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High-frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex restores attention bias to negative information in methamphetamine addicts

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ABSTRACT

Methamphetamine (hereafter, meth) addiction results in various emotional problems linked to structural impairments in the prefrontal cortex (PFC). In this paper, we investigated whether high-frequency (10 Hz) repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral PFC (DLPFC) can improve emotional attention. Thirty-one meth addicts were randomly assigned to a 10 Hz or sham rTMS group; additionally, 31 healthy participants were enrolled, who were required to respond as correctly and quickly as possible to a yellow arrow embedded in an image depicting emotional content (neutral, fear, sadness, or disgust). Results showed that the healthy participants responded more rapidly to negative compared to neutral stimuli, while meth addicts responded indiscriminately to stimuli representing disgust, fear, and neutral content. The randomization check showed no significant differences in the pretest of emotional attention measures between the 10 Hz and sham groups. However, 10 Hz rTMS yielded faster response to negative pictures than to neutral pictures, which was similar to the performance of healthy participants but Sham not. However, this attention bias effect persisted in the 10 Hz group 2 weeks later. These results demonstrate that high-frequency rTMS of the left DLPFC can improve the emotional attention of meth addicts.

1. Introduction

Methamphetamine (hereafter, meth) addiction causes various social and health problems worldwide. It is related to various negative effects, including physical aggression (Payer et al., 2011; Sommers and Baskin, 2006; Stretesky, 2009) and a high level of emotional problems, particularly depression (Darke, 2008; Glasner-Edwards et al., 2009), fear, and anxiety (Hellem, 2016; Zweben et al., 2004). Studies have reported that meth addicts have difficulty in emotional processing, involving emotional perception (Song et al., 2011), recognition (Henry et al., 2009; Kim et al., 2011a) and regulation (Uhlmann et al., 2016). These emotional deficits are not simply a result of meth use, but are also risk factors for drug craving or relapse (Baker et al., 2004). An intervention concerning the emotional attention of meth addicts may assist in avoiding relapses related to emotional problems.

Deficits in emotional processing are closely associated with those in emotional attention. As emotional attention occurs in the early stage of emotional processing, it is an important component of emotional experience (Thompson et al., 2011). Emotional stimulation can only be effectively processed with sufficient attention (Lavie, 2010; Yates et al., 2010). In particular, attention to negative stimuli is important for survival. It allows individuals to identify and respond to threat more rapidly to avoid danger (Cacioppo and Gardner, 1998). Several studies indicate that meth use causes an attention deficit in cognitive task experiments (Kalechstein et al., 2003; Ezzatpanah et al., 2014). Similarly, these deficits may also exist at the attentional stage of emotional processing. Clinical observations show that meth addicts often appear distracted. They have difficulty in focusing (Salo et al., 2002) and show reduced responses to affective stimuli even after prolonged abstinence (Henry et al., 2009; Kim et al., 2011a; Payer et al., 2008; Yin et al., 2012). Song et al. (2011) suggest that the emotional awareness of threatening scenes could be compromised in meth addicts. Indifference to negative information may predispose meth addicts to insensitivity toward important biological or social cues, thus leading to interpersonal problems, danger avoidance deficits, and even mental illness.

The deficits in emotional attention in meth addicts are likely linked to the dorsolateral prefrontal cortex (DLPFC), particularly a hypoactivation of the left DLPFC. It has been shown that the DLPFC subserves

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cognitive control functions (Vierheilig et al., 2016) and underlies top-down attention control (Vanderhasselt et al., 2006), attentional deployment (Li et al., 2010), and attentional processing of emotional information (Jacob et al., 2014; Zwanzger et al., 2014). Furthermore, hypoactivation of the DLPFC is closely associated with emotional problems, such as depression (Grimm et al., 2008; Groenewold et al., 2013; Siegle et al., 2007; Wolkenstein et al., 2014). The interaction of emotion and cognition in the DLPFC may result from its close connection to the amygdala, which is involved in cognition and emotional processing (Pessoa and Adolphs, 2010; Ray and Zald, 2012; Zhang et al., 2016).

Meth use results in dysfunction of the DLPFC (Goldstein and Volkow, 2011; Paulus et al., 2002; Thompson et al., 2004); however, it is uncertain whether this damage is irreversible or malleable. Non-invasive brain stimulation techniques have been widely used to selectively modulate cortical activity (Barker et al., 1986), brain connectivity (Shafi et al., 2012; Shafi et al., 2014), and to improve or disrupt emotional processing (Marine et al., 2015). In this study, we mainly used rTMS, which exerts either inhibitory (< 1 Hz) or excitatory (> 10 Hz) effects on neuronal functions (Maeda et al., 2000a, b). Guse et al., (2010) show that high-frequency rTMS over the DLPFC can enhance cognitive functions in patients with psychiatric and neurological diseases.

