Transcranial Magnetic Stimulation to Understand the Pathophysiology and Treatment of Substance Use Disorders

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Abstract: Recent studies support an association between substance use disorders (SUDs) and cortical excitability. Transcranial magnetic stimulation (TMS) is a non-invasive tool that can be used to assess cortical physiological processes (e.g., inhibition, excitation) and has proven to be a useful diagnostic tool in brain disorders associated with alterations in cortical excitability. In this manuscript, we review studies that employ TMS to evaluate cortical excitability in patients with SUDs. Furthermore, we discuss preliminary studies that examine repetitive TMS (rTMS) as a potential treatment for patients with SUDs. Although the use of TMS to evaluate and to treat those individuals with SUDs is in its early stages, these studies reveal significant alterations in both cortical inhibition and excitation. Specifically, elevated cortical inhibition was reported in both cocaine and nicotine dependent individuals, while one study demonstrated an increase in cortical excitability in those who use 3, 4-methylenedioxyamphetamine (MDMA). Furthermore, three studies examining rTMS as a potential treatment in cocaine and nicotine addiction report decreases in the level of cravings and in the number of cigarettes smoked following rTMS administration to the dorsal lateral prefrontal cortex. Thus, TMS has provided early interesting findings vis à vis cortical excitability in SUDs. Moreover, preliminary evidence suggests that rTMS is efficacious in the treatment of cocaine and nicotine addiction. Further work is needed to enhance our understanding of the altered neurophysiology in SUDs as well as the ways in which rTMS treatment can be directed to optimize treatment.

Keywords: Substance use disorders, cocaine, MDMA, and nicotine dependence, cortical excitability, (repetitive) transcranial magnetic stimulation, pathophysiology and treatment of substance use disorders.

INTRODUCTION

Psychoactive substance use and dependence represents a significant threat to public healthcare worldwide. Accordingly, The United Nations Office on Drugs and Crime estimates that 185 million people use illicit drugs translating to 3.1% of the global population, and 4.3% of the population aged 15 years and older [1]. Dependence on illicit drugs results in 0.2 million deaths (i.e., 0.4%), while an estimated 32,000 of deaths attributed to disability adjusted life years, worldwide. In addition to illicit drug use, 2 billion of the world’s population use alcohol, aged 15 years and older [1]. Although, alcohol consumption has decreased over the past 20 years, its use and dependence remain problematic, and result in an estimated 3.2% of total global mortality. Use and dependence of illicit drugs and alcohol, therefore, represent a global burden, which exacts major health, social, and economic costs.

Use of illicit drugs or alcohol affects the central nervous system. Although extensive animal and human work have helped to identify the immediate effects of these substances on the central nervous system, their exact modes of action on the brain are not completely understood. It is known, however, that these substances exert their immediate effects on synaptic neurotransmission, thereby modulating cellular communication. Furthermore, chronic use leading to substance dependence may ultimately result in deleterious changes in cortical excitability, as a result of repeated alterations in cellular communication. Moreover, such changes in cortical excitability that are important in normal brain function may represent one mechanism contributing to the pathophysiology underlying substance use disorders (SUDs). Transcranial magnetic stimulation (TMS) represents an investigational technique that can index corticospinal excitability, a neurophysiological measure that is linked to both inhibitory and excitatory mechanisms in the cortex. Various TMS paradigms that differentially evaluate inhibitory and excitatory neural mechanisms, therefore, may enhance our understanding of how illicit drugs and alcohol affect cellular communication. In this paper, we will overview the studies that employ TMS to examine the pathophysiology of psychoactive substances on the balance of inhibitory and excitatory mechanisms in patients with SUDs. In addition, studies evaluating the efficacy of repetitive TMS (rTMS) for the treatment of SUDs will be reviewed.
CORTICAL EXCITABILITY

Normal brain function is dependent on cortical excitability, which reflects the optimal balance in inhibitory and excitatory mechanisms. Inhibitory neurotransmission, a process that suppresses cortical activity, is predominantly mediated by inhibitory neurotransmitter, γ-aminobutyric acid (GABA), present in all cortical layers of the brain [2]. GABA is synthesized almost exclusively from the excitatory neurotransmitter glutamate (GLU), and its effects mediated by ionotropic GABA$_A$ and metabotropic GABA$_B$ receptors. GABA$_A$ receptor activity is dependent on the concentration of cation-chloride while GABA$_B$ receptors depend on the presence of calcium and magnesium. Furthermore, GABA$_B$ receptors are mainly located in the presynaptic membrane of aminergic synapses, and when GABA or GABA agonists bind to these receptors, the release of dopamine (DA), noradrenergic, and serotonin is inhibited [3]. GABA$_B$ receptors, therefore, function as heteroreceptors, thereby exercising GABA’s control over many systems involved in neural transmission [3]. Finally, GABA exerts its inhibitory effects on the postsynaptic membrane as a result of neuronal hyperpolarization, but can also induce neuronal depolarization through the detection of high intracellular concentrations of chloride. In contrast, excitatory neurotransmission facilitates cortical activity and is predominately mediated through GLU. Further, GLU is synthesized locally or as a product of the Krebs cycle, and is mediated by a number of different receptors, of which the N-methyl-D-asparate (NMDA) is the most notable. GLU is involved in fast synaptic transmission, and also mediates long-term potentiation, important in memory and learning [3].

