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Left frontal pole theta burst stimulation decreases orbitofrontal and insula activity in cocaine users and alcohol users

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ABSTRACT

Background: Preclinical research has demonstrated a causal relationship between medial prefrontal cortex activity and cocaine self-administration. As a step towards translating those data to a neural circuit-based intervention for patients, this study sought to determine if continuous theta burst stimulation (cTBS) to the left frontal pole (FP), would attenuate frontal-striatal activity in two substance-dependent populations.

Methods: Forty-nine substance dependent individuals (25 cocaine, 24 alcohol) completed a single-blind, sham-controlled, crossover study wherein they received 6 trains of real or sham cTBS (110% resting motor threshold, FP1) each visit. 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 $p < 0.05$)

Results: Among cocaine users, real cTBS significantly decreased evoked BOLD signal in the caudate, accumbens, anterior cingulate, orbitofrontal (OFC) and parietal cortex relative to sham cTBS. Among alcohol users, real cTBS significantly decreased evoked BOLD signal in left OFC, insula, and lateral sensorimotor cortex. There was no significant difference between the groups.

Conclusions: These data suggest that 6 trains of left FP cTBS delivered in a single day decreases TMS-evoked BOLD signal in the OFC and several cortical nodes which regulate salience and are typically activated by drug cues. The reliability of this pattern across cocaine- and alcohol-dependent individuals suggests that cTBS may be an effective tool to dampen neural circuits typically engaged by salient drug cues. Multiday studies are required to determine it this has a sustainable effect on the brain or drug use behavior.

1. Introduction

Through technical and experimental advances in preclinical neuroscience research over the last 10 years, we have an increasingly sophisticated understanding of the neural circuitry of substance dependence. Through optogenetics (Cao et al., 2011; Ferguson and Neumaier, 2012; Steinberg and Janak, 2013) and designer receptors exclusively activated by designer drugs (DREADDs;(Ferguson and Neumaier, 2012)), it is possible to directly increase or decrease cocaine self-administration via stimulation or inhibition of the nucleus accumbens, a core brain region facilitating reinforced behavior and reward saliency. This causal relationship has also been demonstrated in alcohol self-administration (Bass et al., 2013; Cassataro et al., 2014). Beyond direct stimulation of the ventral striatum however, it is also possible to change cocaine self-administration through infralimbic cortical stimulation (Peters et al., 2008). The rodent infralimbic cortex (IL) has strong projections to the multiple regions that modulate arousal, including the medial prefrontal, insular, entorhinal, and amydala cortex (Vertes, 2004). The IL is functionally and anatomically similar to the orbitomedial prefrontal cortex in primates (aka orbitofrontal cortex (OFC)) (Barbas, 1995; Barbas, 2000; Groenewegen and Uylings, 2000)

Given these promising preclinical data, there is strong momentum to develop a neural circuit-based treatment for clinical substance abuse. Transcranial magnetic stimulation (TMS) allows researchers to

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selectively activate or inhibit populations of neurons in humans. Through electromagnetic induction, repetitive pulses of TMS to the scalp will induce long-term potentiation-like (LTP-like) or long-term depression-like (LTD-like) effects in the cortical area beneath the coil in a frequency-dependent manner. Furthermore, 10 Hz rTMS to the frontal cortex induces a change in dopamine binding (Cho and Strafella, 2009; Strafella et al., 2001) in monosynaptic striatal targets. By applying either a single high frequency (> 10 Hz) or intermittent bursting frequency (intermittent theta burst stimulation; iTBS) to the cortex, it is possible to induce an LTP-like effect on both behavior and neural activity (as measured through neuroimaging (Cho and Strafella, 2009; Siebner et al., 2009), as well as electrophysiological recordings (Mueller et al., 2014)). By applying either a single low frequency (1–5 Hz) or continuous bursting frequency (cTBS), it is possible to induce an LTD-like effect. The effects these forms of stimulation have on neural circuits may be investigated using TMS/BOLD imaging. Single pulses of TMS causes a transient increase in BOLD signal beneath the TMS coil and in regions monosynaptically connected to the stimulated area (Baudewig et al., 2001; Bestmann et al., 2003; Bestmann et al., 2005; Bohning et al., 1999; Bohning et al., 2000; Bohning et al., 1998). In addition to a cortical BOLD response, this technique has been previously shown to target anatomically distinct dorsal and ventral striatal targets in the absence of task engagement (Hanlon et al., 2013).

When considering treatment development for addiction, one potential strategy is to attenuate activity in the frontal-striatal reward-motivation circuitry that is engaged by drug-related cues. Elevated resting state functional connectivity among brain regions typically involved in arousal and craving − including the nucleus accumbens, amygdala, cingulate cortex, parahippocampal gyrus, and ventral prefrontal cortex − have all been associated with poor abstinence rates (Camchong et al., 2014; McHugh et al., 2014). As with the IL in rodents, the OFC in primates has direct synaptic projections to a wide distribution of brain regions involved in regulating arousal including the insula, parahippocampal gyrus, and ACC. Consequently, if we could decrease connectivity in this circuit through LTD-like rTMS, we may be able to reduce substance induced pathological connectivity and ultimately dampen craving and improve clinical outcomes. However, before the field moves forward and initiates large scale clinical trials, it is scientifically prudent to determine if, in fact, rTMS to the mPFC can induce a causal change in baseline mPFC-striatal connectivity in a controlled manner is non-treatment seeking adult AUD and SUD individuals.

