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Neurostimulation techniques in the treatment of cocaine dependence: A review of the literature

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HIGHLIGHTS

- Cocaine dependence is very difficult to treat. Therapeutic alternatives are needed such as neurostimulation techniques.
- Chronic cocaine consumption is associated with a dysfunction in areas that monitor executive control and limbic arousal.
- The acute treatment of cocaine dependence should focus on blocking of postsynaptic Nucleus Accumbens dopamine receptors.
- Neurostimulation techniques modulate excitability and have been investigated in the treatment of cocaine dependence.
- rTMS, dTMS and tDCS safe, potentially effective to treat cocaine craving. Future research to identify optimal parameters.

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ABSTRACT

Objective: Cocaine use disorder is a very common condition that represents a substantial public health problem, and no effective pharmacological or psychological therapies have been identified to date. Urgent therapeutic alternatives are therefore needed such as neurostimulation techniques. The purpose of this review is to describe and discuss studies that have evaluated the safety and efficacy of these techniques for the treatment of cocaine dependence.

Methods: The electronic literature on repetitive transcranial magnetic stimulation, theta-burst stimulation, deep transcranial magnetic stimulation, transcranial direct current stimulation, magnetic seizure therapy, electro-convulsive therapy, cranial electro-stimulation, and deep brain stimulation in the treatment of cocaine addiction were reviewed.

Results: Most of these studies which are few in numbers and with limited sample sizes found that some of these neurostimulation techniques, particularly transcranial magnetic stimulation, and transcranial direct current stimulation are safe and potentially effective in the reduction of craving to cocaine. Although deep brain stimulation showed some good results in one patient, no conclusion can be drawn so far concerning the efficacy and safety of this approach.

Conclusion: Given the somewhat promising results of some of the studies, future controlled studies with larger samples, and optimal stimulus parameters should be designed to confirm the short- and long-term safety and efficacy of neurostimulation techniques to treat cocaine addiction.

1. Introduction

Cocaine use disorder (CUD) is very common worldwide with about 14–21 million users in 2014 and represents a substantial public health problem (European Monitoring Centre for Drugs and Drug Addiction, 2014). In spite of the significant morbidity and mortality associated with cocaine use, no effective pharmacological or psychological therapies have been identified to date.

Chronic cocaine consumption is associated with a disruption in frontal-striatal connectivity in the resting state with an elevated activity in the medial prefrontal cortex (MPFC) and ventral striatum or depressed activity in the dorsolateral prefrontal cortex (DLPFC) and dorsal striatum, areas that monitor executive control and limbic arousal (impulsivity, decision-making, risk perception, cognitive evaluation of consequences and errors, goal identification) (Fishbein, Eldreth, Hyde, et al., 2005; Garavan & Stout, 2005; Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006) and a decrease in mesolimbic dopamine transmission that maintain drug intake (Kalivas & Brady, 2012; Koob & Le Moal, 2005; Melis, Spiga, & Diana, 2005).

Cocaine addiction also involves dysfunction of the brain rewarding

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circuitry which includes the nucleus accumbens, the bed nucleus of the stria terminalis, the anterior limb of the internal capsule and the medial forebrain bundle (Heimer, 2003). It also causes damage in the prefrontal cortex (PFC) which is thought to play a critical role in the addiction, including reinforcement learning, craving and loss of inhibitory control which seem to be crucial in compulsive drug-seeking behaviors (Chen, Yau, Hatch, et al., 2013; Jasinska, Chen, Bonci, & Stein, 2014).

Chronic cocaine use also leads to significant brain volume reduction (Goldstein & Volkow, 2002, 2011; Kaufman, Ross, Stein, & Garavan, 2003; Matochik, London, Eldreth, Cadet, & Bolla, 2003; Moreno-López, Catena, Fernández-Serrano, et al., 2012), impairment in executive functions and dysregulation of neurotransmitters systems (Ke, Streeter, Nassar, et al., 2004; Licata & Renshaw, 2010; Volkow, Fowler, & Wang, 2003) such as with dopamine (DA) which plays a key role in the neurobiological mechanisms underlying CUD (Martinez, Narendran, Foltin, et al., 2007; Volkow, Wang, Fowler, et al., 2007).

Human imaging studies have shown a reduction in DA D2 receptors in the ventral striatum of detoxified cocaine-dependent subjects (Volkow et al., 2007) and a blunted DA release linked to a reduction of amphetamine-induced DA release in the limbic striatum (Martinez et al., 2007) leading to a hypo-functioning DA system. Thus, functional "boosting" of the DA signaling (Diana, 2011) may have beneficial effects in reducing drug intake. Additionally, it has been suggested that acute treatment of CUD should focus on preferential blocking of post-synaptic Nucleus Accumbens (NAc) dopamine receptors (D1-D5), whereas long term activation of the mesolimbic dopaminergic system should focus on the activation and/or release of DA at the NAc site with dopamine agonists or aripiprazole (Blum, Chen, Chen, et al., 2008; Meini, Moncini, Cecconi, et al., 2011).

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulation technique that is able to modulate cortical excitability (Hallett, 2007; Wagner, Valero-Cabre, & Pascual-Leone, 2007; Wassermann & Lisanby, 2001). It uses focused electromagnetic pulses of high intensity administered through a coil. The fast passage of a strong electric current in the coil induces a transient, high intensity magnetic pulse that penetrates unimpeded through the scalp and reaches the underlying cortex. In the targeted cortex, the magnetic pulse generates an electric current which can induce depolarization of superficial cortical neurons and interconnected areas beneath the coil.