The interplay of GABA, GLU and associated neuro-modulators, are critical in maintaining optimal cortical excitability through the balance of inhibitory and excitatory neurotransmission. Furthermore, alterations in these mechanisms result in deleterious brain functioning and may contribute to the pathophysiology in brain disorders. Different TMS paradigms are used to evaluate the balance in cortical excitability, reflective of interaction between GABA and GLU neurotransmission, often implicated in the pathophysiology underlying several brain disorders including SUDs.

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is most commonly used to investigate the integrity of the motor pathways in healthy individuals and in those individuals with diseased states. When a TMS pulse is applied to the motor cortex, electromyographic (EMG) activity can be collected from the corresponding target muscle, thus providing a measurement of corticospinal excitability (i.e., cortex to the spinal cord) (Fig. 1A). Resting or active motor threshold (RMT; AMT), are measures of corticospinal excitability, conventionally defined by the minimum intensity required to induce a motor evoked potential (MEP) of at least 1 mV in a resting target muscle (RMT) or 2 mV when the target muscle is tonically activated (AMT), measured via EMG. Furthermore, MT strength is thought to reflect membrane excitability related to the functional status of voltage-gated sodium channels [4], and inhibitory tone [5] critical in regulating axon excitability. To this end, drugs that block voltage-gated sodium channels [5-7], such as an antagonist of NMDA, an amino acid that normally mimics excitatory neurotransmitter GLU, elevates MT [8]. Ultimately, MT provides a measure of the efficacy of the chain of synapses from presynaptic cortical neurons to muscles [9], and an alteration in either inhibitory or excitatory mechanisms directly influences this measure. Corticospinal excitability is also measured by MEP size indexed either by peak-to-peak amplitude or the area under its curve, as well as, input-output (I/O) curves determined by delivering TMS pulses to the motor cortex in a stepwise fashion until a plateau is achieved in MEP amplitude [10, 11]. The evaluation of MT, MEP size, and I/O curves with TMS, therefore, provide robust measures of corticospinal excitability that is often altered in those with various brain disorders, including patients with SUDs.

Paired-pulse TMS paradigms are used to measure both inhibitory and excitatory interactions in the brain. In short interval cortical inhibition (SICI), and intracortical facilitation (ICF), a suprathreshold test stimulus (TS) is preceded by a subthreshold conditioning stimulus (CS), separated with an interstimulus interval of 1-5 msec or 10-20 msec thereby evaluating cortical inhibition or facilitation, respectively [12] (Fig. 1B,C). The neurobiological basis of SICI/ICF phenomenon has been studied through pharmacological studies. In this regard, lorazepam, a benzodiazepine GABA$_A$ agonist enhances inhibition while suppressing facilitation indexed through SICI/ICF, respectively [5]. However, no change in MT strength or MEP amplitude was observed following lorazepam administration, suggesting that these corticospinal excitability parameters are physiologically distinct from corticocortical excitability parameters, SICI/ICF [5]. Collectively, these studies strongly implicate GABA$_A$ receptor-mediated neurotransmission underlying the phenomenon of SICI/ICF in healthy individuals.

Another paired-pulse TMS paradigm that delivers two single TMS pulses at the same suprathreshold intensity to induce a MEP of 1 mV in peak-to-peak amplitude [13, 14] is used to differentially index long interval cortical facilitation (LICF) and inhibition (LICI). In LICF, when the CS precedes the TS by 25-30 msec, the second MEP induced by the TS is facilitated and is believed to be mediated through glutamatergic mechanisms [15]. In LICI, on the other hand, the CS and TS is delivered between by 50-150 msec apart, thereby attenuating the second MEP induced by the TS by approximately 50% [16], compared to when the TS is delivered alone (Fig. 1D). Pharmacological studies have implicated GABA$_B$ receptors’ role in LICI. In this connection, the administration of baclofen, a GABA$_B$ receptor agonist, was observed to enhance inhibition indexed through LICI [17], while this drug has no effect on corticospinal excitability parameters, MT strength and MEP size in healthy individuals [18].

