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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 post-test 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

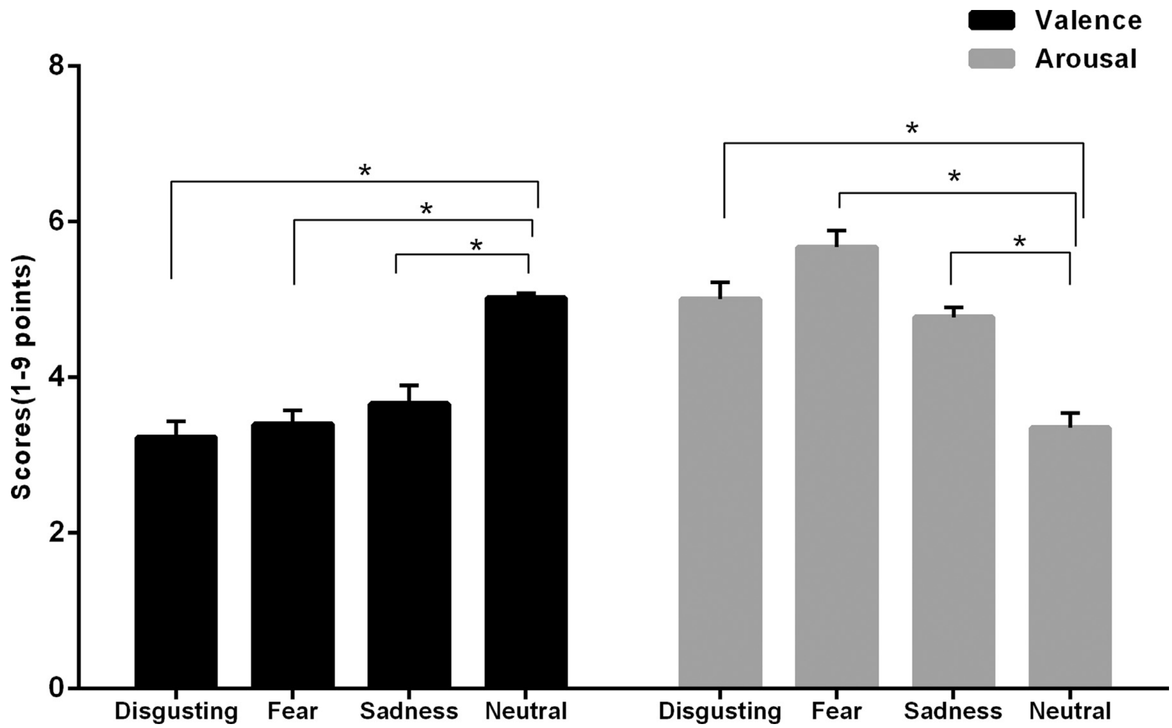

Fig. 1. The emotional valence and arousal of experimental materials.
"*": $P < 0.05$; "**": $P < 0.01$
Error bars represent the standard errors.

from the skull, resting on the scalp with only one edge) TMS were applied to the left DLPFC. For accurately targeted stimulation, we used a figure-8-shaped coil (radius 45 mm for each circle, center distance between two circles 76 mm) with a CCY-I TMS instrument (Yiruide Co., Wuhan, China). The left DLPFC stimulation site was defined as being 5 cm anterior to the area of the optimal site for the primary motor cortex of the left hemisphere (the method of Pascual-Leone). This method has been reported to be accurate in targeting the DLPFC area (Pascual-Leone et al., 1996).

