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Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex reduces resting-state insula activity and modulates functional connectivity of the orbitofrontal cortex in cigarette smokers

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ABSTRACT

Background: Previous studies reported that repetitive transcranial magnetic stimulation (rTMS) can reduce cue-elicited craving and decrease cigarette consumption in smokers. The mechanism of this effect however, remains unclear. We used resting-state functional magnetic resonance imaging (rsfMRI) to test the effect of rTMS in non-treatment seeking smokers.
Methods: We used a single blinded, sham-controlled, randomized counterbalanced crossover design where participants underwent two visits separated by at least 1 week. Participants received active rTMS over the left dorsolateral prefrontal cortex (DLPFC) during one of their visits, and sham rTMS during their other visit. They had two rsFMRI scans before and after each rTMS session. We used the same rTMS stimulation parameters as in a previous study (10 Hz, 5 s-on, 10 s-off, 100% resting motor threshold, 3000 pulses).
Results: Ten non-treatment-seeking, nicotine-dependent, cigarette smokers (6 women, an average age of 39.72 and an average cigarette per day of 17.30) finished the study. rsFMRI results demonstrate that as compared to a single session of sham rTMS, a single session of active rTMS inhibits brain activity in the right insula and thalamus in fractional amplitude of low frequency fluctuation (fALFF). For intrinsic brain connectivity comparisons, active TMS resulted in significantly decreased connectivity from the site of rTMS to the left orbitomedial prefrontal cortex.
Conclusions: This data suggests that one session of rTMS can reduce activity in the right insula and right thalamus as measured by fALFF. The data also demonstrates that rTMS can reduce rsFC between the left DLPFC and the medial orbitofrontal cortex.

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1. Introduction

Nicotine dependence remains a great global public health concern (Rep., 2011). A previous research reported that the overall worldwide economic cost of smoking (from health expenditures and productivity losses together) reached $1852 billion in 2012 (Goodchild et al., 2017). Despite the availability of therapeutic options for smoking cessation, relapse rates persist at a high level (Piasecki, 2006; Pollak et al., 2007). Therefore, there is need of new and effective strategies to help cigarette smokers achieve abstinence.

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique (Barker et al., 1985) which has getting used not only as a research tool (Li et al., 2009; Ziemann, 2004) but also as a therapeutic intervention (Chae et al., 2004; George et al., 1997) for neuropsychiatric disorders. Recent studies, including our groups previous work, reveal a therapeutic effect of repetitive TMS (rTMS) on cigarette consumption (Amiaz et al., 2009; Dinur-Klein et al.,

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2014; Eichhammer et al., 2003) and cue-induced craving in nicotine dependence (Li et al., 2013b; Rose et al., 2011). No matter outstanding development in understanding the mechanisms of TMS for smoking cessation, it is clear that advanced innovative research remains needed.

Resting-state functional MRI (rsfMRI) has become an extremely interesting research field (Biswal et al., 2010; Murphy et al., 2013). Functional MRI was initially used to measure resting-state networks by Biswal and colleagues (Biswal et al., 1995; Fedota and Stein, 2015). rsfMRI is believed in relation to spontaneous, low frequency fluctuations in blood oxygen level-dependent (BOLD) signal (Zou et al., 2008). Two commonly used methods to measure resting-state functional connectivity (rsFC) are linear correlation and independent component analysis (ICA) s (Lee et al., 2013). Signal fluctuation reflects the strength of a functional connection between brain regions and offer a systems-level understanding of neural function (Honey et al., 2009; Rogers et al., 2007; Song et al., 2011). However, for clinical studies, abnormal functional connectivity between two or more related brain regions can not be interpreted as a disordered neural connectivity because the assessment is only the correlation between the two regions (Song et al., 2011). An alternative analytical method for rsfMRI is to measure the amplitude of low frequency fluctuation (ALFF) (Zou et al., 2008). The local spontaneous low frequency oscillations (LFO) are associated with local neuronal activation in brain disorders (Scholvinck et al., 2010; Jiang et al., 2011; Liu et al., 2006; Zang et al., 2007). Recently, clinical treatment studies demonstrated that the accurate localization of abnormal spontaneous brain activity was crucial for the therapeutic effects of drugs in specific diseases, e.g., depression and schizophrenia (Fryer et al., 2015; Liu et al., 2015). As an advance ALFF method, fractional ALFF (fALFF) has also been utilized in resting-state fMRI research (Zou et al., 2008). Therefore, we used fALFF to measure brain function of rsFMRI. fALFF allows, researchers to obtain stable data across scan sessions (Brewer et al., 2011) and making it an ideal tool for longitudinal studies, including pre-post treatment assessments (Song et al., 2011).

