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# Transcranial Magnetic Stimulation (Rtms) In the Treatment of Cocaine use Disorder

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**Abbreviations:** TMS: Transcranial Magnetic Stimulation; SUD: Substance Use Disorder; CUD: Cocaine Use Disorder; DLPFC: Dorsolateral Prefrontal Cortex

## What is the regulatory status for TMS in treatment of CUD?

Currently, Transcranial Magnetic Stimulation (TMS) is not approved for the treatment of any Substance Use Disorder (SUD), including but not limited to Cocaine Use Disorder (CUD). TMS is currently cleared by US FDA and approved in Europe (CE) for Major Depressive Disorder.

### What is cocaine use disorder (CUD)?

Cocaine is an illicit substance found in the South American coca plant that when consumed can result in psychological and physiological effects analogous to amphetamine and amphetamine-like stimulants. Consumption of cocaine was originally categorized into abuse versus dependence in DSM-IV, however, it is now Considered one Unified Diagnosis of CUD in DSM-V with the range of mild to severe subtypes [1]. Commonly referred to as an addiction, CUD can be described as a persistent state in which there is a reduced cognitive capacity to control compulsive drug-seeking behavior despite the risk of negative consequences [1,2]. As is the case for all predominant substance use disorders, CUD is a chronically relapsing disorder with significant biopsychosocial impacts. Though still medically utilized for its anesthetic properties, cocaine as an illicit drug is predominantly used for its ability to induce a fast-onset euphoric effect or high, making it a powerful, addictive CNS stimulant. Cocaine use can be occasional, repeated or compulsive. Compulsive use typically involves binge use, in which the drug is consumed repeatedly in increasing amounts to attempt to achieve and maintain the high. In Europe, cocaine is the most commonly used illicit stimulate drug [3].

Cocaine can be administered in a variety of forms. Traditionally, the coca leaves have been chewed to achieve the desired effect. Cocaine base, also known as crack cocaine, is the base form of the salt and it is consumed by inhalation once the substance is vaporized into smoke. Cocaine hydrochloride is the commonly portrayed powder form that is snorted through nostrils or dissolved in water for intravenous injection [4]. Depending on the route of administration, the high can be as short as 5-10 minutes after smoking or intravenous injection, or it can last for longer periods of 15-30 min when snorted. It is important to distinguish that the predominant route of administration differs between continentals as well as geographically within Europe. Crack is the most common form of cocaine use in North America, whereas cocaine hydrochloride is more commonly used in Europe. In Europe alone, the European Monitoring Centre for Drugs and Drug Addiction estimates that 2.2 million young adults (15-34 years) used cocaine in 2017. Moreover, 55,000 subjects who entered specialized drug treatment in 2012 reported cocaine as their primary stimulant [5]. In the USA, 40% of the drug misuse or abuse-related emergency department visits were ascribed to cocaine, and in 2014 about 913,000 Americans met the criteria for dependence or abuse of cocaine [6].

## How does Cocaine work?

Cocaine's primary mechanism of action is the blockade of a presynaptic transporter, thereby inhibiting the clearance of neurotransmitters (dopamine, serotonin, and norepinephrine) from the neuronal synaptic cleft and ultimately, increasing

their concentrations. Cocaine does not directly stimulate the release of these neurotransmitters [7]. The euphoria associated with cocaine use is attributed to the enhanced and prolonged activity of dopamine in the brain's mesolimbic system, also referred to as the reward pathway. This dopaminergic pathway projects from the midbrain ventral tegmental area to the nucleus accumbens, one the brain's key reward areas, and to the prefrontal cortex [8]. The increased release of dopamine in the prefrontal cortex and amygdala stimulates the glutamatergic projections between prefrontal cortex and amygdala as well as the glutamatergic outputs to the nucleus accumbens and the ventrategmental area. The increased glutamatergic activity in the nucleus accumbens is believed to critically influence gamma-amino-butyric-acid (GABA)-ergic neurotransmission [9]. These brain areas and their associated glutamatergic and GABAergic neurotransmissions have been shown to be heavily involved in the long-term attenuation of cortical excitability and ultimately, the sensitization to substances such as cocaine [10]. Hence, it has been proposed that glutamatergic excitatory activity increases at the expense of the Gamma-Amino-Butyric-Acid (GABA) inhibitory neurotransmission in the nucleus accumbens. Cocaine consumption in smaller amounts is associated with the feeling of euphoria, increased energy, alertness, hypersensitivity, and talkativeness. In larger amounts, cocaine can result in irritability, anxiety, panic, paranoia, bizarre, violent behavior, and reduced need for sleep and food intake [6].