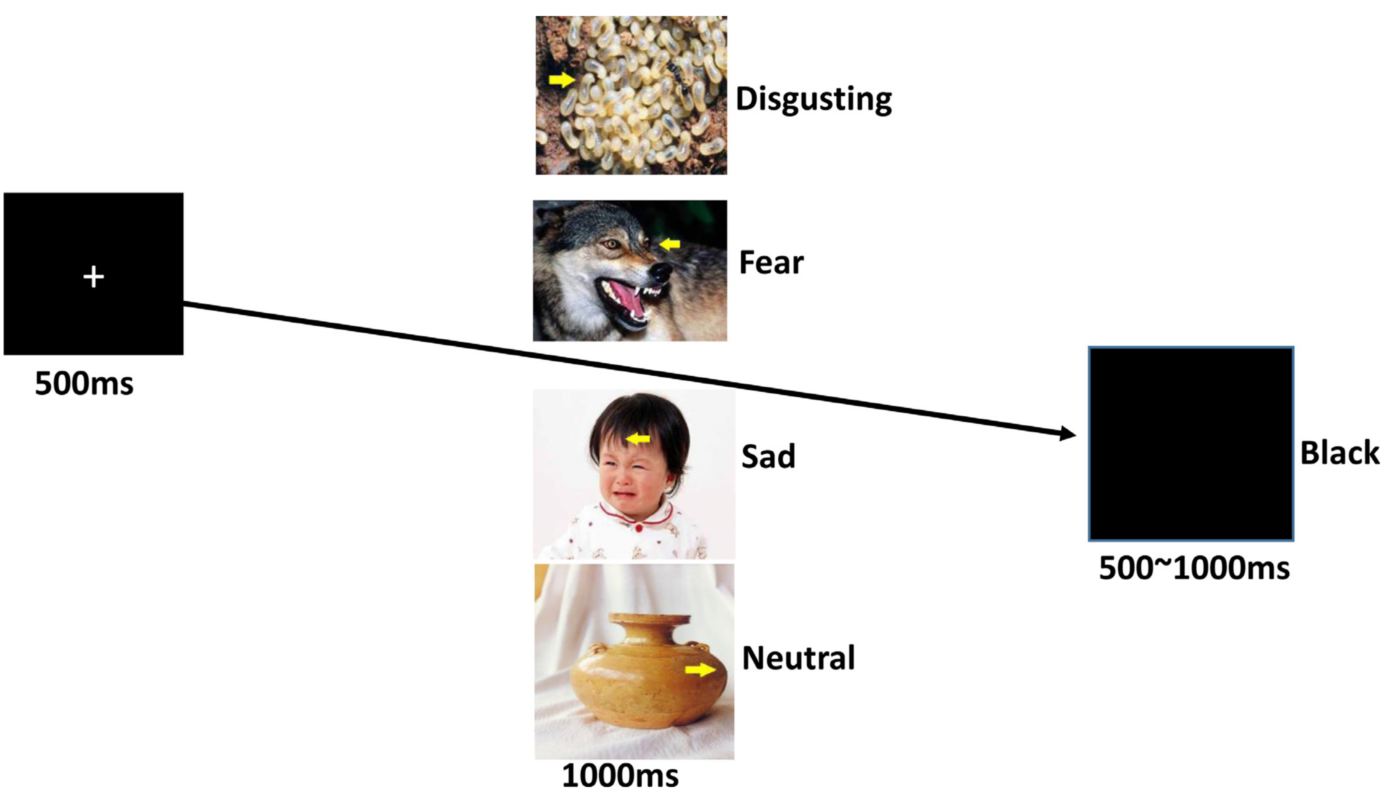

Fig. 2. Experimental procedure.

Table 1
Descriptive Statistics of reaction times and accuracy: Mean and Standard deviation(*SD*).

Training	Time	Emotion	Mean(RTs)	*SD*(RTs)	Mean(ACC)	*SD*(ACC)
10 Hz	Pretest	Disgusting	665.38	79.39	90.83%	7.79%
		Fear	647.05	58.51	97.08%	5.72%
		Sadness	647	68.69	93.75%	8.52%
		Neutral	664.39	68.23	93.33%	7.27%
	Posttest	Disgusting	629.87	64.14	96.67%	5.72%
		Fear	629.51	55.64	96.67%	4.00%
		Sadness	617.02	58.39	97.08%	3.23%
		Neutral	658.64	75.24	92.50%	5.88%
	Tracking	Disgusting	652.46	58.75	95.98%	4.65%
		Fear sad	649.93	56.47	95.98%	5.81%
		Sadness	644.79	52.02	95.98%	6.30%
		Neutral	675.26	59.58	93.33%	6.69%
Sham	Pretest	Disgusting	637.55	71.85	90.3%	12.47%
		Fear	642.71	70.08	96.71%	5.66%
		Sadness	618.59	66.38	95.42%	5.53%
		Neutral	648.44	67.49	91.25%	8.11%
	Posttest	Disgusting	650.59	68.02	94.58%	7.43%
		Fear	647.92	65.90	97.53%	3.87%
		Sadness	633.46	66.82	98.35%	2.83%
		Neutral	658.97	65.20	94.16%	6.07%
Health	Pretest	Disgusting	634.09	44.66	94.96%	5.20%
		Fear	635.89	57.269	95.56%	6.29%
		Sadness	611.67	50.368	94.96%	6.54%
		Neutral	654.37	48.232	92.34%	7.86%

3. Results

The mean and SD of RTs (only from trials with correct responses) and accuracy (ACC) are shown in Table 1. Group characteristics for the sample are shown in Table 2. There was no significant difference between meth addicts and healthy participants in terms of age, education, smoking, drinking, gambling, and neuroticism scores.

