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Developing Repetitive Transcranial Magnetic Stimulation (rTMS) as a Treatment Tool for Cocaine Use Disorder: a Series of Six Translational Studies

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Abstract

Purpose of the Review—Cocaine dependence is a chronic and relapsing disorder which is particularly resistant to behavioral or pharmacologic treatment, and likely involves multiple dysfunctional frontal-striatal circuits. Through advances in preclinical research in the last decade, we now have an unprecedented understanding of the neural control of drug-taking behavior. In both rodent models and human clinical neuroimaging studies, it is apparent that medial frontal-striatal limbic circuits regulate drug cue-triggered behavior. While non-human preclinical studies can use invasive stimulation techniques to inhibit drug cue-evoked behavior, in human clinical neuroscience, we are pursuing non-invasive theta burst stimulation (TBS) as a novel therapeutic tool to inhibit drug cue-associated behavior.

Recent Findings—Our laboratory and others have spent the last 7 years systematically and empirically developing a non-invasive, neural circuit-based intervention for cocaine use disorder. Utilizing a multimodal approach of functional brain imaging and brain stimulation, we have attempted to design and optimize a repetitive transcranial magnetic stimulation treatment protocol for cocaine use disorder. This manuscript will briefly review the data largely from our own lab that motivated our selection of candidate neural circuits, and then summarize the results of six studies, culminating in the first double-blinded, sham-controlled clinical trial of TMS as a treatment adjuvant for treatment-engaged cocaine users (10 sessions, medial prefrontal cortex, 110% resting motor threshold, continuous theta burst stimulation, 3600 pulses/session).

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Summary—The intent of this review is to highlight one example of a systematic path for TMS treatment development in patients. This path is not necessarily optimal, exclusive, or appropriate for every neurologic or psychiatric disease. Rather, it is one example of a reasoned, empirically derived pathway which we hope will serve as scaffolding for future investigators seeking to develop TMS treatment protocols.

Keywords

Transcranial magnetic stimulation; Cocaine; Addiction; Prefrontal cortex; Functional MRI

Introduction

Cocaine dependence is a chronic and relapsing disorder with a negative impact on users, their families, the justice system, and the health care system. Nearly 40 million Americans age 12 and older have tried cocaine or crack and nearly 4 million are regular users [1]. Relative to other drugs of abuse, cocaine use appears to be particularly resistant to behavioral and pharmacologic treatment. Relapse rates following a typical outpatient treatment program are often as high as 75% only 60 days after leaving the program [2]. Given the tremendous societal cost of cocaine use, there is a strong need to develop innovative efficacious treatment options which extend beyond conventional pharmacologic and behavioral modifications.

One promising area of treatment development is transcranial magnetic stimulation (TMS). TMS is a non-invasive brain stimulation technique which, through electromagnetic induction, can induce long-term potentiation (LTP)-like [3] or long-term depression (LTD)-like [4] changes in cortical activity in a frequency-dependent manner (reviews: [5–8]). Repetitive TMS (rTMS) also changes activity in monosynaptic striatal afferents [9, 10]. Specifically, when delivered to the left dorsolateral prefrontal cortex (DLPFC), 10 Hz rTMS selectively increases dopamine in the ipsilateral, left caudate (but not the putamen or ventral striatum) [10]. When delivered to the left primary motor cortex, 10 Hz rTMS selectively increases dopamine in the ipsilateral, left putamen (but not the caudate or ventral striatum). This spatial topography is consistent with established patterns of frontal-striatal structural connectivity [11, 12].

Repetitive TMS was FDA-approved (cleared is the term the FDA uses for devices) as a treatment for major depressive disorder in 2008, and single pulse TMS was FDA-cleared for migraine headache in 2014. There are now rTMS clinics in all 50 United States, throughout Europe, Asia, Australia, South America, and a few new clinics in Africa. This existing network of devices and experienced TMS technicians will enable fast, widespread dissemination and implementation of the next therapeutic indications for TMS, should they emerge. Currently, however, the field of addiction does not have enough data to make a well-informed decision regarding the TMS strategy that is likely best suited for changing substance use behaviors. This amplifies the importance of careful, empirically driven treatment development.

In the last 5 years, there has been tremendous growth in the application of rTMS to substance use disorders (SUDs). The largest clinical trial to date [13], in cigarette smokers (*n*

= 115 enrolled, 77 completed), revealed that 13 sessions of 10 Hz stimulation (990 pulses, 120% resting motor threshold (rMT), H-coil lateral prefrontal cortex) led to a significant decrease in self-reported cigarette consumption, urine cotinine (the major metabolite of nicotine), and improved 6-month abstinence rates compared to 13 sessions of 1 Hz TMS (600 pulses, 120% motor threshold, H-coil lateral prefrontal cortex), or sham. This sham-controlled trial was built upon a foundation of multiple smaller studies of TMS to cigarette smokers [14–19]. It was also the first study to demonstrate that the effects of TMS on substance use behavior were amplified when the participant was exposed to drug cues during the TMS delivery [13].