Sensory afferent inhibition can also be examined with TMS by pairing an electric stimulus applied to the median nerve with a TMS pulse delivered to the contralateral motor cortex. In this paradigm, when a suprathreshold test stimulus (TS) is preceded by a subthreshold electric conditioning stimulus (CS) applied to the median nerve at the wrist, separated with an interstimulus intervals between 20 and 600 msec, the TS MEP is attenuated [19-22]. Furthermore, at
Fig. (1). Surface electromyogram recordings from a right hand muscle following: (A) a single test stimulus (TS) applied to the left motor cortex producing a motor evoked potential (MEP). (B) Short Interval Cortical Inhibition (SICI), a conditioning stimulus (CS) precedes the TS by 2 ms to and inhibits MEP produced by the TS. (C) Intracortical Facilitation (ICF), the CS precedes the TS by 20 ms, this time facilitating the MEP produced by the TS. (D) Long Interval Cortical Inhibition (LICI), the CS precedes the TS by approximately 6 ms and inhibits the MEP produced by the TS. (E) Short afferent inhibition (SAI), an electric CS precedes the TS by 20 ms, the MEP induced by the TMS is attenuated. (F) Long afferent inhibition (LAI), the CS and TS are separated by 200 ms, the resulting MEP is reduced, as compared to the TS alone. (G) The cortical silent period (CSP) induced following a 40% suprathreshold TS applied to the left motor cortex while the right hand muscle is tonically activated. The silent period starts at the onset of the motor evoked potential (MEP) and ends with the return of motor activity.
interstimulus intervals of 20 and 200 msec, inhibition of the TS MEP is generally referred to as short-, and long-latency afferent inhibition (SAI; LAI), respectively (Fig. 1E,F). It has been proposed that different mechanisms underlie SAI and LAI [23], and has been investigated pharmacologically. In SAI, the role of central cholinergic activity, DA, and GABAₐ has been implicated. For example, SAI is significantly reduced in healthy controls following the administration of a muscarinic receptor antagonist scopolamine [21], in patients with Parkinson’s disease on dopaminergic medication [24], and also in patients with Alzheimer’s disease with deficits in central cholinergic activity [25,26]. Accordingly, SAI has been reported to be mediated following the administration of acetylcholinesterase inhibitors in patients with Alzheimer’s disease, and with diazepam in healthy individuals [27,28]. LAI, on the other hand, is less studied. It has been reported that LAI is reduced and unaffected by dopaminergic medication in patients with Parkinson’s disease [24] and significantly lowered in patients with focal dystonia [29]. In addition, LAI is thought to be mediated via GABA₂ receptors as LAI inhibits LICI [23]. This suggests that GABAergic neurotransmission is key to the development of cocaine sensitization [35]. In addition, GABA₂ receptors have been implicated in cocaine exposure in preclinical investigations. For example, a significant relationship was found between the decrease in striatal GABA₂ receptor function and the degree of cocaine-sensitized behaviour in rats, which strongly suggests that GABAergic neurotransmission is key to the development of cocaine sensitization [34]. In addition, GABA₂ receptor antagonists have little effect on corticospinal excitability measures of MT intensity or MEP size, strongly suggesting that these parameters are physiologically distinct from SICI/ICF, LICI, and CSP. The utility of TMS to differentially evaluate cortical inhibitory and excitatory processes in the cortex may enhance our understanding of the role of various neurotransmitter mechanisms, defined above, in the pathophysiology and treatment of SUDs.

CORTICAL EXCITABILITY IN SUBSTANCE USE DISORDERS

Cocaine and Cortical Excitability

Exposure to cocaine acts as a biological stimulus, which is mediated by the neostriatal DA projection pathway thereby releasing DA [34]. More specifically, cocaine binds to DA transporters, blocking the reuptake of synaptic DA, thereby enhancing its lifetime in the synaptic cleft and allowing for DA to diffuse more efficiently between synapses [35]. Repeated increases in DA transmission in chronic cocaine exposure lead to cellular changes that are important in learning behaviours relevant to biological stimuli (i.e., cocaine) [35] thought to, in part, underlie addiction to the drug.

The effect of chronic cocaine exposure is less understood. Conceptually, cocaine addiction is thought to result in excessive excitatory GLU- and accordingly, deficient GABA inhibitory neurotransmission [35] leading to altered cortical excitability. As such, cues associated with cocaine are reported to activate a circuit involving the cortico-limbic brain regions, notably between the prefrontal cortex, amygdala and ventral striatum (nucleus accumbens) in cocaine dependent patients [36]. Moreover, the outputs from the prefrontal cortex to the nucleus accumbens are GLU, and from the nucleus accumbens to the ventral pallidum is GABAergic and peptidergic [35], strengthening the role of GLU and GABA in the pathophysiology underlying cocaine addiction.

As previously described, GABA is the principle neurotransmitter that mediates inhibitory neurotransmission in most areas of the brain. GABA is implicated in cocaine addiction as it is involved in DA projections from prefrontal cortex to the ventral pallidum where neuropeptides that regulate GABA are co-localized [37]. Drugs, therefore, that target either GABA or peptide transmission are potential targets in pharmacological therapies in cocaine addiction. In this regard, both GABAₐ and GABA₂ receptors have been implicated in cocaine exposure in preclinical investigations. For example, a significant relationship was found between the decrease in striatal GABA₂ receptor function and the degree of cocaine-sensitized behaviour in rats, which strongly suggests that GABAergic neurotransmission is key to the development of cocaine sensitization [34]. In addition, GABA₂, an irreversible inhibitor of GABA transaminase, which is the primary enzyme involved in GABA metabolism, has been shown to elevate GABA levels in the rat brain [38]. Moreover, GVG dose dependently decreases cocaine self-administration independent of the feeding regime, thereby indicating that GVG attenuates the reward value of cocaine.