3.1. Emotional attention in meth addicts compared with healthy participants

In the pretest, we analyzed the emotional attention in meth addicts compared to healthy participants, using RTs and ACCs as a measure. All meth addict participants are included in the analysis irrespective of their treatment group. In RTs, there was a significant main effect for Emotion ($F_{(3,\ 177)} = 28.07$, $P < 0.01$, $\eta_p^2 = 0.322$) and a significant interaction between drug use (meth addicts or healthy and Emotion interaction ($F_{(3,177)} = 3.32$ $P < 0.05$, $\eta_p^2 = 0.053$). The subsequent simple effect test of Emotion interaction revealed that for meth addicts the main effect for Emotion was significant ($F_{(3,\ 87)} = 6.13$, $P < 0.05$, $\eta_p^2 = 0.175$) with RTs being similar for disgust, fear, and neutral stimuli. Only the sadness stimulus elicited faster RTs than neutral conditions. In contrast, disgust, fear, and sadness stimuli elicited in healthy individuals faster RTs than neutral stimuli ($F_{(3,\ 90)} = 23.70$, $P < 0.01$, $\eta_p^2 = 0.441$).

Regarding accuracy data, there was in all participants a significant main effect for Emotion ($F_{(3,177)} = 6.78$, $P < 0.01$, $\eta_p^2 = 0.103$) with fear and sadness stimuli eliciting more accurate responses than neutral conditions (both $P < 0.01$) . The interaction between Emotion and drug use ($F_{(3,177)} = 2.61$, $P = 0.057$, $\eta_p^2 = 0.042$) and the main effect for drug use (($F_{(1,\ 59)} = 0.22$, $P = 0.644$, $\eta_p^2 = 0.004$) were not significant.

Overall, these results indicate that in meth addicts the performance of attention bias for negative stimuli is attenuated compared to healthy individuals (see Fig. 3(a)).

3.2. Randomization check: baseline comparison between sham and high-frequency groups

Participants' characteristics of the 10 Hz and sham groups are shown in Table 3. There were no significant differences between groups with respect to age, education, smoking, drinking, gambling, and neuroticism scores.

First, we tested, whether the random assignment of meth addicts to the 10 Hz or sham group was successful. Pretest measures of emotional attention in RTs and ACC were compared between both groups. We performed a repeated-measures ANOVA for reaction times and accuracy with emotional conditions as the repeated factor and Group as the between-subject factor.

We only found a significant main effect of Emotion (RTs: $F_{(3,\ 84)} = 6.33$, $P < 0.01$, $\eta_p^2 = 0.185$; ACC: $F_{(3,\ 84)} = 7.54$, $P < 0.01$, $\eta_p^2 = 0.212$). There was no statistically significant difference among disgust and fear compared to the neutral condition in RTs; only the sadness stimulus evoked faster RTs ($P < 0.01$). Accuracy was higher in the fear and the sadness (both $P < 0.05$), but not in the disgust condition compared to neutral stimuli. The main effect of Group (RTs: $F_{(1,28)} = 0.62$, $P = 0.436$, $\eta_p^2 = 0.022$; ACC: $F_{(1,28)} = 0.01$, $P = 0.934$, $\eta_p^2 = 0$) and the Emotion*Group interaction (RTs: $F_{(3,84)} = 1.97$, $P = 0.124$, $\eta_p^2 = 0.066$; ACC: $F_{(3,84)} = 0.63$, $P = 0.597$, $\eta_p^2 = 0.022$) were all not significantly different.

These results suggest a similar baseline performance of emotional attention for both groups (see Fig. 3(b)).

3.3. Influence of high-frequency rTMS on emotional attention

We performed an ANOVA with repeated measures on RTs and ACCs with Emotions and Time (pre- and posttest) as repeated factors and Group (10 Hz and sham) as the between factor. The results showed a significant interaction between Emotion, Time and Group in RTs ($F_{(3,\ 84)} = 2.73$, $P < 0.05$, $\eta_p^2 = 0.089$).