Within cocaine use disorder however, far less is known. The first study in this field [20] demonstrated that a single session of left dorsolateral prefrontal cortex rTMS (DLPFC, 2000 pulses, 90% rMT) led to a significant reduction in self-reported craving, relative to sham or right DLPFC 10 Hz TMS in six cocaine-dependent individuals. In 2008, Politi and colleagues demonstrated that in cocaine users ($n = 36$), 10 sessions of 15 Hz TMS to the left DLPFC (600 pulses, 100% rMT) led to a significant reduction in self-reported craving [21]. There was, however, no active sham control in this study. The next published study of rTMS to the DLPFC in cocaine users was conducted 8 years later in 2016 [22]. Thirty-two individuals with cocaine use disorder were recruited from an outpatient clinic and randomized to receive either rTMS alone ($n = 16$) or pharmacotherapy alone ($n = 16$). For the TMS (treatment group, individuals received eight sessions of real TMS treatment (15 Hz DLPFC TMS (2400 pulses), 100% rMT, daily for the first 5 days, weekly for the next 3 weeks). For the pharmacotherapy group, individuals received daily pramipexole, buprenorphine, oxazepam, trizolam, and gamma hydroxybutyrate. At the conclusion of the initial phase of the study (29 days), the group receiving rTMS alone had significantly more cocaine-free urines and lower self-reported craving than the pharmacotherapy group. Although the lack of a “sham TMS + real pharmacotherapy” control condition or “real TMS + placebo pharmacotherapy” control condition limits the interpretation of this study, the data are promising and an important addition to the field.

It is also not clear that the left DLPFC is the optimal target for treating cocaine users with rTMS. Many of the current investigations in cocaine and nicotine dependence are based on the parameters used for depression rather than on evidence from SUD literature. For example, drug cue-associated craving is one of the strongest predictors of relapse in cocaine dependence [2] and this process is related to elevated activity in the frontal-striatal circuits involved in arousal (medial prefrontal cortex, ventral striatum, insula) and habitual drug taking (dorsal striatum) (reviews: [23–25]). Additionally, preclinical research has revealed that stimulation and inhibition of the prelimbic cortex can respectively decrease or increase cocaine administration [26]. By harnessing the knowledge we have acquired from clinical neuroimaging and preclinical stimulation studies, it may be possible to develop rTMS as an evidence-based, therapeutic treatment for cocaine use disorder.

Our laboratory has spent the last 7 years systematically and empirically developing a non-invasive, neural circuit-based intervention for cocaine dependence. Utilizing a multimodal approach of functional brain imaging and brain stimulation, we have attempted to design and optimize an rTMS treatment protocol for cocaine dependence. This manuscript will briefly

review the data that motivated our selection of candidate neural circuits, and will then summarize the results of six studies, culminating in the first double-blinded, sham-controlled clinical trial of TMS as a treatment adjuvant for cocaine-dependent individuals in treatment (10 sessions, medial prefrontal cortex, 110% rMT, continuous theta burst stimulation, 3600 pulses/session; Clinical Trials.gov ID: NCT03238859).

The intent of this review is to highlight one example of a systematic path for TMS treatment development in patients. This path is not necessarily optimal, exclusive, or appropriate for every neurologic or psychiatric disease. Rather, it is one example of a reasoned, empirically derived pathway which we hope will serve as a scaffolding for future investigators seeking to develop rTMS treatment protocols.

Finding a Framework for Cocaine Treatment Development

The first step in TMS treatment development for cocaine users was to identify a biologic and behavioral framework to serve as a foundation for evaluating hypotheses. When developing a model for TMS treatment delivery, it is important to consider conceptual models of the neural circuitry engaged in addiction, most of which are complementary (reviews: [23, 24, {Goldstein, 2011 No. 2698}]). The Competing Neurobehavioral Decisions System (CNDS) is a model that unites behavioral phenotypes with frontal-striatal circuits involved in cocaine use [27]. The CNDS specifies that the frontal-striatal circuits involved in limbic reward and impulsive action are relatively hyperactive, while the executive control circuits are relatively hypoactive in individuals with addictive disorders. The impulsive system is comprised of the limbic and paralimbic brain regions. The executive system is comprised of the lateral prefrontal and parietal cortices. These are interdependent systems which compete for relative control during decision-making. Normal functioning results when the systems are in regulatory balance; however, pathologic behavior may result when the two systems are not in regulatory balance [28].