GABA₂ has also been reported to be involved in cocaine’s mediation. For example, preclinical evidence using baclofen, a GABA₂ agonist, inhibits cocaine administration in a dose-dependent fashion [39]. Accordingly, CGP56433A, a GABA₂ antagonist also attenuates baclofen’s effect on cocaine self-administration in rats under a number of different feeding regimes [39]. Furthermore, GABA₂ receptors are thought to be critical in the reward properties of cocaine, as baclofen decreases extracellular DA in the ventral tegmental area and other structures of the DA system [39]. In addition, clinical trials have also demonstrated a reduction in cocaine cravings and cocaine use following the administration of baclofen [40-42], thus strengthening the consideration of GABA₂ as a therapeutic target in the treatment of cocaine addiction.

In addition to GABA, GLU is also a major neurotransmitter in the mediation of cocaine exposure. As previously noted, repeated cocaine exposure leads to alterations in GLU and metabotropic GLU receptors (mGLURs) in neurotrans-
mission [35], therapeutic targets that as been investigated in preclinical studies. For example, preclinical studies have shown that GLU antagonists (i.e., selective NMDA antagonists) block the locomotor stimulant effects of cocaine [43], and decrease the incidence of cocaine induced convulsions and mortality in mice [44]. In addition, Shoshi et al. [45] examined both acute and chronic cocaine exposure on inhibitory and excitatory transmission in rats, and reported that cocaine’s mechanism of action influences GABA and GLU, as well as biogenic amines. Amine transport sites which uptake biogenic amines are reportedly inhibited with chronic cocaine exposure, thereby elevating the actions of endogenous neuromodulators, such as DA, serotonin, and norepinephrine [45]. Although several mechanisms of GLU transmission have been targeted with pharmacological therapies in animal models in the treatment of cocaine addiction, clinical studies in patients, still needs to be investigated.

Chronic cocaine exposure typically results in the sensitization to the drug implying that an individual may demonstrate an increase in response to cocaine over time. Cocaine sensitization is believed to be related to its intense euphoria [46], a process dependent on the activity of GLU receptors [47], and is paralleled by an increase in sensitivity to the proconvulsant effects of cocaine [48]. It is clear that cocaine abuse can result in alterations of cortical excitability through its influence on both GABA, and GLU neurotransmitters, and their associated neuromodulators, which lead to alterations in cortical excitability. The interplay between these elements is thought to be involved in the sensitization of cocaine that underlies the cravings for the drug. Furthermore, the hypothesis that cravings for cocaine involves a distributed neural network including the amygdale, anterior cingu late, orbitofrontal, and dorsal lateral prefrontal cortex (DLPFC) is starting to emerge [49]. To this end, the DLPFC, may serve as a suitable target for the treatment of cocaine addiction because of its connections to the limbic brain areas (i.e., the ventral pallidum) mediated by both GABAergic and peptidergic transmission.

To date, there is no effective treatment for cocaine abuse despite the number of pharmacotherapy regimes proposed [50]. An effective treatment for cocaine users, which targets the neural mechanisms associated with chronic cocaine administration and sensitization, is needed. Accordingly, TMS can provide a means to diagnose alterations in cortical excitability using different TMS paradigms. Importantly, rTMS applied to the DLPFC represents a potential treatment in cocaine addiction given that rTMS has been shown to enhance GABA’s neurotransmission [17] through increased cortical inhibitory activity [51].

TMS and Cocaine Abuse

Boutros and colleagues in 2001 were the first to demonstrate altered cortical excitability in SUDs using TMS (Table 1). In this study they compared the resting MT (RMT) in cocaine users to healthy controls. A significant elevation in RMT in both the right and left hand motor area was found in cocaine-dependent subjects as compared to the healthy controls. Furthermore, the authors posit that this increase in RMT reflects an increase in cortical inhibition that may also be associated with adaptation to cocaine’s effects that promote cortical excitability via changes in brain GABA and GLU neurotransmission.

The second and third studies that employed TMS to evaluate changes in the cortical excitability of chronic cocaine users through examined CSP [52], and LICI/ICF [53]. In these studies, an elevation in RMT in chronic cocaine users was replicated. Furthermore, active MT (AMT), where subjects are instructed to contact their hand at 25% of maximal effect, was also elevated in 19 cocaine-dependent users as compared to 12 age-matched healthy controls [52]. Boutros and colleagues (2005) also examined the CSP in cocaine-dependent users and its relationship with cocaine-induced paranoia, and found no differences in CSP duration between cocaine users and healthy controls. However, in cocaine-dependent subjects who also suffered from cocaine-induced paranoia demonstrated longer CSPs in comparison to cocaine-dependent subjects free from cocaine-induced paranoia. In a later study that examined LICI/LICF with paired pulse TMS paradigms found, an increase in LICF was found in ten cocaine-dependent subjects as, however, LICI was reported normal compared to ten age-matched healthy controls [53].