To address this question, we designed a single-blind, sham-controlled crossover study of 50 substance-dependent individuals who all received 6 trains of LTD-like cTBS (or sham) to the left frontal pole in a single day while viewing drug cues. Immediately before and after cTBS or sham, the brain response to mPFC stimulation was measured via interleaved TMS/BOLD imaging. This study design was based on pilot data from our laboratory that demonstrated that this paradigm induced selective decrease in OFC and striatal BOLD signal in a small cohort of chronic cocaine users. In the present study, we aimed to determine if this would generalize to a new, larger group of cocaine-dependent individuals and if it would affect alcohol-dependent individuals in a similar manner.

2. Methods

2.1. Overall protocol design

This single-blind, sham-controlled pilot study involved 1 Screening visit and 2 Scanning/Stimulation visits (occurring within 7–14 days of each other). At each scanning/stimulation visit, interleaved TMS/BOLD imaging data was acquired before and after exposure to 6 trains of real or sham continuous theta burst stimulation (cTBS). The order of real and sham visits was counterbalanced across study participants. Continuous TBS was applied over the left FP (landmark based on EEG 10–20 system: FP1). This landmark was coregistered with the T1 MRI for each individual in order to calculate the scalp-cortex distance. Immediately prior to the cTBS procedure, participants were prompted to recall their most recent experience using cocaine or alcohol through a standardized series of cue-induction questions. During the cTBS procedure they were instructed to imagine themselves in that scenario again (See Supplemental Data for standardized scripts). We tested the hypothesis that cTBS over the FP would induce LTD-like stimulus evoked brain activity in the FP and its projection regions, including cortical limbic areas and the ventral striatum, using interleaved TMS/BOLD imaging.

2.2. Participants and screening

Non-treatment seeking chronic cocaine users (n = 25) and alcohol-dependent individuals (n = 24) were recruited from the Charleston, SC metropolitan area using word-of-mouth advertising and digital and print media. Individuals were prescreened for TMS and MRI safety over the phone prior to being invited to the Center for Biomedical Imaging at the Medical University of South Carolina (MUSC). Participants signed informed consent documents approved by the MUSC Institutional Review Board. Following informed consent, participants completed several screening assessments including a brief medical history, an MRI/TMS safety screen, the DSM-IV based Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), the Becks Depression Inventory (Beck et al., 1996), and the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001). Participants were required to be TMS naïve, which was verified by participant report and prior study logs in our center. A multidrug urine panel (Quikvue 5-panel urine drug screen, Quidel, San Diego, CA) was given to all participants at the screening and scanning/stimulation visits. Participants were informed that they would be required to abstain from cocaine use for 48 h prior to cTBS due to the sensitivity of the test. Participants were allowed to drink alcohol in their typical patterns, but were required to have an undetectable breath alcohol level ($p < 0.001$) upon their arrival to the laboratory. This was done to minimize the risk of acute withdrawal. Participants were required to have a negative urine drug screen (including cocaine, methamphetamine, benzodiazepines, opiates) at the Scanning/Stimulation visits. Eleven of the cocaine-dependent participants, and none of the alcohol-dependent participants, had a positive UDS for cannabinoids at screening. Demographics and drug/alcohol use variables are described in Supplementary Table 1 (cocaine users), Supplementary Table 2 (alcohol users). For cocaine SUD gender was equally represented and they used cocaine on average for 19 ± 10 years on an average 3.6 ± 3.9 days a week but had less alcohol use but more smoking severity than AUD individuals. AUD individuals were younger (27 ± 5.7 yrs) more males than females, drank on average 7.4 ± drinks per drinking day and had AUDIT scores in the mild-moderate range. The MINI exam tested for potential influences of major depression, PTSD, panic disorder, manic episodes, social phobia, OCD, anorexia, general anxiety, and personality disorder. No participants met criteria for current diagnoses in any of these domains.

2.3. Scanning and stimulation visits

During both the real and sham stimulation visits, interleaved TMS/BOLD imaging data was acquired immediately before and after the cTBS protocol. Interleaved TMS/BOLD was acquired through a Magstim SuperRapid stimulator. The cTBS protocol was given via a Magventure X100-Magoption. Resting Motor Threshold (rMT) was determined in the MRI scanning room while the participant sat upright on the retracted bed (Fig. 1). Resting Motor Threshold (rMT) was determined separately for the cTBS. A thin foam sheet was placed under the coil for both hygiene purposes and patient comfort (Staples ©, Item: 425888, 0.02”/0.5 mm thick). The presence of this sheet likely caused a small decrease in the dose of rTMS delivered to all individuals. This was