In the 10-Hz group, there was a significant interaction between Emotion and Time ($F_{(3,\ 42)} = 3.83$, $P < 0.05$, $\eta_p^2 = 0.21$). The simple effect analysis of the interaction showed a main effect for Emotion in the pretest ($F_{(3,\ 42)} = 2.93$, $P < 0.05$, $\eta_p^2 = 0.173$). There were no significant differences between disgust, fear and neutral conditions, only sadness stimuli caused shorter RTs ($P < 0.01$). In contrast, all emotion stimuli elicited faster RTs than neutral stimuli in the posttest ($F_{(3,\ 42)} = 7.37$, $P < 0.01$, $\eta_p^2 = 0.345$). However, the sham rTMS group only showed a significant main effect for Emotion ($F_{(3,\ 42)} = 7.22$, $P < 0.01$, $\eta_p^2 = 0.34$) without significant differences between emotion and neutral conditions except as described above for the sadness

Table 2
Group characteristics of the full sample in mean and standard deviations(*SD*).

	Meth addicts(N = 30) Mean(*SD*)	The health(N = 31) Mean(*SD*)	Group comparison χ^2 or t	*df*	*P*
Age	43 (± 9.15)	40.42 (± 9.14)	1.484(t)	59	0.143
Smoking(Yes)	n = 27	n = 26	0.503(χ^2)	1	0.478
Drinking(Yes)	n = 14	n = 20	1.969(χ^2)	1	0.161
Gambling(Yes)	n = 13	n = 11	0.349(χ^2)	1	0.530
Education	n = 8(P);n = 11(J);n = 11(H)	n = 7(P);n = 15(J);n = 9(H)	0.866(χ^2)	2	0.649
Neuroticism(NEO-FFI)	34.17(± 7.08)	33.32(± 5.05)	0.537(t)	59	0.593

Table 1. Note: (P): represents primary school; (J): junior high school; (H): high school.