The aforementioned studies are the first to demonstrate altered cortical excitability in cocaine-dependent individuals using TMS. These findings indicate that the RMT and AMT are elevated in cocaine-dependent subjects that were absten nent from cocaine for at least 3 weeks, and may be associated with an adaptation to those effects of cocaine that promote cortical excitability and seizures [52, 54]. Although, MTs were found to be elevated in the cocaine users indicative of elevated cortical inhibition, no alteration in cortico-cortical inhibitory paradigms (i.e., CSP or LICI) was observed. To this end, the authors posit that the main compensatory or protective mechanism for balancing excitatory and epileptogenic effects of chronic cocaine use is mediated via membrane cellular mechanisms, as MT is reflective of sodium channel conductivity and neuronal stability [55]. The fact that LICF was enhanced in this group complicates the authors’ claim that enhanced MT is in part due to enhanced cortical inhibition, as LICF is reflective of excitatory mechanisms. As such, Sundaresan et al. (2007) suggests that glutamatergic excitability via NMDA and/or non-NMDA receptors may be responsible for the elevation in LICF [15, 56], in line with animal models that report an attenuation of cocaine-induced seizures with NMDA and non-NMDA antagonists. Moreover, GLU-mediated LICF, and not LICI, may be more closely associated with the risk of seizures in mice [39, 57]. Finally, the combined decrease in axonal excitability measured via MT and increased facilitation measured via LICF demonstrates that the effects of chronic cocaine use on the motor cortex are complex and still not completely understood [53].

MDMA and Cortical Excitability

3, 4-methylenedioxymethamphetamine (MDMA) is typically used synonymously with ecstasy; however, ecstasy does not necessarily contain MDMA [58]. For the purposes of this paper, the term, ecstasy users will be referred to as MDMA users. Animal and human studies both indicate that MDMA has toxic effects on the brain, especially in the occipital cortex [59-61]. Furthermore, MDMA exerts its prin-
Specifically, MDMA has been shown to induce both the release serotonin, and also block its reuptake, followed by a depletion of neuronal serotonin stores. Moreover, the initially released serotonin activates post-synaptic receptors located on GABA interneurons leading to a decrease in GABAergic transmission. In addition to MDMA’s effect on the serotonin system, MDMA also modulates norepinephrine, DA, and the cholinergic neurotransmitter systems. Due to MDMA’s effect on neurotransmission, it is hypothesized to induce changes in the pathophysiology of MDMA users. In the next reviewed study, TMS is utilized to examine cortical excitability in NMDA users.

### TMS and MDMA Abuse

To date, one study has examined cortical excitability in heavy MDMA users with TMS [65] (Table 1). Heavy MDMA users, in this study, were defined as individuals who use 50 or more tablets containing MDMA as the active ingredient at a does of 100 mg per tablet. Excitability of the visual cortex was examined in 10 MDMA users and ten age-matched healthy controls by measuring the phosphene threshold (PT). The phosphene threshold, like the MT, is a method used to derive the intensity used in TMS stimulation, and is defined as the minimum intensity required to induce light sensations, called phosphes. In MDMA users, PT was found to be significantly lower as compared to healthy individuals, and was negatively correlated with the frequency of consumption. Furthermore, the frequency of MDMA use was also positively correlated with MDMA users who experience visual illusions. These findings, therefore, provide evidence of increased excitability in the visual cortex as a result of chronic MDMA use, which may be linked to its effects on the serotonin system.

### Nicotine and Cortical Excitability

The subjective and physiological effects of smoking are caused by the central actions of nicotine [66], the primary

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### Table 1. Review of Studies Examining TMS to Study Cortical Excitability in Substance Use Disorders

<table>
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<tr>
<th>Study</th>
<th>Objectives</th>
<th>Substance Use Status</th>
<th>No. of Subjects</th>
<th>Findings</th>
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<tr>
<td>Boutros et al. 2001</td>
<td>RMT in cocaine dependent vs healthy subjects</td>
<td>3 week cocaine and alcohol abstinence</td>
<td>10 cocaine dependent and 10 healthy subjects</td>
<td>↑ RMT (right and left hemisphere) in cocaine dependent vs healthy subjects</td>
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<td>↑ CSP (right hemisphere) in paranoid cocaine-dependent vs non-paranoid cocaine-dependent</td>
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<td>Sundaresan et al. 2007</td>
<td>RMT, LICF, LICI in cocaine dependent vs healthy subjects</td>
<td>3 week cocaine and alcohol abstinence</td>
<td>10 cocaine dependent and 10 healthy subjects</td>
<td>↑ RMT (left hemisphere) in cocaine dependent vs healthy subjects</td>
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<td>↑ LICF (left hemisphere) in cocaine dependent vs healthy subjects</td>
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<td>↔ LICI (left hemisphere) in cocaine dependent vs healthy subjects</td>
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<td>Oliveri &amp; Calvo 2003</td>
<td>PT in MDMA dependent vs healthy subjects</td>
<td>3 day MDMA abstinence</td>
<td>10 MDMA dependent and 10 healthy subjects</td>
<td>↓ PT in MDMA dependent vs healthy subjects</td>
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<td>Lang et al. 2007</td>
<td>Exp 1: SAI, LAI; Exp 2: RMT, AMT, SICI/ICF, LICI, active MEP, CSP, I/O curves in nicotine dependent vs healthy subjects</td>
<td>Nicotine dependent subjects allowed to smoke until 1 hr prior to testing</td>
<td>Expt 1: 12 nicotine dependent and 12 healthy subjects; Expt 2: 19 nicotine dependent and 19 healthy subjects</td>
<td>Expt 1: ↑ SAI in nicotine dependent vs healthy subjects</td>
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<td>↑ LICI (left hemisphere) in cocaine dependent vs healthy subjects</td>
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<td>↓ ICF in nicotine dependent vs healthy subjects</td>
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constituents of tobacco. Nicotine’s action on the brain has been well studied. For example, neuroimaging studies report that even acute administration of nicotine induces reductions in global brain activity, particularly in the prefrontal cortex, thalamus, and visual systems. At the cellular level, nicotine binds to nicotinic acetylcholine receptors (nAChRs), which are ligand-gated ion channels consisting of 5 different subunits [67]. Moreover, post-mortem studies indicate that nAChRs are located throughout the brain with highest to lowest distribution being: thalamus, basal ganglia, cerebral cortex, hippocampus, and cerebellum [68].