Uniting the behavioral data with a neurobiologic foundation in fronto-striatal circuitry [11], there are two neurobehavioral systems that could be viable candidates for TMS treatment development: (1) an impulsive system, likely involved in drug-associated craving and use, and (2) an executive control system, likely involved in resisting drug use. The frontal-striatal correlates of these are the following: (1) ventral medial frontal-striatal system and (2) the dorsal lateral frontal-striatal system, respectively. As stated earlier, TMS can lead to either an increase in cortical excitability or a decrease in cortical excitability in a frequency-dependent manner. It is possible to induce increased cortical excitability by applying a train of TMS pulses at a high frequency (> 10 Hz) or intermittent bursting frequency (intermittent theta burst stimulation; iTBS) to the cortex. Likewise, it is possible to attenuate cortical excitability, by applying either a single low frequency (1–5 Hz) or continuous bursting frequency (cTBS) [3, 4, 29, 30]. These rate-dependent effects of TMS on cortical excitability are sometimes referred to as “LTP-like” and “LTD-like” effects, respectively—phrases used in preclinical research to describe long-term potentiation and long-term depression of hippocampal neurons (see {[51] No. 40}).

It follows then that there are at least two promising strategies for approaching rTMS treatment development for cocaine dependence: (1) decrease activity in the ventral medial prefrontal cortex (VMPFC)-caudate circuit using an attenuating form of rTMS (e.g., 1 Hz or cTBS) or (2) increase activity in the DLPFC-dorsal striatal circuit using a potentiating form of rTMS (e.g., 10 Hz or iTBS) (Fig. 1). The first step in evaluating these two potential strategies was to determine, empirically, if it was possible to differentiate these circuits in healthy controls.

Study 1: Is It Possible to Dissociate VMPFC-Caudate Circuit from the DLPFC-Dorsal Striatal Circuit in Healthy Controls?

To address this question, we utilized an integrated TMS/MRI approach (interleaved TMS/BOLD imaging) [31–34], wherein single pulses of TMS could be delivered to the cortical targets of interest (left DLPFC and MPFC) [35]. Seventeen healthy individuals were recruited from the community. Each participant received two experimental runs of TMS/BOLD imaging with the coil positioned over the dorsolateral (EEG: F3; Fig. 2, blue) and ventromedial PFC (EEG: FP1; Fig. 2, red). The EEG 10–20 system coordinates were used in order to standardize the position of the coil. BOLD signal change, the primary dependent measure, was calculated in the areas directly stimulated by the coil and in subcortical regions with afferent and efferent connectivity to the TMS target areas. To ensure the rigor and reproducibility of our results, a cohort of five individuals were also tested on two occasions to determine test-retest reliability.

TMS led to significant BOLD signal increases in the cortex in the vicinity of the TMS coil as well as in the striatum and the thalamus. Medial PFC TMS (FP1) led to a significantly larger BOLD signal change in the caudate than DLPFC TMS (F3). Likewise, DLPFC TMS led to a significantly greater BOLD signal in the hippocampus. Post hoc voxel-based analysis revealed that within the caudate, the location of peak activity was in the ventral caudate following medial PFC TMS and the dorsal caudate following DLPFC TMS. To further address rigor and reproducibility, the visual cortex and auditory cortex were incorporated as negative and positive controls (respectively). There was no difference in these control areas when the TMS coil was moved between the two cortical locations. Test-retest reliability data revealed consistent BOLD responses to TMS within each individual but a large variation between individuals.

In summary, these data demonstrated that it was possible to differentially activate these established cortical-subcortical networks in healthy individuals through TMS/BOLD. These initial data provided us with the confidence to move forward and evaluate these circuits in cocaine users, using interleaved TMS/BOLD.

Study 2: Which Circuit Is More Disrupted in Cocaine Users?

Having demonstrated that it was possible to differentiate these circuits in controls, the next step was to evaluate the integrity of these circuits in cocaine users [36]. Eighteen cocaine-dependent individuals with a history of failed quit attempts and 18 age-matched controls were recruited from the community. Single TMS pulses were applied to the MPFC

(Brodmann area 10) and the DLPFC (lateral Brodmann 9) while participants rested in the MRI scanner (TMS/BOLD imaging). The methods from study 1 were repeated with the addition of several improvements in methodology (described below). Relative to the controls, cocaine users had a lower ventral striatal BOLD response to MPFC stimulation (Fig. 3). The dorsal striatal BOLD response to DLPFC stimulation however was not significantly different between the groups. Among controls, DLPFC stimulation led to an attenuation of MPFC activity (BA 10); however, this pattern did not exist in cocaine users. No relationship was found between regional diffusion metrics and functional activity. These data suggest that cocaine users can mobilize their executive control system (when the DLPFC is activated by a single TMS pulse) in a manner similar to controls. The cocaine users do not mobilize their limbic system (when the MPFC is activated by a single TMS pulse) as robustly as controls however. These data support the notion that the “set point” for mobilizing the limbic arousal system has been elevated—an interpretation consistent with opponent process theories of addiction [37, 38].