It has been reported that nicotine affects different neuronal circuits which are relative to disparate cognitive and affective processes (e.g., reward, learning, affect, executive control) (Fedota and Stein, 2015; Koob and Volkow, 2010). As shown in task activation studies (Hartwell et al., 2011; Li et al., 2013a), chronic nicotine exposure leads to abnormal functional connectivity in specific networks (Sutherland et al., 2013) and large-scale networks (Weiland et al., 2015). The left dorsolateral prefrontal cortex (DLPFC) is considered to be integral in the exertion of executive control over emotions of craving and limbic reward circuits related with smoking (da Silva et al., 2013; Goldstein and Volkow, 2011). In fMRI studies, researchers reported that smokers had hypo-activation of the DLPFC and hyper-activation of subcortical areas as compared to both controls and former smokers (Nestor et al., 2011). Recently another study demonstrated that decreased left DLPFC and increased PCC of percent BOLD signal change predicted subsequent smoking relapse (Loughead et al., 2015). Therefore, these findings suggest that hypo-activation of the DLPFC can cause the lack of control over smoking cigarette.

High frequency rTMS (greater than 5 pulses/s) can increase cortical excitability as demonstrated in motor cortex excitability paradigms (Chen, 2000). Subsequently, rTMS may exert its anti-craving effect by normalizing DLPFC function in smokers (Ni and Chen, 2015). In this study, we hypothesized that high-frequency TMS applied to the DLPFC would modulate rsFC in the frontostriatal pathway including the DLPFC, medial orbitofrontal cortex, and insula. Thus, we used rsfMRI to investigate the effect of a single session of rTMS on brain activity using fALFF and intrinsic functional connectivity of the left DLPFC-related circuits.

2. Methods and materials

2.1. Study design

This was a randomized, single-blind, sham-controlled crossover study in which participants received both active and sham rTMS over the left DLPFC, with a 1-week interval between treatments to avoid carryover effects (Fig. 1). The order of stimulation was randomized and counterbalanced across participants. The randomization was performed with a web-based randomization generator (www.randomization.com). Participants were blinded to treatment condition. Structural and resting state functional MRIs were performed before and after each rTMS session. At baseline, demographic and smoking habits profile data were collected. Participants were instructed to keep their regular smoking habits with the exception of not smoking for 2 h prior to each experimental visit. This brief period of abstinence was to ensure that participants had some degree of baseline craving and responsiveness to cigarette cues without the potential confound of a ceiling effect from prolonged abstinence (Hartwell et al., 2013a; Li et al., 2013a,b). Craving assessments were performed before and after each cigarette cue presentation in a fashion validated in our previous experiment (Li et al., 2013b).

2.2. Participants

We recruited 11 (6 women and 5 men) healthy, non-treatment seeking, nicotine-dependent cigarette smokers (DSM-IV) (≥10 cigarettes/day) between the ages of 18 and 60 through flyers, newspaper and internet advertisements. We excluded potential participants who used tobacco products other than cigarettes, those who currently used nicotine replacement therapy, those currently taking smoking cessation medications (Exe. bupropion or varenicline), or any other psychoactive medications, those with any medical conditions, those with significant current or past DSM-IV Axis I disorders, those who were pregnant, and those with non-nicotine substance dependence or abuse. All study procedures were approved by the Medical University of South Carolina Institutional Review Board and were in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. Participants provided informed consent and completed an initial assessment. Recent smoking was confirmed by collecting an exhaled carbon monoxide (CO) level (≥10 ppm) measured with a Micro-Smokelyzer (Bedfont Scientific Ltd., Kent, UK). We also completed a detailed tobacco use history, including the Fagerström Test for Nicotine Dependence (FTND) (Fagerstrom, 1978), and the Questionnaire of Smoking Urges-Brief (QSU-B) (Cox et al., 2001). We assessed current health by performing a physical examination, and we collected a urine sample to screen for illicit drug use.

2.3. Repetitive TMS

2.3.1. Determining resting motor threshold (rMT) and locating cortical targets. We determined the rMT of each participant at the beginning of each experimental visit prior to any exposure or ratings. RMT was determined using a MagPro double blinded rTMS Research System (MagVenture, Denmark) with a Cool-B65 Butterfly Coil (a combined active and sham coil). We positioned the coil over the area of the skull corresponding to the motor cortex, and adjusted the location until each pulse resulted in isolated movements of the right thumb (abductor pollicis brevis – APB). We then adjusted the output of the magnetic pulse until we found the lowest intensity that reliably produced thumb movement 50% of the time (Ziemann and Hallett, 2000). We used the position of the coil used for rMT assessment as the motor cortex target (M1). We then determined the approximate location of the left DLPFC by moving

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