Original Article

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The Use of Neuromodulation in the Treatment of Cocaine Dependence

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Abstract

Cocaine-related disorders are currently among the most devastating mental diseases, as they impoverish all spheres of life resulting in tremendous economic, social, and moral costs. Despite multiple efforts to tackle cocaine dependence, pharmacological as well as cognitive therapies have had limited success. In this review, we discuss the use of recent neuromodulation techniques, such as conventional repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation, and the use of H coils for deep rTMS for the treatment of cocaine dependence. Moreover, we discuss attempts to identify optimal brain targets underpinning cocaine craving and withdrawal for neurodisruption treatment, as well as some weaknesses in the literature, such as the absence of biomarkers for individual risk classification and the inadequacy of treatment outcome measures, which may delay progress in the field. Finally, we present some genetic markers candidates and objective outcome measures, which could be applied in combination with transcranial magnetic stimulation treatment of cocaine dependence. We anticipate future research in this area combining genetic and physiological markers, neurodisruption, and clinical behavioral measures.

Key Words: transcranial magnetic stimulation, deep rTMS, DBS, addiction, habenula, medial forebrain bundle

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Cocaine dependence has become a substantial public health problem, resulting in a significant number of medical, psychological, and social problems, including the spread of infectious diseases (eg, AIDS, hepatitis, and tuberculosis), crime, violence, and neonatal drug exposure. Prevalence rates for lifetime use of cocaine are typically 1% to 3% in developed countries, with higher rates in the United States and in the producer countries (WHO). Among people who have taken cocaine on at least 1 occasion, cocaine dependence develops in an estimated 16% to 17%.[1] Relapse to cocaine dependence is frequently associated with subjective reports of craving, which usually precedes the seeking and taking of drugs. Understanding the pathophysiology of addiction and the neurobiological basis of craving in particular, is essential for designing better index of treatment response and for developing new therapeutic interventions.

THE ANATOMIC BASIS OF COCAINE DEPENDENCE

Several investigations have concluded that the most likely final common pathway underpinning drugs' dependence is dopamine neurotransmission. Tonic release of dopamine in the nucleus accumbens (NAc) has been associated with cravings due to sensitization, whereas increasing phasic release in response to consumption is thought to underlie sustained or increased reinforcement and addictive behavior.[2] The source of dopamine to the NAc is the ventral tegmental area (VTA) of the midbrain, which receives top-down modulation from amygdala and the prefrontal cortex (PFC) as part of the valuation of reward process. Consolidation of engrams to obtain rewards depends on the dorsal striatum, which receives dopamine projections from the substantia nigra (SN), which lies besides the VTA.[2]

Importantly, the components of the described network seem to be involved in drug dependence at different stages. At the binge or intoxication stage, the NAc and the VTA have a central role as dopamine release within these structures in the phasic phase is increased, whereas the amygdala plays a

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role in the withdrawal phase.[3] A more disperse cortico-subcortical network composed by the orbital PFC, amygdala, hippocampus, insula, and striatum play a role in craving and relapse processes as this circuit underlie the subjective experiences of drug such as evaluation of the rewarding effect of drugs.[3] Parallely, disruption within the dorsolateral PFC-cingulate circuit is associated with poor inhibitory control observable in the craving stage such as drug-seeking behaviors.[3] Repeated intake of drugs induces long-term neuroadaptations caused by hyperactivity of dopamine transmission (acute effect of drug), which leads to alteration in cortical excitability, leading to heightened motivation to consume drugs and diminished ability to regulate the behavioral response to drug cues.[4] See Figures 1 A and B showing the brain circuitry underlying addiction.

TRANSCRANIAL MAGNETIC STIMULATION ON THE THREATMENT OF COCAINE DEPENDENCE

Pharmacological treatments on drug dependence have had limited success.[5,6] For example, ecopipam, a selective dopamine D1/D5 receptor antagonist, diminished acute intake of cocaine, however, when administered repeatedly it seems to have the opposite effect increasing D1 dopamine receptor density in the brain.[7] Fortunately, there are nonpharmacological tools of potential use for the treatment of drug dependence. Transcranial magnetic stimulation (TMS) may target the dopaminergic circuits involved in drug dependency with fewer side effects and fewer contraindications than medication treatments.[8]

TMS uses rapidly changing magnetic fields to induce electric fields in the brain, leading to excitation of neurons. TMS has attracted considerable interests as a therapeutic option for various psychiatric and neurological disorders. Standard TMS devices induce neuronal stimulation in cortical regions lying mainly superficially under the windings of the coil.[9] It should be noted that neuronal stimulation occurs only in the vicinity of the scalp surface because the field rapidly decays with increasing distance from the coil. More recently, stimulating deeper subcortical brain regions by deep brain TMS has received increased attention,[10] and several recent studies have indicated that stimulation of some deep structures may play