The main purposes of the current study are to examine whether attention bias to negative information in meth addicts is different compared to that in healthy participants and whether high-frequency rTMS of the left DLPFC modulates their emotional attention. It has been reported that meth addicts show reduced DLPFC activation in the emotion-matching task (Kim et al., 2011b). A related study shows that high-frequency rTMS to the left DLPFC can modulate attentional engagement by negative information in healthy individuals (De et al., 2010). High-frequency rTMS of the right DLPFC results in diminished attentional engagement (De et al., 2010), negative information inhibition (Leyman et al., 2009), and attentional bias toward negative information, especially in individuals who have higher state anxiety (Vanderhasselt et al., 2011). Thus, we inferred that the diminished emotional attention in meth addicts may be associated with DLPFC hypoactivation. The current study focused on the attention bias to negative stimuli because negative emotions are significant for adaptation and survival (Crawford and Cacioppo, 2002; Smith et al., 2003). In real-life settings, people often do not focus on the emotion itself, but on cognitive tasks that may be modulated in the emotional context (Delplanque et al., 2005; Yuan et al., 2007). Hence, we adopted a non-emotional task that asks participants to respond to non-emotional targets in different emotional contexts.

Because negative affective information catches one's attention more quickly (Pérez-Edgar et al., 2010; Peltola et al., 2015; Vaish et al., 2008) and elicits more focused attention (Fenske and Eastwood, 2003), we predicted that in healthy individuals, the response to negative stimuli will be faster and more accurate than to neutral stimuli. Because the left DLPFC was reported to be important in mediating attention recruitment for emotional information (Grimm et al., 2008; Heeren et al., 2015; Heeren et al., 2017; Marine et al., 2015), high-frequency rTMS of this area may restore its prioritized attention processing of negative information. Thus, we predicted that after high-frequency rTMS responses to targets in negative contexts may be faster and more accurate than to those in neutral contexts.

2. Methods

2.1. Participants

Thirty-one male meth addicts (age: 24–53 years, mean value [M] = 43 ± 9.15 years) with a history of meth-related drug use (2–26 years, M = 13.03 ± 7.45; exclusive meth use for at least 2 years; minimum meth intake 3 times per week for at least 2 months; intake dose of 0.5–2 g) were enrolled. They did not receive additional drug therapy, were abstinent for not more than 2 months (based on the criteria suggested by Huang et al. 2017), and were diagnosed with addiction according to DSM-V criteria (American Psychiatric Association, 2013). Additionally, 31 age- and education-matched male healthy participants (25–53 years, M = 40.42 ± 9.14 years) were recruited for the present study. All participants were healthy, not diagnosed with mental disorders, did not have a history of epilepsy or cardiovascular complications, had a normal or corrected vision, and were right-handed. All participants participated voluntarily in this study; informed consent was obtained. The study was approved by the local Ethics Committee of Human Research at Southwest University in China.

2.2. Materials

Four types of emotional pictures (disgust, fear, sadness, and neutral) were selected from the native Chinese Affective Picture System (Lu et al., 2005), each category consisting of eight pictures. These pictures showed among others animals, conflicts, accidents, fires, poverty, mourning, natural disasters, and daily activities. For images depicting disgust, fear, and sadness, we controlled for a similar valence strength, and all were perceived significantly more negative than neutral stimuli (all $P < 0.05$). Descriptive statistics are shown in Fig. 1. Before the experiment, we standardized brightness, saturation, and size of all pictures to avoid potential confounds of the attentional bias by physical properties.

2.3. Experimental tasks

Before the experiment, we collected demographic data including age, education, smoking, drinking, and gambling. We measured the emotional stability of the participants with the neuroticism subscale of NEO five-factor inventory (NEO–FFI, Costa and MacCrae, 1992).

In this single-blind study, meth addicts were randomly assigned to the high-frequency 10-Hz (n = 15) or sham (n = 16, one was eliminated for deviating by 3 standard deviations from the mean accuracy) rTMS groups according to their age. The experimental task was the same for both groups except for differences in the rTMS protocol. The high-frequency group received a 10-Hz rTMS, while the sham group received sham rTMS. Each experiment consisted of a pretest and a posttest with the same task, which was conducted 5 minutes before and after the rTMS treatment. Healthy participants (n = 31) only participated in the pretest.

The experimental procedure consisted of 80 trials, each trial starting with a fixation cross presented for 500 ms. Next, one picture containing a yellow arrow was presented for 1000 ms. The arrow's orientation was either to the left or the right, and the arrow fell into the central feature of the emotional pictures to focus participants' eyes instead of distract attention. The arrow's location was random in every trial. Participants were asked to indicate the arrow's orientation by pressing keys as accurately and quickly as possible.

The inter-stimulus interval ranged from 500 to 1000 ms (see Fig. 2). Accuracy and reaction times were recorded. Before the experiment, 18 practice trials with neutral pictures were used to familiarize participants with the procedure. The same task was ~~unexpectedly~~ presented to the 10 Hz rTMS group 14 days later without their prior knowledge, to test the durability of the treatment effect. During this period, they did not receive any addiction-related treatment or intervention.

For rTMS or sham stimulation, the motor threshold was determined in all groups over the left motor cortex as the lowest intensity that evoked a motor response in the right abductor pollicis brevis muscles and produced five motor-evoked potential responses of at least 50 mV in 10 trials. During the treatment, the coil was placed over the left prefrontal area 5 cm anterior to the scalp position at which the motor threshold was determined. High-frequency (10 Hz, strength at 90% resting motor threshold, 5 s on, 10 s off for 10 min; 2000 pulses divided into 40 repeats at 15 s interval) or sham (1 Hz, the coil turned 90° away