Method Improvement—Incorporating Scalp to Cortex Distance as a Factor

One of the improvements for this study included the incorporation of scalp-to-cortex distance as a covariate in the analyses. This was done because the effects of TMS on cortical depolarization are proportional to the distance between the skull and the cortex [39, 40]. We calculated the distance from the scalp to the cortex on the transverse plane on MPRAGE images of each individual (Mango ver. 3.7; Research Imaging Institute, UTHSA, Lancaster and Martinez 2005). Recently, we have developed a freely available, open access tool (BrainRuler [41]) which is available to the brain stimulation community (<https://www.mathworks.com/matlabcentral/fileexchange/61847-brain-ruler>). The average distance from the participant-specific placement of FP1 to the nearest cortex was $13.5 \text{ mm} \pm 2.8$ in controls and $14.2 \text{ mm} \pm 3.3$ in cocaine users. The average distance from F3 to the nearest cortex was $14.5 \text{ mm} \pm 1.7$ in controls and $15.1 \text{ mm} \pm 3.1$ in cocaine users. Notably, some of the cocaine users had noticeable cortical atrophy but this did not appear to have a significant effect on the distance between the gyri and the skull. These distances were used as covariates in the analyses and are now a standard part of the analysis pipeline in our laboratory as they are directly related to the actual dose of TMS that the cortex is likely exposed to during rTMS studies.

Method Improvement—Incorporating White Matter Tract Integrity as a Factor

The other methodologic improvement in this study was the inclusion of diffusion tensor imaging in the study. The primary goal of acquiring the diffusion data was to determine if there was a relationship between fractional anisotropy and TMS-evoked BOLD response in the frontal-striatal circuits of interest. Diffusion weighted images were obtained by using a twice-refocused echo-planar sequence with 2 diffusion weightings ($b = 0, 1000 \text{ s/mm}^2$) along 30 diffusion-encoding directions (50 slices, 0% distance factor, 222×222 field of view, 74×74 matrix, $\text{TR} = 6700 \text{ ms}$, $\text{TE} = 87 \text{ ms}$, slice thickness = 3 mm, partial Fourier encoding 6/8, no interpolation, 2 averages). Fractional anisotropy maps were created for each individual and track-based spatial statistics (TBSS) was used to compare the groups (FSL’s Randomize tool). Once the TBSS tracks were made, ROI-based parcellation was conducted in MNI space using the John Hopkins white matter brain segmentation atlas. This was done using

FSL tools by first isolating 8 ROIs (in the vicinity of the medial and lateral prefrontal cortex as well as the dorsal and ventral striatum) from the Johns Hopkins Standardized white matter atlas, masking each with the binary mean FA skeleton mask from TBSS and then making it a binary mask. The resulting binary ROI skeleton mask was then overlaid onto each subject FA map and the mean value of all non-zero voxels was acquired. The groups were compared using analysis of variance. Tract-based spatial statistics revealed that there were no significant differences in regional anisotropy between the groups. Additionally, FA values along the tracts connecting the cortical target areas (FP1 and F3) to the subcortical areas of interest were not significantly correlated with the TMS-evoked BOLD changes. While these data suggest that white matter integrity between the site of stimulation and the target area may not have a large effect on the resulting evoked BOLD response, this study was not intended to (nor powered to) address that question directly.

Studies 3 and 4: Can We Change This Circuit with MPFC cTBS? Feasibility and Efficacy

Choosing the Left MPFC as a Target

Having demonstrated that the brain response to MPFC stimulation was more affected in cocaine users than the brain response to DLPFC stimulation, we decided to focus on the MPFC as our TMS target. This decision was based on the outcome of study 2 and buttressed by evidence from other human neuroimaging studies demonstrating that the MPFC is hyperactive in response to cocaine cues [42–46] with the left being more active than the right [42]. Additionally, McHugh and colleagues demonstrated that connectivity between the VMPFC and amygdala was a powerful predictor of relapse (79.2% specificity and 66.7% sensitivity) [47]. Beyond target selection, however, there were still many design considerations to address, including the (a) frequency, (b) number of pulses, and (c) intensity of pulse to be used. Additionally, based on data from the large smoking cessation trial [13], the use of a cue-exposure paradigm for the participants to engage in during the TMS stimulation appeared to be important (see part E below).