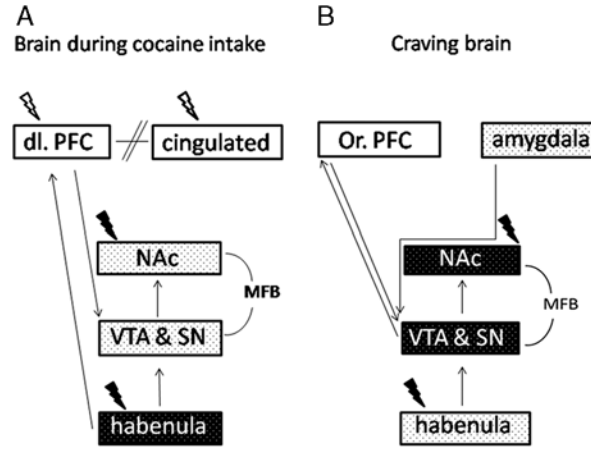

FIGURE 1. Model of the neural circuitry underpinning cocaine abuse. A, The neural response during the acute (phasic) cocaine consumption. B, The brain response during cocaine withdrawal. Black pointers indicate DBS targets reported in the literature, and white pointers indicate TMS targets reported in the literature. Boxes in black with small white dots stand for hyperactivity and boxes in white with small back dots stand for hypoactivity. Arrows represent unidirectional connections between structures and arrows crossed by double lines represent disconnectivity. DBS indicates deep brain stimulation; MFB, media forebrain bundle, NAc, nucleus accumbens; PFC, prefrontal cortex; SN, substantia nigra; TMS, transcranial magnetic stimulation; VTA, ventral tegmental area.

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a role in the study of reward and motivation mechanisms.

Although scientific research on TMS treatments for addictions is still in its infancy, some promising studies have shown moderate success. A recent study shows that repeated high-frequency TMS on the left dorsolateral PFC reduced cigarette consumption and nicotine craving in smokers, although the effect tends to disappear over time.[11] A single case study on an alcoholic patient applied TMS on the dorsal anterior cingulate cortex, which temporarily stopped alcohol cravings but again, the TMS effect disappeared over time.[12] In opposition, a study on healthy women found that TMS on the left PFC did not have an inhibitory effect on food craving.[13] One of the reasons why the previous studies show only moderate or null effects of TMS on craving may lie in the structures they targeted. Although pivotal dopaminergic projections underlying addictions correspond to the mesolimbic pathway, the cited studies targeted more superficial cortical structures. Again, traditional TMS performed with round coils or figure-8 coils has an important limitation as it cannot stimulate farther than 2 cm from the skull.[14]

DEEP BRAIN STIMULATION ON THE THREATMENT OF COCAINE DEPENDENCE

Deep brain stimulation (DBS) offers the possibility to stimulate deep brain structures. Such technique involves a neurosurgical intervention in which implanted electrodes deliver electrical pulses to stereotactically targeted areas of the brain. The use of this technique in the treatment of addiction has been investigated, revealing that targeting the NAc and subthalamic nucleus is effective in reducing drug-seeking behavior and drug consumption.[3] Animal models present promising evidence on the efficacy of this technique targeting the lateral habenula for addiction treatment.[15,16] The lateral habenula innervated the VTA and PFC,[17] providing negative reinforcement signals to midbrain dopamine cells in the SN and VTA.[18] Specifically, it is postulated that the habenula releases GABA onto dopaminergic cells of the VTA and SN, resulting in a decrease in midbrain dopamine.[19] Matsumoto and Hikosaka observed that midbrain dopamine increases with unexpected rewards and decreases with denied rewards, which is exactly the opposite pattern the habenula presents, meaning that these structures are anticorrelated.[20] Noteworthy, cocaine intake conveys a rewarding feeling. On the basis of the presented evidence, it has been proposed that continuous drug consumption results in habenular hyperactivity to counterbalance excessive dopamine release in the VTA and SN. Drug withdrawal may correspond to habenular hyperactivity underpinning reward deny.[19] It has been shown that the lateral habenula electrical stimulation in rats trained to self-administered cocaine weakens cocaine-seeking behavior, probably due to extinction of lateral habenula inhibitory effect on midbrain dopaminergic cells after denied reward.[15] However, DBS is an invasive procedure that may produce several and severe adverse effects. Unfortunately, because addiction is often seen as a volitional problem,[21] a self-induced condition, or even a life choice,[22] reluctance toward the use of invasive techniques such as DBS for the treatment of cocaine addiction is expected.