In repetitive TMS (rTMS), trains of several pulses are delivered through repeated stimulation over the same area with frequencies ranging from 1 to 20 Hz. The effects of rTMS lead to long-term changes in cortical functioning which vary depending on the frequency of stimulation. Generally, high frequency (HF) rTMS (> 5 Hz) transiently increases cortical excitability whereas low-frequency (LF) rTMS (≤ 1 Hz) decreases it (Daskalakis et al., 2006; Fitzgerald, Fountain, & Daskalakis, 2006).

A modified version of rTMS is deep rTMS (dTMS) that uses an H-coil enabling direct stimulation of extensive neuronal pathways in deeper cortical and sub-cortical regions, without significantly increasing the electric field induced in cortical layers (Levkovitz et al., 2007; Roth, Zangen, & Hallett, 2002; Roth, Amir, Levkovitz, & Zangen, 2007).

Theta-burst stimulation (TBS) is a patterned rTMS paradigm with brief stimulation sessions generating lasting modulatory after-effects on cortical motor neurophysiology (Di Lazzaro, Dileone, Pilato, et al., 2011). Continuous theta-burst stimulation (cTBS) consisting of 50 Hz bursts of three sub-threshold stimuli repeated at 5 Hz has inhibitory effects on corticospinal excitability, while intermittent theta-burst stimulation (iTBS) consisting of 50 Hz bursts of three sub-threshold stimuli repeated at 5 Hz for 2 s with an inter-train interval of 8 s (600 pulses) has excitatory effects (Di Lazzaro et al., 2011).

The safety of rTMS, dTMS, and TBS has been reported in a number of studies and the most recent guidelines for their use have been published in 2009 (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Based on existing data, rTMS is safe when administered according to recommended guidelines and its safety record supports its further development as a treatment (Rossi et al., 2009; Loo, McFarquhar, & Mitchell, 2008). The only absolute contraindications to rTMS, TBS, and dTMS are the presence of metallic implants or elements in the brain (Lefaucheur, André-Obadia, Antal, et al., 2014). These techniques are associated with headaches, local pain at the stimulation site, neck pain, dizziness, syncopal vagal episodes, rarely mania, and very rarely seizures during the session (Loo et al., 2008; Rossi et al., 2009).

Transcranial direct current stimulation (tDCS) is a technique that modulates cortical excitability by passing a weak electrical current (1–2 mA) between two electrodes placed on the scalp, which, depending on the polarity, intensity, and duration of the current flow is capable of depolarizing or hyperpolarizing neuronal resting membrane potentials (Nitsche & Paulus, 2000; Nitsche, Cohen, Wassermann, et al., 2008; Nitsche et al., 2003; Priori, 2003). The anodal electrode generally increases cortical excitability and the cathodal electrode decreases cortical excitability (Nitsche & Paulus, 2000). The mechanisms of tDCS-induced depolarization/hyperpolarization remains poorly understood, but pharmacological studies have shown that the effect of tDCS may be linked to shifts in the membrane potential (Bindman, Lippold, & Redfearn, 1964). The effects of tDCS on cortical excitability are probably mediated by GABA-ergic and glutamatergic mechanisms (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Monte-Silva, Kuo, Hessenthaler, et al., 2013; Stagg & Nitsche, 2011), possibly leading to long-term depression and long-term potentiation-like mechanisms (Liebetanz et al., 2002). The technique is relatively safe with side effects limited to local tingling and skin irritation.

Finally, deep brain stimulation (DBS) is a promising neurosurgical technique that involves MRI-based stereotactic placement of electrodes in deep brain regions under the dura connected to an implanted programmable pulse generator placed allowing current to be delivered to specific targets. The neurostimulator provides continuous stimulation of a certain frequency that is focused on a specific brain region to regulate abnormal impulses (Schlaepfer & Lieb, 2005; Schlaepfer & Bewernick, 2009). DBS has been proven to be an effective treatment for certain neuropsychiatric diseases (Parkinson's disease, essential tremor, depression, and obsessive–compulsive disorder [OCD]). It is a relatively well-tolerated therapy, the most common adverse events being infection, hemorrhage, seizure, and lead fracture.

This paper reviewed the literature on the safety and efficacy of the neurostimulation techniques described further as a treatment for cocaine dependence and discussed future directions for research in this growing area of attention.

2. Materials and methods

Using the search terms "cocaine," "cocaine dependence," "cocaine addiction," "transcranial magnetic stimulation," "theta-burst stimulation," "deep transcranial magnetic stimulation," "transcranial direct current stimulation," "magnetic seizure therapy," "electroconvulsive therapy," "cranial electro-stimulation," and "deep brain stimulation," controlled and open-label studies as well as case series on humans published from 1966 to April 2017 were retrieved through NCBI Pubmed search. Overall, 10 clinical studies (de Almeida Ramos, Taiar, Trevizol, Shiozawa, & Cordeiro, 2016; Batista, Klauss, Fregni, Nitsche, & Nakamura-Palacios, 2015; ; Camprodon, Martínez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007; Gonçalves-Ferreira et al., 2016; Gorini, Lucchiari, Russell-Edu, & Pravettoni, 2014; Hanlon, Dowdle, Austelle, et al., 2015; Politi, Fauci, Santoro, & Smeraldi, 2008; Rapinesi, Del Casale, Di Pietro, et al., 2016) were included and involved the clinical effects of these techniques on cocaine dependence (see Table 1). Three studies involved rTMS, one involved TBS, two dTMS, three tDCS and one DBS. There were no studies involving ECT, MST or CES and cocaine addiction.