Choosing a Frequency

Nearly all brain stimulation studies published to date in addiction have used a single continuous stimulation frequency (often 10 or 1 Hz) to modulate craving. While 10 and 1 Hz are the oldest, most established, and most commonly used brain stimulation protocols, theta burst stimulation (TBS; a patterned form of TMS) appears to produce comparable effects on motor cortex excitability [29] as well as attenuating depressive symptoms [48], in a fraction of the length of time typically used in 1 or 10 Hz protocols. A single session of TBS stimulation (600 total pulses; 3 pulses at 50 Hz (a burst), repeated in 200 ms intervals (5 Hz)) has effects that last up to an hour [29, 49]. Modeled from basic science methods [50, 51], human TBS induces a potentiation and depression of cortical excitability when given in an intermittent (LTP-like) and continuous (LTD-like) manner, respectively [29]. Given the role of LTP in the acquisition and maintenance of drug-use behaviors, and the clinical reality that a more efficient treatment (2 versus 20 min) would be more manageable for addiction

treatment programs, we decided to use continuous TBS rather than rTMS at 1 Hz to modulate activity.

From a pragmatic standpoint, TMS will likely be coupled with behavioral therapy in a longer term comprehensive treatment strategy. This means that shorter sessions will be more feasible in terms of overall patient and program burden. That being said, there are several challenges with cTBS which might suggest 1 Hz to be a better choice. These include the high levels of variability in response to TBS [52] and the discomfort people experience when TBS is applied to the forehead (when stimulating the frontal pole). Future studies exploring 1 Hz TMS to the MPFC (frontal pole) in substance-dependent individuals are warranted and may be very fruitful.

Choosing the Number of Pulses

Another parameter that can be varied in TMS protocol development is the number of pulses applied. As we had already decided to use a novel location (MPFC), and a relatively novel frequency (cTBS), we chose to keep the number of pulses and amplitude of stimulation relatively consistent with prior studies. The initial FDA-approved protocol for depression included 10 Hz rTMS sessions delivered at 110% of resting motor threshold (rMT; see the next section) for 3000 pulses per session (4 s on, 26 s off; 20 min). With cTBS, LTD-like effects on cortical excitability are observed after only 600 pulses. While 600 pulses of cTBS would have been a well-reasoned strategy, this protocol only takes 40 s, which would not allow the participants to engage in a cue-exposure protocol (which likely improves TMS efficacy for craving [13]).

Method Improvement—Ramping the Dose for Patient Tolerability

It was also apparent that TMS delivered to the MPFC would require judicious “ramping” of the TMS intensity during each session. Ramping is the process of starting the TMS intensity below the intended dose at session initiation and steadily increasing the amplitude as the patient adapts to the sensory aspects of the treatment. In many individuals, rTMS pulses over the prefrontal cortex induce scalp discomfort, especially at high intensities (100% of motor threshold or higher) or frequencies (1 Hz or greater). Although this discomfort can be alleviated with lidocaine injections under the coil [53], this approach is not ideal as the injection itself is associated with discomfort and anxiety for many individuals. Another way to dampen the painfulness of TMS is to slowly ramp the TMS dose. Although the mechanism is not completely understood, as predicted by the gate control theory of pain [54], an initial non-painful level of TMS intensity applied to the forehead appears to blunt the pain associated with subsequent, higher intensity TMS pulses.

With these considerations in mind, we used two 1800-pulse trains of cTBS (120 s on, 60 s off, 120 s on; 3600 pulses over a total of 5 min) to ramp the TMS dose, and still deliver at least 3000 TMS pulses at the full intensity.

Choosing the Amplitude of Stimulation

The amplitude of TMS stimulation is described as a percentage of the resting (or active) motor threshold (rMT)—the minimum machine output required to induce a motor-evoked

potential on at least 50% of the trials. While rMT is fairly stable within an individual, the effects of TMS on cortical depolarization are proportional to the distance between the skull and the cortex [39, 40]. Consequently, areas of an individual's brain which are farther away from the scalp than the motor cortex likely require stronger TMS intensities in order to get comparable depolarization (assuming tissue composition is similar between the motor cortex and the target area for stimulation). In depression literature, 110% rMT was chosen as the intensity to be given over the DLPFC, due to its relative distance from the scalp. In SUD literature, many studies have used lower amplitudes (90–110%) when targeting the DLPFC. While this approach minimizes seizure risk, doses of TMS below the motor threshold are unlikely to reliably depolarize the cortex, especially in populations with known cortical atrophy (including cocaine users).