POSSIBLE TARGET FOR DEEP REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN COCAINE DEPENDENCE

To circumvent the invasiveness of DBS and the lack of power to stimulate deep structures of traditional TMS, H coil TMS was created. H coils are capable of stimulating deeper structure and yet, the technique is noninvasive.[10] H coil TMS seem to be optimal for the treatment of drug dependence, as the most consistent neural nodes underpinning this affection are deep and it is a low-risk noninvasive procedure compared with DBS. Surprisingly, to the best of our knowledge there are no reported studies applying this technique for the treatment of addiction in humans.

Neuromodulation techniques are most effective when using a well-defined target region. A well-defined target should be succinct and it should have clear anatomic boundaries, facilitating its location on the patient's structural MR images. Using anatomic or functional mapping/navigation techniques aimed at well-defined targets, researchers should be able to predict the stimulation outcome accurately and facilitate replication of findings. Moreover, the ideal target should be a central node of the neural network underlying the behavior to modify. Although the habenula is a structure with clear anatomic boundaries and strongly connected within the neural network underlying cocaine dependence, it has a remarkably small size and thus deep TMS, which has a spatial resolution of several centimeters, could not accurately target it. Instead, because of its ubiquitous projections to the neural network underlying cocaine craving, and its larger size, the media forebrain bundle (MFB) is a privileged target for deep TMS stimulation to treat cocaine use disorders. The MFB connects the VTA, the lateral hypothalamus, and the NAc.[23] Moreover, a connection of the dopamine projecting VTA neuron groups with the limbic forebrain is established directly through the MFB. It is through the MFB that the VTA connects to numerous forebrain structures, including the medial hypothalamus, sublenticular region, lateral and medial preoptic region, diagonal band, septal nuclei, ventral pallidum, and ventral parts of the bed nucleus of the stria terminalis.[24] The superolateral branch of the MFB has direct connections to the ventral striatum and NAc. Upon following the slMFB anteriorly, the connections extend to the orbitofrontal cortex and dorsolateral PFC.[25] The MFB importance as a central node for addiction and the reward system has been highlighted; in fact, a recent animal study implanted electrodes for intracranial self-stimulation on this fiber tract and used it as a model of drug-seeking behavior.[26] It is possible that MFB has been excluded as a target for substance-related disorders in human studies because it not accessible with standard 8 coils for TMS stimulation; however, newly designed H coils can reach this white matter track (Fig. 2).

PHYSIOLOGICAL AND GENETIC TECHNIQUES AS OBJECTIVE OUTCOME MEASURES AND BIOMARKERS FOR COCAINE DEPENDENCE TREATMENT

So far, we have addressed a number of methodological problems for the therapeutic use of neuromodulation techniques in substance abuse disorders. An additional methodological problem in the addiction treatment literature is that outcomes are too often measured by self-reported information and self-reported scales, lacking objectivity and with low reliability. In drug addiction research, the sensitive nature of the data collected, the tendency to minimize use and its impact, and lack of insight or denial, may lead study participants to misreport their drug use. Conversely, relying on urine drug screens alone may miss drug use events occurring too far in the past to be detected.[27] A good outcome measure should estimate the prognosis accurately. Secondly, the effect of treatment on drug dependence must be explained by the effect of the treatment on the outcome. Thirdly, for an outcome not restricted to use with a single, specific treatment, evidence must exist that treatments of various classes affect the outcome in the same and predictable manner.[28] The objective, sensitive, and quantitative changes measured using functional MRI (fMRI) have made it an attractive tool for measuring outcome of new treatments. There is a single case study that collected resting state fMRI and qEEG before and after treatment in an alcoholic patient, revealing a strong correlation between the functional imaging data and the clinical picture. Precisely, when the patient craves for alcohol, activations in the dorsolateral PFC-cingulate circuit is found, which also correlates with β activity in the same network. Post–repetitive transcranial magnetic stimulation (rTMS), when the patient is not craving, activations in the described network are absent.[12] Importantly, it has been proposed that the use of a combination of psychophysiology