Chronic nicotine exposure generates tolerance to the drug, and like cocaine abuse, cravings and withdrawal symptoms result when the drug is terminated. Unlike most neurotransmitter receptors, nAChRs are upregulated in both animals and humans from chronic nicotine exposure [69], thereby increasing the number of nicotine receptors [70, 71]. Moreover, an increase in nAChRs results in an influx of calcium ions mediating an increase in DA, serotonin, acetylcholine, GABA, and GLU levels in the brain [67]. Nicotine receptors, thus, are considered neuromodulators of other neurotransmitter pathways. In particular, animal studies collectively show that nicotine: 1) enhances GLU transmission in cortical pyramidal neurons [72]; 2) increases the levels of norepinephrine in striatal neurons to activate the release of GABA from hippocampal neurons [73]; and 3) releases serotonin from the dorsal raphe neurons [74] and of striatal neurons in rat brain slices [75] via activation of nicotinic receptors. In addition to nicotine receptor’s ability to modulate other neurotransmitter systems, they also have been reported to propagate fast ACh neurotransmission in certain areas of the rat brain, including hippocampal interneurons [76]. Finally, chronic exposure can also lead to oxidative stress. For example, chronic smokers have more than 25% lower circulating concentrations of antioxidants, as compared to healthy individuals [77], which may be linked to enhanced levels of GLU leading to neurotoxicity, and ultimately, cell death [78].

Together these studies indicate that nicotine’s mode of action on the brain involves several neurotransmitters and their associated neuromodulators, leading to alterations in the brain that underlie nicotine addiction and withdrawal. In this connection, a study examining the cortical excitability in chronic smokers using both single and paired-pulse TMS paradigms will be reviewed in the following section.

**TMS and Nicotine Dependence**

Lang and colleagues were the first to examine cortical excitability in chronic cigarette smokers using TMS [79] (Table 1). In this study, chronic smokers were defined as individuals who continuously consumed at least 10 cigarettes per day within the last 4 years with a score on the Fagerstrom Test for Nicotine Dependence of 1-5. Prior to experimental testing, chronic smokers were instructed to smoke their final cigarette one hour prior to the test in order to control for acute nicotine effects across this group. Experiment one examined afferent inhibition; while in experiment two, motor cortical excitability was measured using single and paired-pulse TMS paradigms in chronic smokers and healthy subjects. Altered cortical excitability in chronic smokers was observed as compared to healthy individuals. More specifically, SAI and CSP were significantly elevated, while ICF and active MEP were reduced in chronic smokers relative to the healthy group. However, no differences were found in LAI, I/O curves or the intensities of 1 mV peak-to-peak MEP, electric motor threshold, RMT, and AMT. Lang et al., therefore, are the first to use TMS to demonstrate cortical excitability alterations in chronic smokers. These two experiments demonstrate enhanced cortical inhibition in chronic smokers evidenced by: 1) a reduction active MEP which is a global measure of cortical excitability; 2) enhanced SAI, reflective of the inhibitory effect on the motor cortex induced by somatosensory afferents; 3) decreased ICF; and finally 4) prolonged CSP. These findings, therefore, demonstrate nicotine’s effect on the cholinergic inhibitory circuits, either directly or indirectly, which may account for enhanced cortical inhibition found in chronic smokers mediated possibly through enhanced GABA_R neurotransmission.

**REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION**

Repetitive TMS (rTMS) involves trains of repeated pulses applied to the cortex at the same stimulus intensity. Cortical changes induced by rTMS have been demonstrated in both preclinical animal models, and in combined rTMS and neuroimaging techniques in humans. For example, in the rat brain, rTMS has been reported to induce significant changes in the neuronal circuits indicated by specific alterations in behaviour, and an attenuation of hypothalamo-pituitary-adrenocortical system [80, 81]. Further, rTMS has been shown to increase DA in the dorsal hippocampus [81], and the nucleus accumbens [81, 82] using microdialysis in rodents. In humans, rTMS applied to the motor cortex in healthy individuals was found to significantly lengthen the CSP, a measure of GABA_R receptor-mediated cortical inhibition [51]. In addition, a combined rTMS/positron emission tomography (PET) study reported elevations in extracellular DA concentration following 10 Hz rTMS administered to the DLPFC [83]. In this regard, rTMS has shown great promise in medication-resistant patients who suffer from schizophrenia [84], depression [85], Parkinson’s disease [86], obsessive-compulsive disorder and Tourette’s syndrome [87], and more recently, SUDs [88, 89] through its effects on neurotransmission.