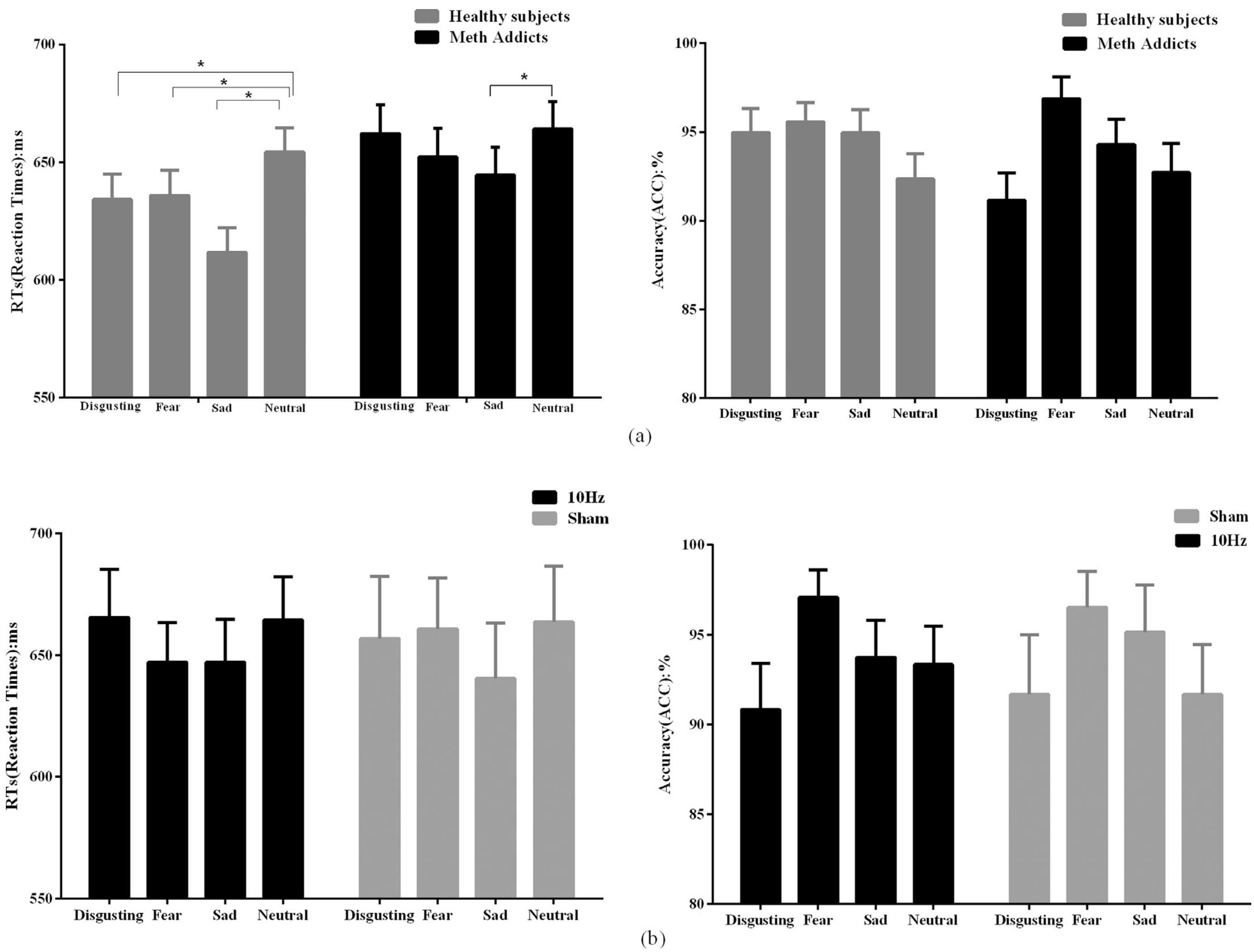

Fig. 3. (a) The emotional attention in meth-addicts compared to healthy participants; (b) Randomization check: the contrast of baseline between Sham and 10 Hz. Error bars represent the standard errors.

Table 3
Randomization check: The contrast of baseline between Sham and 10 Hz.

	10 Hz(N = 15) Mean(SD)	Sham(N = 15) Mean(SD)	Group comparison χ^2 or t	df	p
Age	42.89(± 9.56)	43.13(± 9.054)	0.078(t)	28	0.938
Smoking(Yes)	n = 14	n = 13	0.370(χ^2)	1	0.543
Drinking(Yes)	n = 9	n = 5	2.143(χ^2)	1	0.143
Gambling(Yes)	n = 6	n = 7	0.136(χ^2)	1	0.713
Education	n = 3(P);n = 6(J);n = 6(H)	n = 5(P);n = 5(J);n = 5(H)	0.682(χ^2)	2	0.711
Length of use(Year)	11.47(± 7.67)	14.6(± 7.149)	1.157(t)	28	0.257
Neuroticism(NEO-FFI)	32.8(± 7.17)	35.53(± 6.958)	1.059(t)	28	0.299

Table 1. Note: (P): represents primary school; (J): junior high school; (H): high school.

condition. Neither Time ($F_{(1,\ 14)} = 2.82$, $P = 0.115$, $\eta_p^2 = 0.168$) nor Emotion by Time interaction ($F_{(3,\ 42)} = 0.37$, $P = 0.774$, $\eta_p^2 = 0.025$) showed a significant main effect in the sham group (see Fig. 4(a)).

Compared to the pretest, RTs for the sadness, disgust and fear condition were faster after the 10 Hz intervention (all $P < 0.05$), but there was no statistically significant difference for the neutral condition. In contrast, the sham group performed similarly for pre- and posttest in all conditions (all $P > 0.1$). These results suggest that our intervention by the 10 Hz rTMS protocol improved response times to emotional, but not neutral stimuli. This effect was absent in the sham group (see Fig. 4(b)).

In ACC, the repeated measures ANOVA revealed only an interaction between Time and Emotion ($F_{(3,\ 84)} = 3.25$, $P < 0.05$, $\eta_p^2 = 0.104$). The main effect for Emotion was significant in both, pretest ($F_{(3,\ 84)} = 8.73$, $P < 0.01$, $\eta_p^2 = 0.231$) and posttest ($F_{(3,\ 84)} = 6.41$, $P < 0.01$, $\eta_p^2 = 0.181$). Meth addicts responded in all tests more accurately to fear and sadness conditions than to the neutral condition ($P < 0.05$, see Fig. 4(c)). The main effects for Group ($F_{(3,84)} = 0.01$, $P = 0.938$, $\eta_p^2 = 0$), Emotion*Group ($F_{(3,84)} = 0.55$, $P = 0.649$, $\eta_p^2 = 0.019$), Group*Time ($F_{1,28)} = 0.08$, $P = 0.778$, $\eta_p^2 = 0.003$) or