Due to the increased the concentration of other neurotransmitters such as noradrenaline in the synaptic cleft, cocaine can produce physiological effects like the constriction of blood vessels, increased heart rate, increased blood pressure, increased body temperature, and dilated pupils. Some users also experience tremors, vertigo and muscle twitches. The medical complications of cocaine overdose can become severe, and potentially deadly. Any route of administration has the potential to cause toxic levels of cocaine that can result in fatal outcomes such as heart attacks, seizures, strokes or coma [5,6]. In rare cases, sudden death on first time use or shortly thereafter have been reported [7].

## What are the long-term effects of cocaine use?

When the brain is repeatedly exposed to cocaine, the reward system becomes de-sensitized to natural reinforcers while the brain's stress response becomes hyper-sensitized. By continually blocking the re-uptake and recycling of catecholamine neurotransmitters, cocaine can eventually deplete the brain's stores, particularly of dopamine. Thus, when the drug is not taken, a subject can experience intense craving, displeasure, withdrawal symptoms, anhedonia, lethargy, and difficulties with muscle movement [6]. Depletion of the dopamine stores can also produce parkinsonism or other movement disorders, especially following long-term use. Because of the drug's powerful effect on the monoamine system, cocaine use has also been associated with depression [5]. In fact, depression is a common comorbidity in subjects diagnosed with CUD [11,12]. In general, a range of cognitive functions become impaired such as impulse control, memory, decision-making, and attention/concentration. It is important to note that some long-term effects can also differ depending on the route of administration. Snorting carries the risk of problems with swallowing, nosebleeds and loss of smell while intravenous injection carries a higher risk for development of HIV, Hepatitis and other blood-borne diseases [13].

## What are the common treatments of CUD?

Currently, the primary treatment option for CUD encompasses psychosocial interventions. Studies indicate that contingency management has been especially effective [5]. Other behavioral treatments include cognitive-behavioral therapy that focus on motivational incentives that reward patients who remain abstinent, or that establish therapeutic communities for patients in recovery [13]. At present, there is no effective pharmacological treatment option for patients who are dependent on cocaine or other CNS stimulants, although several drugs have been trialed. These drugs include Disulfiram, anticonvulsants, antidepressants, psychostimulants, and opioid receptor antagonists [5,13]. Fortunately, the past decade of research has elucidated TMS as an emerging potential treatment modality for the purpose of reducing craving and reducing intake of cocaine.

## What are the rationale and the targets for TMS in treatment of CUD?

TMS is a non-invasive neuromodulation technique that directly affects cortical excitability to stimulate the release of dopamine within the mesolimbic system, thereby enabling the modulation of neuronal activity within networks involved in behavior and cognition. The use of consecutive stimulation, referred to as repetitive TMS (rTMS), can range from low frequency (i.e. 1 Hz or less), which inhibits cortical excitability, to high frequency (i.e. 5-20 Hz), which increases cortical excitability. Accordingly, the rationale for using rTMS for the treatment of SUD like CUD hinges on the idea that repeated applications of TMS can override the neuroadaptation induced by chronic substance use [2,14]. In 2001, Boutros et al. were the first to demonstrate that cocaine-dependent subjects had significantly elevated resting Motor Threshold (MT) compared to healthy controls, demonstrating the existence of altered cortical excitability among chronic cocaine users. The MT levels were elevated in both the right and left hand motor area, suggesting that cocaine-dependent subjects had either increased inhibition or decreased excitability of particular cortical neuronal networks [15]. A follow-up study in 2005 demonstrated that cortical silencing periods were longer in cocaine-dependent subjects who suffered from cocaine-induced paranoia [16]. This evidence further strengthened the theory that cocaine use results in decreased excitability among cortical networks. A more recent study discovered the same decreased cortical activity while


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also demonstrating that cortical inhibition was largely intact in subjects with CUD [17]. The proposed use of TMS for treatment of CUD was further fueled by an animal study that found rescuing cocaine-induced prefrontal cortex hypoactivity in rats could prevent compulsive drug-seeking behavior. Consequently, this study established a link to the human studies that suggests deficits in the prefrontal cortical area and loss of inhibitory control is critically involved in compulsive drug use. The results by Chen et al. [18] therefore, pointed to the prefrontal cortex as a stimulation target for rTMS in humans as a potential treatment option for CUD.