**REPETITIVE TMS IN THE TREATMENT FOR SUBSTANCE USE DISORDERS**

**RTMS Treatment in Cocaine Abuse**

Recently, Camprodon and colleagues (2007) examined rTMS as a potential treatment for the cravings experienced by cocaine-dependent individuals (Table 2). In this randomized cross-over design, two sessions of 10 Hz rTMS was administered to the right and left DLPFC at 90% RMT. Visual analogue scales were administered to obtain level of cocaine cravings 10 minutes before, immediately, and 4 hours following rTMS treatment. RTMS applied to the right, but not the left DLPFC, was found to decrease subjects’ level of cravings for cocaine with these differences existing between baseline and immediately after rTMS session, and baseline and 4 hours post rTMS session. These findings, therefore, provide the first demonstration that a single session of rTMS applied over the right DLPFC is effective in reducing co-
Repetitive TMS Treatment and Nicotine Dependence

Although, eight treatments including: 1) bupropion; 2) varenicline; 3) nicotine polacrilex (nicotine chewing gum); 4) transdermal nicotine administration (nicotine skin patch); 5) nicotine nasal spray; 6) nicotine lozenges; 7) nicotine inhaler; and 8) psychosocial therapy, are proven to be approximately double to triple the rate of smoking cessation [91, 92], an effective treatment is still needed to target the proximately double to triple the rate of smoking cessation.

In the second double-blind cross-over design study, 14 individuals who wished to stop smoking were administered 2 active, and 2 placebo-control sham rTMS in a randomized order for 4 consecutive days. High-frequency (20 Hz) rTMS was applied to the left DLPFC at an intensity of 90% RMT, and smoking cravings were measured at baseline and 30 minutes after the rTMS session using a 100-point visual analogue scale. In addition, the number of cigarettes freely smoked in a 6-hour time period was also recorded following the rTMS session. During this 6 hour time period, the number of cigarettes smoked following rTMS applied to the left DLPFC was significantly decreased, with no change in the level of cravings. These findings strongly suggest that the effect of rTMS may be similar to nicotine’s action on the reward systems of the brain via blocking neuronal uptake of DA [95], as demonstrated in both animal and human studies [81, 83, 93] that is likely mediated through GABA_B receptor mechanisms [51]. Treatment with high-frequency rTMS was, therefore, found to reduce the level of cravings for cigarettes in the pilot study, although this finding was not replicated in the second study. Additionally, the second study demonstrated reduced smoking consumption following rTMS treatment, thus contributing to the preliminary evidence of the utility of rTMS treatment in smoking dependence. Future replication studies are greatly needed to evaluate the potential of rTMS in the treatment of nicotine dependence through a reduction in the levels of cravings and its consumption.

LIMITATIONS AND FUTURE DIRECTIONS

The studies reviewed in this paper provide strong evidence of altered cortical excitability in individuals with SUDs indexed through TMS. The ability of TMS to differentially measure inhibitory and excitatory neural mechanisms has provided insights into the neurotransmitter systems affected following chronic use of psychoactive substances. The studies, however, are limited in several important ways. First, alterations in corticospinal measures (e.g., MT or MEP amplitude) observed in individuals with SUDs may be a result of brain atrophy associated with cocaine, MDMA or nicotine use rather than modifications in cortical excitability. As such, with brain atrophy, the distance between the scalp and the cortex increases, an increase in MT is reported [96]. Future studies, therefore, examining the relationship between brain atrophy and cortical excitability in a population of people with SUDs should ascertain the underlying mechanisms leading to alterations in cortical excitability.

Another critical limitation of the aforementioned studies reviewed is the lack of data collected on other comorbidities associated with the subject group studied. As such, studies that examined cortical excitability in cocaine and MDMA dependent individuals did not record the use of other psychoactive substances such as, alcohol and nicotine use often associated with cocaine and MDMA abuse. Furthermore,
psychopathology was not ruled out in these individuals to directly attribute drug abuse to alterations in cortical excitability. Replication studies would therefore benefit from increased control over these variables to strengthen the evidence of altered cortical excitability underlying the pathophysiology in SUDs.

Additionally, these studies examining cortical excitability deficits in SUDs are limited in that they tested small sample sizes and more importantly, these afflicted groups with altered cortical excitability may simply be vulnerable to the abuse of psychoactive substances rather than the reverse. As such, much work has investigated the association between personality types and the gene, catechol-o-methyltransferase (COMT), important in DA regulation [97-99]. Genetic studies have revealed that individuals with the higher activity COMT genotype (i.e., homozygous Val allele), results in lower synaptic DA levels, and is associated with patients with SUDs [98, 100] with a stronger association in women [99]. Repetitive TMS, therefore, may prove to be the most optimal treatment in individuals with high activity COMT genotypes that abuse substances, as rTMS is known to enhance DA levels in the brain [81, 82].