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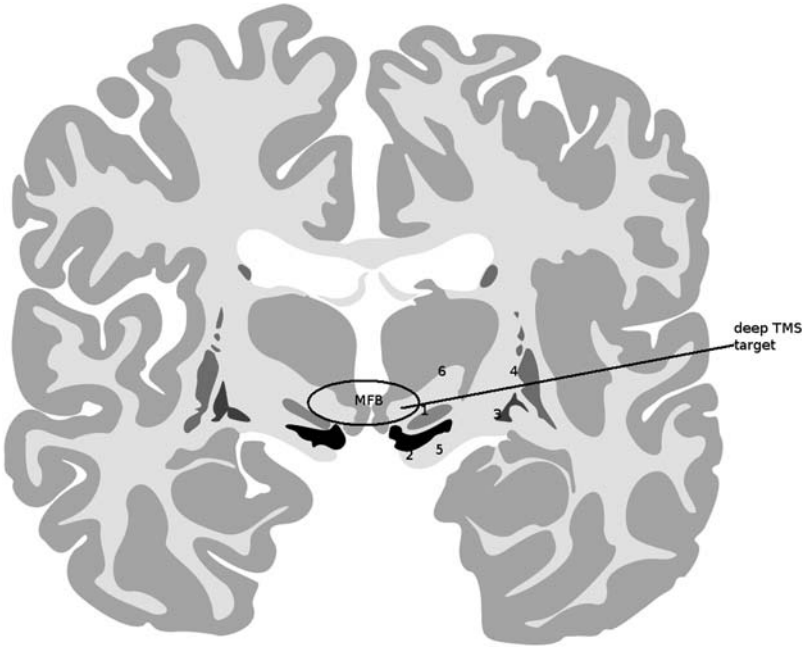

FIGURE 2. Coronal view showing the middle forebrain bundle as a promising deep rTMS target for cocaine dependence. (1) subtalamic nucleus, (2) substantia nigra, (3) globus pallidus, (4) striatum, (5) ventral tegmental area, and (6) nucleus accumbens. MFB indicates media forebrain bundle; TMS, transcranial magnetic stimulation.

and genetics outcome measures is more reliable than clinical markers and has more potential in establishing treatment predictors.[29,30] Surprisingly, previously obtained potential outcome measures in substance dependence treatment have been investigated in isolation. It is reasonable to think that integrated fMRI, qEEG, and genetic markers would allow to predict treatment outcome more accurately. One of the ultimate goals of personalized medicine is to predict the optimal therapy for each single patient.[31] The search for psychophysiological and genetic markers will make an invaluable contribution to this goal.

Identification of gene mutations, polymorphisms, or other genetic variants that predispose certain individuals to cocaine addiction would not only provide an ''at-risk'' diagnostic for substance abuse, but it would also be useful to personalize treatments making them patient specific and thus more effective. There are certain genes that have been associated with cocaine dependence, which are also related to dopaminergic functions. Specifically, associations between specific genotypes within the of the dopamine transporter gene (*DAT1/SLC6A3*), the dopamine B hydroxylase gene (*DBH*),[32] and the dopamine receptor D2 gene (*DRD2*)[33] have been reported in the literature. Importantly, one of the advantages of rTMS for the treatment of cocaine dependence is that this technique can exert persistent effects through gene induction. Evidence from 3 groups, using very different methods, have reported that rTMS modulates the expression of immediate early genes.[34–36] After this strand of research, it might be possible that future combined rTMS-genetic studies may not only reveal which subjects are vulnerable to cocaine dependence but also the use of TMS treatment might trigger genetic modification leading to symptoms control.

CURRENT HYPOTHESES AND FURTHER EXPERIMENTS

To date, there is no pharmacological treatment guidelines for cocaine dependence disorder; and a proportion of patients do not respond to cognitive behavioral treatment. Alternatively, TMS trails only had moderate success because it has targeted the surface of the

cortex, although the brain circuit underpinning addiction is mesial. Future studies should target mesial structures such as the MFB with deep TMS as it is known to be a pivotal node of the neural circuitry underlying craving behavior. To obtain a better understanding of the use of deep TMS in the treatment of addiction, it is necessary to overcome current methodological issues. That is, in most of the current studies, the use self-reported scales (a subjective measurement) or the analysis of urine or blood tests isolated to measure drug consumption (although cocaine metabolites clear out in 3 d) results in poor assessment of drug intake. Further studies should combine different measurements (such as self-reported cocaine use, urine test, and a cocaine craving questionnaire) to allow to look for inconsistencies in the data. In addition, fMRI and qEEG data could be collected to improve the reliability of outcome measures. The physiological data may reveal brain biomarkers, such as intrinsic connectivity patters associated with treatment outcome, giving objective empirical support to the efficacy of TMS treatment for cocaine dependence. Another weakness in the literature consists in that the mechanisms by which TMS treatment modifies behavior are poorly understood. New studies could benefit from modeling resting state fMRI and qEEG imaging modalities. Such analysis could be used to identify psychophysiological interactions within neural nodes revealing the TMS treatment mechanism of action and how it could be used to diminishing cocaine craving. Lastly, physiological measures and a gene panel map may be used for cluster analysis. Such novel approach could potentially develop individualized treatment optimizing effectiveness. The ultimate goal should be to develop diagnostic models that improves clinical outcome.

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