC significantly decreases compulsive cocaine seeking behaviors. Operationally, this hypothesis can be tested by using transcranial magnetic stimulation (TMS), a non-invasive, and safe, human brain stimulation technology based on electromagnetic induction (Lefaucheur et al., 2014; Barker et al., 1985). The TMS-induced intracranial electric field can be of sufficient magnitude to depolarize neurons (Terao and Ugawa, 2002; Di Lazzaro et al., 2008). The extent of the induced field depends on the TMS coil geometry and size; figure-of-eight coils allow relatively focal targeting of the brain surface (Cohen et al., 1990). While the effects of an individual TMS pulse lasts only a fraction of a second, when TMS pulses are applied repetitively, they can modulate long-term cortical excitability. Specifically, repetitive TMS (rTMS) at a low frequency (about 1 Hz) is typically considered to have inhibitory effects, (Chen et al., 1997) while high-frequency rTMS ($\geq$ 5 Hz) is excitatory (Pascual-Leone et al., 1994). Therefore, this pilot study was conducted to test whether excitatory rTMS of the left DLPFC in cocaine-dependent patients is safe and reduces cocaine use.

2. Experimental procedures

2.1. Study design

This was a between-subject open-label randomized clinical trial with rTMS *vs.* standard treatment (experimental *vs.* control group, respectively) conducted at the Department of Neuroscience Outpatient Clinic of the teaching hospital affiliated with the medical school of the University of Padua, Italy. The appropriate local Ethics Committee reviewed and approved the study. Patients were individuals seeking outpatient treatment for CUD. For inclusion/exclusion criteria, see Table 1.

2.2. Treatment conditions

2.2.1. Experimental group:

The experimental group was treated with rTMS. The stimulator device was a MagPro R30 with the Cool-B70 figure-of-eight coil (MagVenture, Falun, Denmark). Resting Motor Threshold (rMT) measurements were performed via visual twitch in the contralateral (right) hand. The coil was positioned over the supposed motor cortex area, then the coil was moved until the location at which a reproducible APB (*abductor pollicis brevis*) response, elicited at the lowest stimulator intensity could be identified. We determined the lowest device output to produce the thumb movement 50% of the trials (Ziemann and Hallett, 2000), using single-pulse TMS with at least 6 seconds between pulses, and that was set as rMT. To best identify the target of the rTMS stimulation, the left