To determine the minimum percentage of rMT necessary to depolarize the medial prefrontal cortex when placing a TMS coil on the left frontal pole (our chosen target), we developed a tool to automatically calculate scalp-to-cortex distance at multiple cortical locations (Brain Ruler, Summers and Hanlon 2017). We calculated the distance from the scalp to the cortex on the transverse plane on MPRAGE images of each individual. The average distance from the participant-specific placement of FP1 to the nearest cortex (controls 13.5 mm $\pm$ 2.8; users 14.2 mm $\pm$ 3.3) and F3 to the nearest cortex (controls 14.5 mm $\pm$ 1.7; users 15.1 mm $\pm$ 3.1) was not significantly different between the groups. Of note, while some of the cocaine users had noticeable cortical atrophy, easily visualized as sulcal enlargement, this did not appear to have a significant effect on the distance between the gyri and the skull. Hence, consistent with depression literature, we decided to use 110% of rMT as the intensity of TMS.

Choosing a Task for the Participants to Perform While Receiving rTMS

While TMS for depression is typically given in the absence of any task, recent data from a large clinical trial of TMS for smoking cessation demonstrated that the effects of TMS are amplified when an individual is exposed to a smoking cue during TMS delivery [13]. In this prospective, double-blind, sham-controlled study, 115 regular cigarette smokers were randomized to receive 10 daily treatments of 10 Hz real, 10 Hz sham, 1 Hz real, or 1 Hz sham rTMS, delivered to the left prefrontal cortex and insula (Brainsway H-ADD coil; 120% resting motor threshold). Immediately before each TMS session, half of the participants in each of the four groups were presented with visual smoking cues. The results demonstrated that, relative to sham, 10 Hz TMS (but not 1 Hz), there was reduced cigarette consumption and nicotine dependence, and that these effects were greatest in the individuals that were exposed to smoking cues. Specifically, there was a significant interaction between smoking cue exposure and change score on the Fagerstrom Test for Nicotine Dependence (FTND). Individuals that received smoking cue exposure and 10 Hz TMS had significantly lower FTND scores, a 44% abstinence rate after the 10 days of treatment, and a 33% abstinence rate after 6 months.

The amplifying influence of cue exposure on TMS treatment outcome was also demonstrated in a study of post-traumatic stress disorder (PTSD) [55]. In this study, 30 PTSD patients were randomized to one of three groups: sham rTMS, real rTMS following

exposure to a 30-s patient-tailored trauma script, or real rTMS following exposure to a 30-s patient-tailored neutral script. The participants received 12 sessions of real or sham rTMS (3 sessions/week, 4 weeks, Brainsway H-coil). The only group with a significant improvement in the Clinician-Administered PTSD Scale (CAPS) was the group that received exposure to 30-s trauma scripts before their rTMS treatment.

Although the mechanism through which cue exposure enhances the behavioral effects of rTMS is not clear, one possibility is that cue exposure reactivates latent memory traces (frequently referred to as the engram [56]), enabling them to be manipulated and reconsolidated [57, 58]. This was suggested by Dinur-Klein and colleagues, but to our knowledge, the effects of rTMS plus cue exposure on the reconsolidation of fear or drug-related memories has not been directly evaluated in patients with either substance dependence or PTSD.

Based on these empirical results from rTMS experiments and from a strong preclinical foundation regarding manipulation and reconsolidation of memories, we have been using a standardized drug cue-exposure paradigm for our studies. Using techniques described in the COPE handbook, the patients are prompted with several questions regarding their most recent (index) drug use event. The questions include details regarding the day of the week, time of the day, people they were with, and the sensory aspects of the experience. This procedure takes about 5 min. Immediately before the rTMS session begins, the participants are told “During the stimulation, it is important for you to try to focus on (insert their drug of choice: cocaine, crack, alcohol, liquor, beer, wine, cigarettes, pain killers). This tablet will be displaying various pictures of (insert: cocaine/crack, alcohol drinking, cigarettes, pain killers). We would also like you to keep your eyes open, look at the screen and think about your most recent experience with (insert: cocaine/crack, alcohol drinking, cigarettes, pain killers).” Full details of the standard operating protocol and a description of the questions used to create these “participant-tailored” drug use scripts are included in published [59] Supplemental Material.

Study 3—Feasibility—In order to ascertain that cocaine users would tolerate this paradigm (3600 pulses of cTBS to the left frontal pole, 110% rMT, 30 s ramp from 80 to 110% rMT) [60], 11 cocaine-dependent individuals were recruited for a single-blind, sham-controlled pilot study (Fig. 4). The study involved one screening visit and two scanning/stimulation visits (occurring within 7–14 days of each other). At each scanning/stimulation visit, fMRI data was acquired before and after exposure to a session of real or sham TBS. Self-reported craving on a scale of 0–10 was sampled 3 times before treatment (baseline, after cue exposure, after interleaved TMS) and 3 times after treatment (immediately after treatment baseline, after interleaved TMS, after cue exposure). The TMS coil was placed over FP1 (EEG: 10–20 system) for both the interleaved TMS/BOLD scan (left and right panel) and the cTBS session (center panel). The red area represents the region of interest to which the coil is targeted (AAL: left superior and middle orbital prefrontal cortex inferior to the anterior commissure).

