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Low frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex transiently increases cue-induced craving for methamphetamine: A preliminary study

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) can temporarily interrupt or facilitate activity in a focal brain region. Several lines of evidence suggest that rTMS of the dorsolateral prefrontal cortex (DLPFC) can affect processes involved in drug addiction. We hypothesized that a single session of low-frequency rTMS of the left DLPFC would modulate cue-induced craving for methamphetamine (MA) when compared to a sham rTMS session.

Methods: In this single-blind, sham-controlled crossover study, 10 non-treatment seeking MA-dependent users and 8 healthy controls were randomized to receive 15 min of sham and real (1 Hz) DLPFC rTMS in two experimental sessions separated by 1 h. During each rTMS session, participants were exposed to blocks of neutral cues and MA-associated cues. Participants rated their craving after each cue block.

Results: In MA users, real rTMS over the left DLPFC increased self-reported craving as compared to sham stimulation (17.86 ± 1.46 vs. 24.85 ± 1.57, $p = 0.001$). rTMS had no effect on craving in healthy controls. One Hertz rTMS of the left DLPFC was safe and tolerable for all participants.

Conclusions: Low frequency rTMS of the left DLPFC transiently increased cue-induced craving in MA participants. These preliminary results suggest that 1 Hz rTMS of the left DLPFC may increase craving by inhibiting the prefrontal cortex or indirectly activating subcortical regions involved in craving.

1. Introduction

Methamphetamine (MA) abuse is a substantial public health problem in the United States and in other parts of the world. Each year, 24.7 million people use amphetamine or methamphetamine (MA) worldwide, which represents more consumers than that for heroin or cocaine (United Nations Office on Drugs and Crime, 2008; http://www.unodc.org/documents/about-unodc/AR08_WEB.pdf). Approximately 13 million people 12 years and older have abused MA in their lifetimes, with approximately 353,000 current users in the US in 2010 (National Survey on Drug Use and Health, 2010; http://www.drugabuse.gov/publications/topics-in-brief/methamphetamine-addiction-progress-need-to-remain-vigilant). Unfortunately, there are no Food and Drug Administration (FDA) approved medications for MA dependence and thus behavioral interventions remain the mainstay of treatment programs (Colfax et al., 2010; Karila et al., 2010). These data emphasize the importance of developing new treatment approaches for MA users.

Chronic MA abuse is associated with profound alterations in brain circuits and neurochemical markers, particularly in early abstinence (Baicy and London, 2007; Chang et al., 2007). These changes include higher activity in the amygdala and lower activity in the infralimbic cortex, deficits in global metabolism, and altered neural integrity (Volkow et al., 2001a). Previous imaging studies also reported that MA users showed reduced activation in frontal cortex regions while they performed a color-word Stroop task, which requires cognitive control (Nestor et al., 2011; Salo et al., 2013, 2009). In a recent animal study by our group, we reported that prefrontal cortex-specific alterations in neuronal function might play a key role in MA induced attentional deficits and drug seeking (Parsegian et al., 2011). Together, these data suggest that dysfunction in prefrontal cortical areas that are important for executive function underlies cognitive control deficits associated with MA dependence (Nestor et al., 2011).

Craving for an addictive substance may be described as an intense subjective urge to acquire and ingest drug(s), and may be

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elicited even after periods of sustained abstinence by exposure to stress, to a priming dose of the drug, or to environmental cues previously associated with use of the drug (Carter and Tiffany, 1999; Mahoney et al., 2007). Craving for MA is commonly reported by heavy users of the drug and may increase the risk of relapse in newly abstinent individuals (Tolliver et al., 2010). MA cravings have been shown to involve activation of the prefrontal cortex, nucleus accumbens, and the anterior insula, similar to cravings for other addictive substances such as cocaine, opiates, and alcohol (Berman et al., 2008; Brody et al., 2002; George et al., 2001; Myrick et al., 2004). Recently, a treatment study showed that bupropion reduced acute MA-induced subjective effects and reduced cue-induced craving (Newton et al., 2006). As such, reducing cue craving might be a strategy to help prevent relapse and treat MA dependence.

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technology that can focally stimulate the brain in awake individuals (Barker et al., 1985). This relatively new method allows modulation of discrete brain areas of the awake and conscious subject under study. The pulsatile electromagnetic field generated around the coil crosses the skull and directly depolarize neurons in the underlying cortices, with immediate excitatory effects (Padberg and George, 2009). In humans, repetitive TMS (rTMS) can induce changes in cortical excitability. Distinct from the immediate effects of TMS, rTMS leads to different cumulative effects within the region of the brain being stimulated (Fitzgerald et al., 2006). Depending on the frequency of the pulsed magnetic fields, rTMS can be used to either stimulate (high frequency) or suppress (low frequency) neural activity in a particular cortical region (Chen et al., 1997; Pascual-Leone et al., 1994). Growing evidence generally indicates that serial rTMS at 1 Hz has an overall inhibitory effect on the region stimulated. An example of this is temporary inhibition of the motor cortex during digit movement and on the size of motor evoked potentials (Chen, 2000; Hallett, 2000). In contrast, some evidence has shown that high-frequency ($\geq$5 Hz) rTMS is excitatory in nature (Fitzgerald et al., 2006; Haraldsson et al., 2004). In addition, the effects of rTMS are not limited to the exact site of stimulation and can induce changes in distant interconnected sites of the brain, including subcortical regions (Bohning et al., 1999; Li et al., 2004). In clinical depression, studies have reported opposite effects of high and low frequency rTMS on regional brain activity, with high frequency leading to increased regional cerebral blood flow (rCBF) and low frequency producing decreased rCBF (Speer et al., 2000).