## What are the results of investigational clinical research on the use of TMS for CUD?

To date, only a handful of pilot studies have been published on the use of TMS for the treatment of CUD [19]. In 2007, Camprodon et al. [20] published the first study to demonstrate the potential of high frequency rTMS to treat CUD. This was a randomized, crossover study conducted on a total of 6 subjects with CUD who had completed medically-assisted withdrawal and remained hospitalized throughout the study. The primary end point (a reduction in cravings) as well as secondary end points (changes to anxiety, happiness, sadness, discomfort) were measured using the Visual Analogue Scale (VAS) that ranged from not at all to more than ever. Subjects were administered rTMS at 10 Hz, 90% MT in two sessions (right and left DLPFC) with 20 trains, 10 sec in length with 1 sec inter-train interval, for a total of 2000 pulses. The study demonstrated that only one session of 10 Hz rTMS at 90% RMT above the right Dorsolateral Prefrontal Cortex (DLPFC) transiently decreased cravings immediately after treatment compared to baseline values. Important to note, the effect dissipated after 4 hours following treatment and furthermore, these results were not observed with administration of rTMS above the left DLPFC. Subjects also reported significant decreases in anxiety and increased happiness following rTMS to right DLPFC. In 2008, Politi et al. [21] published an open study investigating the effect of high-frequency rTMS on craving in 36 detoxified cocaine-dependent subjects. In this study, subjects were treated with 10 daily sessions of 15 Hz rTMS applied to the left DLPFC at 100% subjective MT (20 trains, 2 sec on with 30 second inter-train intervals, for a total of 600 pulses). As in the previous study, outcomes were assessed through the VAS to evaluate psychopathological symptoms associated with craving. Researchers found a gradual decrease in cravings over successive sessions with the greatest reduction in cravings after the 7th session. This study's results further supported the DLPFC as a central figure in craving involved in CUD.

In 2016, Terraneo et al. [22] published a between-subject, open-label, randomized study that focused on an objective primary outcome, cocaine consumption, as well as secondary outcomes of craving and depressive symptoms. In this study, 32 subjects diagnosed with CUD were randomly assigned to either a control or active rTMS group with a figure 8 coil and outcomes temporally divided into 2 distinct stages: 1) 29-day study and 2.) 63-day follow-up. The control group received pharmacological treatment (pramipexole .35 mg three times daily, bupropion 150 mg daily, oxazepam 15 mg three times daily, triazolam. 25 mg daily, gamma hydroxybutyrate 1.75 g daily) while the active group was administered rTMS 1 session/day during the first 5 days then, once/week for the following 3 weeks for a total of 8 sessions. Each session consisted of 15 Hz rTMS at 100% MT (60 pulses per train, inter-train interval of 15 sec, 40 trains, and 2400 pulses for a total duration of 13 mins) selectively targeting the left DLFPC. The study found significantly reduced cocaine intake (assessed via urine drug tests) in the active group compared with the control group. There was also a reduced cocaine craving (measured via VAS twice/week) in the active group. Interestingly, the study allowed patients in the control group to switch to receive active rTMS treatments during stage 2, and the 10 control patients who switched to the active group subsequently demonstrated significant improvement compared to the initial active group. Overall, the study demonstrated statistically significant differences in positive outcomes in the active group compared to the control group. Importantly, there were also no significant adverse events observed with only mild discomfort reported by the active group during initial stimulation. Rapinesi et al. [23] investigated the effect of high frequency rTMS with an H1 coil on craving for patients with CUD. In this study, a total of 7 subjects diagnosed with CUD received 12 sessions over 4 weeks using 15 Hz rTMS delivered in 20 trains with 2 sec inter-train interval for a total of 8640 pulses above bilateral DLFPC (with preference for the left hemisphere).