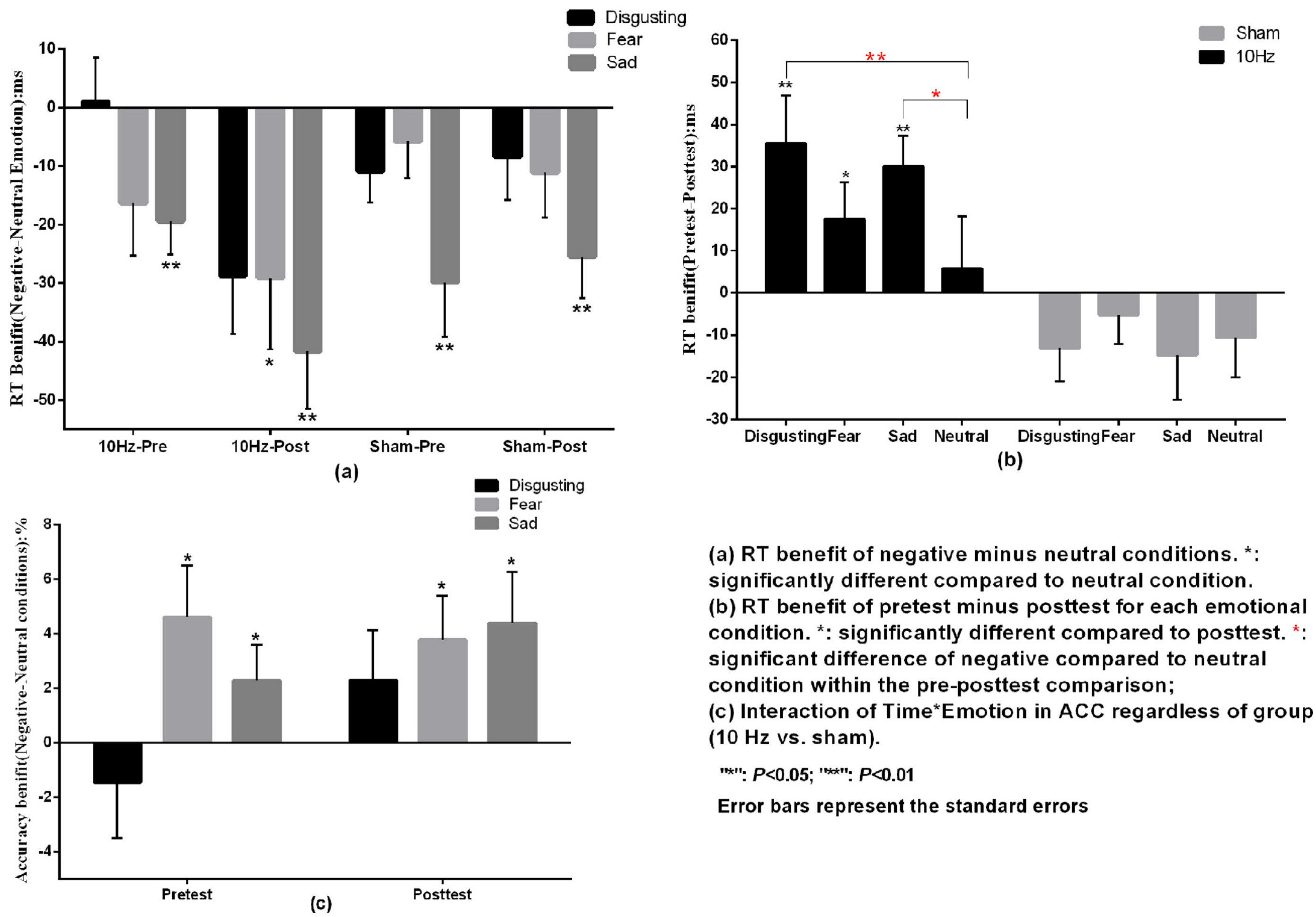

Fig. 4. The influence of high-frequency (10 Hz) rTMS on emotional attention
(a) RT benefit of negative minus neutral conditions. The "*" represents a significant difference compared to neutral conditions; (b)RT benefit of Pretest minus Posttest under each emotional conditions. The "*" represents a significant difference compared to Posttest. The "*" represents a significant difference of negative conditions compared to neutral condition within pre-posttest; (c)The interaction of Time*Emotion in ACC, regardless of Group (10 Hz vs. Sham).
"*": $P < 0.05$; "**": $P < 0.01$
Error bars represent the standard errors.

Group*Time*Emotion ($F_{(3,84)} = 1.17$, $P = 0.328$, $\eta_p^2 = 0.04$) interaction were all not significantly different.