All participants tolerated the real and sham cTBS well and the integrity of the blind was confirmed. All participants returned for both TMS visits and no one terminated a visit part

way through the procedure. Real cTBS (LTD-like) led to a significant decrease in BOLD signal in the left orbital/medial prefrontal cortex and ventral striatum (SPM8, $p < 0.05$ family-wise error correction). Changes in craving following real cTBS were significantly different than those in sham stimulation [$\chi^2 = 19.14$, $p < 0.0001$; increase craving 0, decrease craving 6, no change in craving 5].

This was the first study to apply cTBS to the left frontal pole, the first study to demonstrate that this protocol could decrease TMS-evoked BOLD signal in the ventral striatum, and the first study to evaluate the frontal pole as a feasible treatment target in cocaine users.

Study 4—Efficacy as a Tool to Dampen Cortical-Striatal Circuits—In a subsequent study, we replicated these procedures in a larger cohort of cocaine users [59]. Briefly, 49 individuals were recruited from the community (25 current cocaine users, 24 heavy alcohol users). The inclusion of alcohol users in this subsequent study was motivated by concerns that the cocaine users in our community sample also had very high alcohol use histories. As in study 3, baseline-evoked BOLD signal was measured immediately before and after real and sham cTBS (interleaved TMS/BOLD imaging: single pulses to left FP; scalp-to-cortex distance covariate, FWE correction $p < 0.05$). In the cocaine users, real cTBS led to a significant decrease in evoked BOLD signal in the caudate, accumbens, anterior cingulate, orbitofrontal (OFC), and parietal cortex relative to sham cTBS. In the heavy alcohol users, real cTBS led to a significant decrease in the left OFC, insula, and lateral sensorimotor cortex. There was no significant difference between the groups (Fig. 5).

The results of studies 3 and 4 suggest that 3600 pulses of cTBS to the left frontal pole can induce reliable decreases TMS-evoked BOLD signal in several frontal and striatal regions activated by drug cues. The reliability of this pattern in both cocaine users and alcohol users suggests that cTBS may have effects on these frontal-striatal circuits in a number of conditions.

Study 5: Can We Change Cocaine Cue Reactivity in This Circuit in Cocaine Users with MPFC cTBS?

In the next study, the effect of cTBS on cue reactivity in cocaine users was evaluated (study 5). This study revealed that, relative to sham, real cTBS decreased the cocaine cue-evoked BOLD signal in the MPFC, ACC, and striatum in individuals with significant levels of baseline cocaine cue reactivity ($n = 18$, blue) (Fig. 6, manuscript in progress).

The results of studies 3, 4, and 5 together suggest that cTBS to the left frontal pole is (1) feasible and (2) can attenuate the fundamental frontal-striatal neural circuitry involved in cocaine dependence, and (3) cocaine cue reactivity in these circuits.

Clinical Trial: Do Multiple Session of MPFC cTBS Have a Sustainable Effect on Cocaine Cue Reactivity and Cocaine Use in Treatment-Seeking Cocaine-Dependent Individuals?

With proof of principle data from studies 1–5, a double-blinded placebo-controlled trial of MPFC cTBS in treatment-seeking cocaine-dependent individuals was the next step. This clinical trial is ongoing and expected to finish enrollment in December 2017 (Clinical Trials.gov ID: NCT03238859). The primary goal is to collect critical data to assess feasibility and determine effect size before moving forward with multisite clinical trials. Questions to be addressed are as follows: in cocaine-dependent treatment engaged, does MPFC cTBS (1) improve retention and abstinence and (2) produce an acute and sustainable change in frontal-striatal connectivity?

Patients are randomized to receive 10 sessions of either real or sham cTBS while enrolled in a 4–5-week intensive outpatient treatment program for cocaine dependence (including cognitive behavioral therapy, group and individual counseling sessions). The cTBS sessions last 5 min and occur immediately before their intensive outpatient visits. Clinical assessments and neuroimaging data are acquired at 4 time points: baseline (V1), after 10 sessions of cTBS (V2), 1 month later (V3), and 2 months later (V4). The primary hypothesis is that patients receiving real cTBS will have a higher retention rate and lower cocaine use while in the outpatient treatment program and at 1- and 2-month follow-up visits. This will be measured by the number of clean urine drug screens, quantitative cocaine metabolites in the urine, and 1-month timeline follow-back for cocaine use. Additionally, we hypothesize that real VMPFC cTBS will cause a larger decrease in functional connectivity between the VMPFC and striatum than sham cTBS (Aim 2). The relationship between baseline functional connectivity and changes in functional connectivity will also be investigated as factors that affect clinical outcomes such as retention and drug use (Integration of Aims 1 and 2).