Neurostimulation was delivered concomitantly with the administration of the subject's prior medications. The primary outcome evaluated was cocaine craving assessed via VAS the week before, each week during, and 1 month after rTMS treatment. Researchers found subjects reported significantly reduced craving gradually during treatment at 2 and 4 weeks compared to baseline as well as post-treatment at 1 month compared to baseline. Bolloni et al. [24] published a randomized, double-blind study on efficacy of bilateral deep rTMS in reducing cocaine intake. In the study, 18 treatment-seeking subjects diagnosed with CUD were randomized to 12 total sessions (3 sessions/week for 4 weeks) of either active or sham treatments. The active treatments consisted of 10 Hz dTMS using the H1 coil above bilateral DLPFC at 100% MT (20 trains, 50 pulses, 5 sec on with 15 sec inter-train intervals, 1000 total pulses per session). The outcomes were measured before treatment and after treatment at 1, 3 and 6 months. While researchers found a decreased trend of cocaine consumption (measured with hair analysis) from baseline to 3 and 6 months later in the active group and not in the sham group, there was no significant difference in cocaine intake observed between active and sham groups along time.

In March of published a pilot study investigating the effect of rTMS on cocaine self-administration among 18 volunteer


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subjects randomly and equally divided into one of three groups high frequency (10 Hz), low frequency (1 Hz), and sham treatment. The investigators delivered rTMS with an H7 coil targeting the medial prefrontal cortex (mPFC) and dorsal anterior cingulate (dACC). The high frequency treatment consisted of a train of 3 sec (40 trains/session), an inter-train interval of 20 sec, and total of 1200 pulses per train, compared to the low frequency treatment which had 900 pulses per train. The primary outcome of cocaine self-administration (e.g. cocaine-seeking behavior) was performed at three time points (baseline, after 4 days of treatment, and after 13 days of treatment) in which subjects were asked to chose between smoking a low-dose (12 mg) of cocaine or receive money ($5). The study demonstrated a significant group by time effect in which the choices for cocaine decreased between sessions 2 and 3 in the high frequency group compared to low frequency and sham groups, and there was no effect on cocaine self-adminsitration between these two groups. Later on demonstrated rTMS focused on the left DLFPC improved symptoms of anhedonia in patients with long-standing history of CUD. This study included a total of 15 subjects who were given 10 sessions (twice/day, 5 days/week, 15 Hz frequency, pulse intensity 100% rMT, 60 pulses per train, inter-train pause of 15 sec, 40 trains, 2400 pulses/session). Following treatment, hedonic experience improved and additionally, craving significantly reduced compared to baseline. Taken together, these studies indicate that stimulation of the left prefrontal cortex with high frequency TMS can be a potential and encouraging treatment opportunity for CUD as the preliminary evidence suggests that rTMS is able to reduce the intake and reduce the craving of cocaine [22].

More recent studies have elucidated additional brain areas (e.g. OFC, VMPFC) and other TMS protocols such as continuous theta-burst stimulation (cTBS) can be relevant targets for future investigation in the treatment of CUD [12,25]. cTBS differs from rTMS in that it delivers bursts of 50 Hz of several sub-threshold stimuli repeated at 5 Hz. In 2017, Hanlon et al. [25] demonstrated that cTBS of left frontal pole decreased orbitofrontal and insula activity in both cocaine users and alcohols users. The study included a total of 49 substance-dependent subjects, of which were diagnosed with CUD. Among the CUD subjects, cTBS significantly decreased Blood-Oxygen-Level Dependent (BOLD) responses in caudate, the accumbens, anterior cingulate, orbitofrontal (OFC) and parietal cortex compared to sham treatments. These results indicate that TMS may be used to decrease activity in brain areas responsible for salience and drug cues. Furthermore, the OFC itself may serve as a potential target for treating CUD. However, it is important to note that the protocol used in the study is not likely to have a sustainable effect on drug seeking behaviors since the protocol used consisted of single pulses delivered in 6 trains on a single day. More recently, Kearney-Ramos et al. published a study in 2018 that found administration of cTBS above the ventromedial prefrontal cortex (VMPFC ) attenuated neural activity to cocaine cues in the frontrostriatal circuits [26]. Thus, targeting the VMPFC may also have potential clinical effect in treatment of CUD.

## What is the future of TMS in CUD?

In conclusion, only a limited number of pilot studies have been published to date. The DLFPC appears to be the preferential target choice and it holds solid neurobiological rationale to transform treatment of CUD in the future. Although the results are highly encouraging, larger proof-of-concept trials are required to fully elucidate the effect and safety of TMS treatment in CUD. The full potential of TMS in treatment of SUD has yet to be uncovered, as different brain areas are emerging as potential therapeutic targets as well as new TMS protocols gaining more traction in clinical research.

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