We also tested how the emotional attention measures differed between the 10 Hz group after the rTMS intervention and healthy subjects. A comparison of the addicts' posttest data with those of healthy participants showed a main effect of Emotion in RTs ($F_{(3,132)} = 25.56$, $P < 0.01$, $\eta_p^2 = 0.367$) and in ACCs ($F_{(3,132)} = 5.94$, $P < 0.01$, $\eta_p^2 = 0.117$), while the Emotion by Addiction interaction was not significantly different for both parameters (RTs: $F_{(3,132)} = 0.75$, $P = 0.526$, $\eta_p^2 = 0.017$; ACCs: $F_{(3,132)} = 0.25$, $P = 0.859$, $\eta_p^2 = 0.006$). Compared to neutral conditions, disgust, fear and sadness were all associated with faster reaction times and more accurate responses in both, addicts and healthy participants.

3.4. Long-lasting effects of the 10 Hz rTMS treatment

Two weeks after the initial experiment, we repeated the test in the 10 Hz group without their prior knowledge. One addict dropped out; sham group and healthy participants did not participate in this experiment. We were able to replicate the main effect for Emotion in regard to reaction times ($F_{(3,\ 39)} = 4.16$, $P < 0.05$, $\eta_p^2 = 0.242$). Disgust, sadness, and fear stimuli were still all linked to faster RTs in comparison to neutral stimuli (disgust, fear, $P < 0.05$; sadness, $P < 0.01$). However, we did not see the main effect of Emotion in terms of accuracy 2 weeks later ($F_{(3,\ 39)} = 0.98$, $P = 0.412$, $\eta_p^2 = 0.07$).

Additionally, we tested how the emotional attention parameters differ between meth addicts after 2 weeks and healthy participants. This comparison showed only a main effect for Emotion in RTs ($F_{(3,129)} = 18.88$, $P < 0.01$, $\eta_p^2 = 0.305$), while the main effects for Emotion (ACCs: $F_{(3,129)} = 2.37$, $P = 0.073$, $\eta_p^2 = 0.052$), Addiction (RTs: $F_{(1,43)} = 1.88$, $P = 0.177$, $\eta_p^2 = 0.042$; ACCs: $F_{(1,43)} = 0.41$, $P = 0.524$, $\eta_p^2 = 0.01$), and Emotion by Addiction interaction (RTs: $F_{(3,129)} = 1.39$, $P = 0.248$, $\eta_p^2 = 0.031$; ACCs: $F_{(3,129)} = 0.03$, $P = 0.994$, $\eta_p^2 = 0.001$) were not significantly different. Disgust, fear and sadness conditions were all associated with faster RTs compared to neutral conditions (all $P < 0.01$) irrespective of the participants' addiction status (10 Hz group or healthy participants; see Fig. 5).

These results suggest that the 10 Hz rTMS intervention effect on emotional attention in meth addicts is, at least for the RT parameter, durable and may last for a dozen days.

4. Discussion

Emotional attention is a fundamental precondition of emotional perception and later emotional processing steps (Thompson et al., 2011). Indifference to negative information is detrimental to environmental adaptation. This indifference has been shown to underlie various psychosocial dysfunctions and mental illnesses (Yang et al., 2016;