Conclusions

As stated in the introduction, the purpose of this review was to highlight the systematic approach that was taken to identify a candidate neural target and a feasible TMS treatment protocol for cocaine dependence with sufficient proof of principle data to warrant initiation of a double-blinded placebo-controlled clinical trial.

In TMS treatment development, there are a number of parameters that can be manipulated, including the cortical target, the frequency, the intensity of stimulation, the number of pulses, and the number of sessions required to produce a durable effect. It is important to balance full exploration of these parameters with the time-sensitive need to develop new treatments for life-threatening diseases like addictions. With limited time and resources in any given laboratory, it is clear to require collaborative efforts across multiple laboratories in order to make significant progress in developing an optimal TMS treatment protocol for SUDs. This is particularly true for drugs of abuse such as cocaine, methamphetamine,

marijuana, and opiates wherein there has been very little TMS treatment development work to date.

We have attempted to acknowledge the limitations of each of the parameters that we have chosen. Should the clinical trial not reveal a significant effect however, this framework we have established will again provide a robust platform for further optimization of a neural circuit-based treatment protocol for cocaine dependence. Moving forward, we hope that this review serves as a primer for future researchers to read and consider when creating evidence-based TMS treatment protocols for various neurologic and psychiatric diseases.

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Fig. 1.
Conceptual model for developing TMS as a therapeutic tool for cocaine dependence

Fig. 2.

Study 1. Dissociating the frontal-striatal circuits in healthy controls. The location of the peak BOLD response for each individual following TMS pulses to the F3 location (blue spheres) and to the FP1 location (red spheres). The locations of the peak BOLD response for each individual have been normalized to standard space and projected to the surface of standard cortical mask such that all points are visible in a common space. The mean location of peak activity in the cluster beneath the coil is shown (larger blue and red spheres)

Fig. 3. Study 2. Determining frontal-striatal circuit irregularities in cocaine users. A series of single pulses of transcranial magnetic stimulation were applied to the left dorsolateral prefrontal cortex (DLPFC, top) and the left ventral medial prefrontal cortex (VMPFC, frontal pole; bottom) in healthy controls and cocaine users while they rested in an MRI scanner (EEG International 10–20 system (black dots show standard positions)). During DLPFC stimulation, cocaine users had less TMS-evoked change in the MPFC. During frontal pole stimulation, cocaine users had significantly less TMS-evoked change in the striatum and the cingulate cortex. The statistical maps for all of these comparisons arose from the same full factorial design (SPM12; family-wise error-corrected clusters $p < 0.05$). Only voxels that fell within those significant clusters are displayed

Fig. 4.

Study 3. Initial feasibility and proof of concept data for frontal pole continuous theta burst stimulation in cocaine users. In this pilot study, interleaved TMS/BOLD imaging was used to measure TMS-evoked BOLD signal immediately before and after cocaine users were given a dose of cTBS to the left frontal pole. The TMS coil was placed over FP1 (EEG: 10–20 system) for both the interleaved TMS/BOLD scan (left and right panel) and the cTBS session. Using standardized imaginal techniques from exposure therapy, participants were prompted to mentate on their last drug use session during the TMS. The red dot represents the region of interest to which the coil is targeted (AAL: left superior and middle orbital prefrontal cortex inferior to the anterior commissure). Real cTBS (LTD-like) led to a significant decrease in BOLD signal in the left orbital/medial prefrontal cortex and ventral striatum (SPM8, $p < 0.05$ family-wise error correction). The cTBS protocol was 2 trains of 1800 pulses, 110% rMT, 60 s intertrain interval, intensity ramped from 80 to 110% over first 30 s

Fig. 5.

Study 4. Basic science question. Quantifying the effects of frontal pole cTBS on frontal-striatal circuitry in cocaine users. Real cTBS to the left frontal pole led to a significant decrease in TMS-evoked BOLD signal in the caudate, nucleus accumbens, anterior cingulate cortex, orbitofrontal cortex, and parietal cortex in cocaine users, relative to sham cTBS. Clusters shown reflect the results of the positive interaction terms of the factorial design {real versus sham for the “before cTBS” greater than “after cTBS” contrast}. Family-wise error multiple comparison correction $p < 0.05$. Color bar contains T -values 0–5

Fig. 6.

Study 5. Clinically relevant question. Quantifying the effects of frontal pole cTBS on cocaine cue-evoked brain activity. cTBS decreased cocaine cue-evoked BOLD signal in the medial prefrontal cortex, anterior cingulate cortex, and striatum in individuals with significant levels of baseline cocaine cue reactivity (FEW corrected, $p < 0.05$, slice numbers in MNI space are shown above each image, $n = 18$, blue)