Repetitive TMS has been shown to induce cortical changes in preclinical and clinical investigations through its effects on neurotransmission [51, 80, 81, 83, 101]. The treatment studies that examined the efficacy of rTMS in the treatment of cocaine and nicotine dependence are the first in this field. Although the reviewed work represents promise in the use of rTMS in the treatment of SUDs, certain limitations must be addressed. First, the use of larger sample sizes in the examination of rTMS as a potential treatment in persons with SUDs with aims to reduce the level of cravings and consumption would strengthen this preliminary evidence with increased statistical power. Second, the studies reviewed here are limited to the short-term effects of rTMS on the level of cravings and consumption, and fail to examine the efficacy of rTMS’ long-term effects and its potential to achieve abstinence. Future longitudinal treatment studies in larger SUD patient populations, thus has the potential to reveal the optimal rTMS parameters in the treatment of SUDs.

In addition, preclinical studies using animal models to examine the efficacy of rTMS in the treatment of SUDs represents an area that needs to be further explored. In this connection, preliminary studies using animal models report increases in DA levels following rTMS in cocaine [81], and in morphine-sensitized rodents [82], thereby exerting its effects directly on the reward system involved in SUDs. Animal models, therefore, provide an invaluable means to examine cortical excitability changes induced by rTMS at a molecular level, and to evaluate its effect on the level of cravings and consumption in the treatment of SUDs.

Recently transcranial direct current stimulation (tDCS) has been examined as an alternative to rTMS in the treatment of brain disorders. Similar to rTMS, tDCS has the potential to modulate brain activity in a non-invasively; however with this method, a weak DC current is applied to the brain that is polarity-dependent. To this end, anodal stimulation applied to the motor cortex has been reported to enhance cortical excitability, while cathodal currents reduce cortical excitability [102, 103]. The ability of tDCS to differentially enhance cortical excitability or inhibition is invaluable in treating brain disorders with altered cortical excitability including SUDs. By connection, tDCS has shown promise in the treatment of major depression [104], Parkinson’s disease [105], and most recently, in the treatment of alcoholism [106]. The utility of tDCS as a potential treatment for brain disorders is in its infancy. Future studies, therefore, are needed to further evaluate the efficacy of tDCS as a treatment in SUDs.

CONCLUSIONS

Transcranial magnetic stimulation has provided a safe and non-invasive method to evaluate the neurophysiology of the human cortex. Moreover, TMS has shown promise in the diagnosis of several patient populations, including SUDs. Although, this research remains in its infancy, TMS paradigms have demonstrated alterations in cortical excitation in chronic cocaine, nicotine, and MDMA users. Moreover, rTMS has been reported to modulate neurotransmission, and early studies suggest that it may be a promising treatment for a number of SUDs. Future studies, therefore, are clearly needed to further our understanding of SUDs vis-à-vis cortical excitability and its treatment.

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ABBREVIATIONS

| AMT      | Active Motor Threshold |
| COMT     | Catechol-O-Methyltransferase |
| CS       | Conditioning Stimulus |
| CSP      | Cortical Silent Period |
| DA       | Dopamine |
| DLPFC    | Dorsal Lateral Prefrontal Cortex |
| EEG      | Electroencephalography |
| GABA     | γ-aminobutyric Acid |
| GVG      | Gamma-vinyl γ-aminobutyric Acid |
| GLU      | Glutamate |
| I/O      | Input-Output |
| LAI      | Long Afferent Inhibition |
| LIC1     | Long Interval Cortical Inhibition |
| mGlU Rs  | Metabolic Glutamate Receptors |
| MDMA     | 3,4-methylenedioxymethamphetamine |
| MEP      | Motor Evoked Potential |
| MT       | Motor Threshold |
| nAChR    | Nicotinic Acetylcholine Receptors |
| NMDA     | N-methyl-D-aspartate |
| PT       | Phosphene Threshold |
PET = Positron Emission Tomography
rTMS = Repetitive Transcranial Magnetic Stimulation
RMT = Resting Motor Threshold
SICI = Short Interval Cortical Inhibition
SAI = Short Afferent Inhibition
S/L ICF = Short/Long Intracortical Facilitation
SUD = Substance Use Disorder
TS = Test Stimulus
tDCS = Transcranial Direct Current Stimulation
TMS = Transcranial Magnetic Stimulation

Key Learning Objectives:
1. Summarize the studies which employed TMS to measure cortical excitability in patients with SUDs.
2. Better understanding of the effect of psychoactive substances on cellular communication leading to alterations in cortical excitability in patients with SUDs.
3. Examine the efficacy of rTMS as a treatment in SUDs targeting both the level of cravings and consumption of the drug abused.

Future Research Directions:
1. Examine the effect of brain atrophy on cortical excitability in patients with SUDs in a longitudinal design.
2. Further examine the effect of rTMS delivered over the right versus left DLPFC in the treatment of SUDs.
3. Examine the efficacy of daily rTMS administration to the DLPFC in the treatment of SUDs in a longitudinal design.
4. Determine the optimal rTMS parameters (i.e., frequency, intensity, and duration) in the treatment of SUDs.

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