Commonly employed as a clinical research tool, daily rTMS for 4–6 weeks is a recently approved US Food and Drug Administration (FDA) treatment for depression (George et al., 2010; George and Post, 2011). While some studies have shown potential efficacy in treating some aspects of drug addiction (Barr et al., 2011; Feil and Zangen, 2010), it has not been studied before in MA addiction. As noted above, low frequency ($\leq$1 Hz) rTMS inhibits neuronal firing in a localized area and is used to induce virtual lesions in order to examine a brain region's role in different tasks (Chen et al., 1997; Iyer et al., 2003), while high frequency rTMS ($\geq$5 Hz) tends to be excitatory and can cause an increase in neuronal depolarization under the stimulating coil (Haraldsson et al., 2004). Previous studies of rTMS over the DLPFC support the ability of rTMS to transiently reduce the level of craving in tobacco (Li et al., 2013), alcohol (Mishra et al., 2010), and cocaine (Camprodon et al., 2007) addicted patients. To the best of our knowledge, no study has used rTMS to modulate cue-induced craving in a MA dependent population. As such, it would be very important as a first step to evaluate whether a single session of rTMS is safe, tolerable, and efficacious for craving modulation in MA users.

The purpose of this randomized, single blind sham-controlled study was to test whether low frequency rTMS of the left DLPFC would modulate cue-induced craving in adult MA users. We hypothesized that low frequency active rTMS would modulate self-reported MA cravings more than sham rTMS in MA users. In the current study, we used low frequency rTMS (and not high frequency rTMS) to investigate cue craving in MA users. This choice was primarily done for safety reasons. Individuals with a history of MA use exhibit significantly increased cortical excitability (Flavel et al., 2012) and MA users often show increased seizure susceptibility (Slamberova et al., 2011). Thus, the potential exists that high frequency TMS in MA users may cause seizures. Moreover, no study has been done in an addicted population with low frequency rTMS. If the theory of prefrontal governance over craving is correct, then low frequency rTMS, which is inhibitory, might influence craving and perhaps even worsen it.

2. Methods and materials

2.1. Participants

Ten healthy, non-treatment seeking individuals who met DSM-IV-TR (First and Tasman, 2004) criteria for current MA dependence participated in this study. Eight healthy control participants who had never used MA were also recruited. Control subjects were matched to the MA group for gender, race, and other biographical characteristics. All control subjects had negative urine drug screens during screening. No control subjects currently used tobacco products or had a lifetime history of any drugs of abuse. All participants were financially compensated for their participation.

Participants were recruited through local television, radio advertisements, and word-of-mouth. Participants underwent 1–2 weeks of telephone and in-person screening. The first in-person screening was preceded by oral and written informed consent approved by the Institutional Review Board (IRB) of the Medical University of South Carolina (MUSC). Screening included the MINI diagnostic psychiatric interview (Sheehan et al., 1998), general medical history, general physical and neurologic assessments, timeline follow back for multiple drugs and alcohol prior to informed consent, and concurrent medication history. Laboratory studies included the following: hematology, comprehensive blood chemistries, routine urinalyses, and daily urine drug screens for amphetamine, MA, opiates, marijuana, benzodiazepines, cocaine and barbiturates. Participants with significant hepatic, renal, cardiac or neurological (including stroke, seizure, migraine, head trauma) impairment or a history of major Axis I disorders such as bipolar disorder, schizophrenia, dementia, or current depressive disorder were excluded. Participants were also excluded if they had ferromagnetic implants or if they had taken any medication during the previous thirty days that might alter central nervous system (CNS) function or CNS blood supply (e.g., calcium channel agonists, sedative-hypnotics, over-the-counter CNS agents). Control subjects were subjected to daily urine drug screens and breathalyzers. Demographic and MA using-habits profile data were collected at baseline.

2.2. Experimental design

A randomized, single-blind, sham and healthy controlled study was employed in 10 MA users and 8 healthy controls who received 2 different types of brain stimulation during one visit: sham rTMS and real rTMS of the DLPFC, with an hour interval between treatment sessions (see Fig. 1 for details). The order of stimulation was randomized and counterbalanced across participants. The randomizations were performed with a web-based randomization generator (www.randomization.com). Participants were blind to the treatment arm.

2.3. Cue craving presentation and assessments

Each cue craving presentation lasted for approximately 15 min. The cue exposure presentation consisted of 40 MA pictures and 40 neutral pictures. These pictures of MA-related (drug, paraphernalia, or persons using the drug) and neutral pictures were selected as described previously (Tolliver et al., 2010). Each picture was presented twice for 4 s. Participants were instructed to pay close attention to the pictures. Standard visual analog scales (VAS) that consisted of 100 mm lines with anchoring statements at both ends were completed after each block of picture presentation on a desktop computer. Subjects were asked to rate craving with 0 mm being "no craving at all" and 100 mm representing "the most craving I have ever had". Cue craving presentation and VAS were conducted during real rTMS or sham stimulation as well as pre experiment baseline.

2.4. rTMS procedure

2.4.1. Determining motor threshold and locating cortical targets. Focal TMS was delivered by a focal figure-of-eight magnetic air-cooled coil (each wing 70 mm in diameter) connected to a MAGSTIM Super Rapid stimulator (Magstim Co., Whitland, Dyfed,