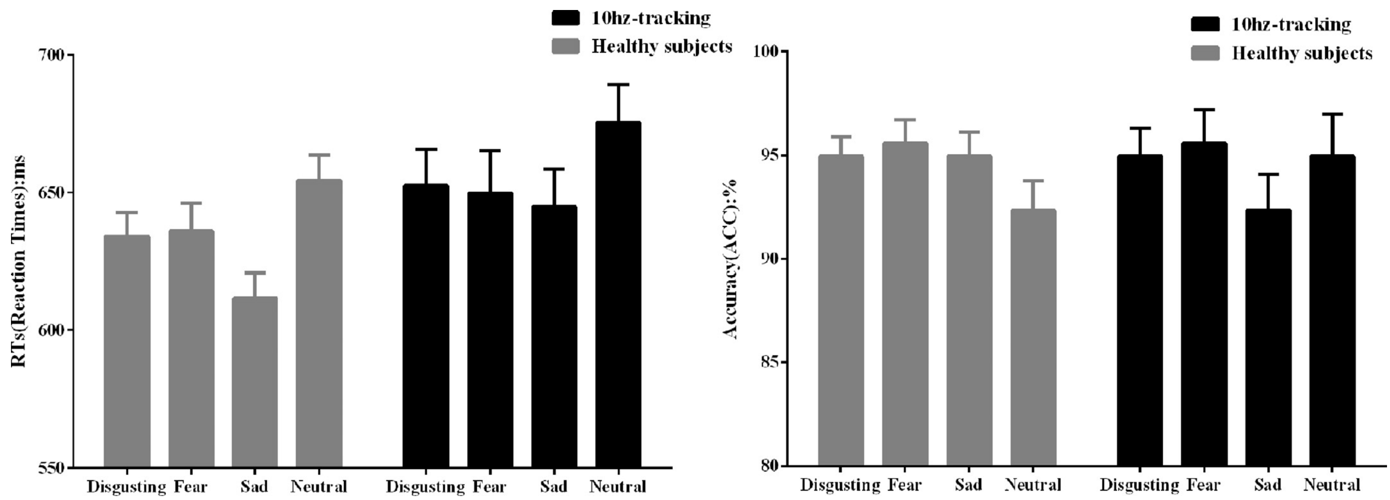

Fig. 5. The long-term effect of 10 Hz. Error bars represent the standard errors.

Russell et al., 2008) like aggression and depression that accompany meth addiction (Glasner-Edwards et al., 2009; Lapworth et al., 2009; Plüddemann et al., 2013).

In our study we assumed that facilitated attention to negative relative to neutral information, which is typical for healthy individuals, may be diminished in meth addicts. Consistent with our hypothesis, we did not observe in pretests of meth addicts any significant differences between negative and neutral contexts except for the sadness condition. In contrast, healthy participants responded reliably faster to targets embedded in negative contexts. These results suggest that healthy individuals are able to prioritize attention orientation to threat over neutral information, an adaptive phenomenon termed negativity bias (Huang and Luo, 2006). This significant adaptive function of attention bias for threats may be compromised in meth addicts. After an intervention with high-frequency rTMS of the left DLPFC, the inadequate performance of emotional attention by meth addicts was ameliorated, which was signified by faster RTs for negative relative to neutral stimuli. This led in the addiction group to RTs similar to those in healthy participants. Moreover, the effect of high-frequency rTMS on meth addicts' emotional attention is probably durable, lasting for days to weeks.

Studies have demonstrated that negative events can attract attentional resources more rapidly than neutral and positive events (Dong et al., 2011; Estes and Adelman, 2008; Wentura et al., 2000). An important function of negative emotion is to motivate individuals to perform analytic and focused processing of threatening information from the environment (Mitchell and Phillips, 2007). Consistent with this view, there is an abundance of evidence showing that, in comparison to neutral emotions, negative emotions are linked to more localized, contracted or focused attention, which facilitates goal-directed behaviors (Eastwood et al., 2001; Fenske and Eastwood, 2003; Tipples, 2006). This most likely explains why targets on the negative picture elicited faster RTs compared to neutral conditions.

Our observation of faster RTs for emotion versus neutral conditions in posttests of the addiction group is consistent with prior studies reporting enhanced performances in face emotion recognition after anodal transcranial direct current stimulation (tDCS) or high-frequency rTMS of the left DLPFC (Clarke et al., 2014; De et al., 2010; Nitsche et al., 2012). In addition, Clarke et al. (2014) found enhanced attentional bias acquisition for threats in participants receiving anodal tDCS of the left DLPFC compared to those receiving sham stimulation. Clarke's findings are most likely caused by the enhancement of goal-directed and focused attention on negative relative to neutral contexts after excitatory stimulation of the addicts' left DLPFC. For instance, anodal tDCS of this region improves task performances by enhancing inhibitory control of internally-generated, task-irrelevant mood distractors (Plewnia et al., 2015). The interaction of emotion and cognition in the DLPFC may be due to the anatomical and functional integration with the anterior cingulate cortex (Hoffman et al., 2008; Hwang et al., 2015; Kondo et al., 2004; Luks et al., 2002; Nestor et al., 2011; Salo et al., 2007; Yang et al., 2016) and the amygdala (Pessoa and Adolphs, 2010; Ray and Zald, 2012; Zhang et al., 2016). These regions are considered to be vital in mediating attention recruitment for emotional information. For example, excitatory stimulation of the left DLPFC by high-frequency rTMS enhances activation levels of the frontoparietal cognitive control network, including dorsal anterior cingulate cortex, posterior parietal lobe and orbitofrontal cortex (De et al., 2010).

In contrast, the observed effects of high-frequency rTMS in our study may also be caused by increased activity of the dopaminergic system. It has been reported that chronic meth use leads to loss of dopaminergic transporter intensity in the DLPFC (Krasnova and Cadet, 2009; Sekine et al., 2003), which is considered to be involved in emotion and attention functions (Nieoullon and Coquerel, 2003; Sevy et al., 2006; Sonugabarke et al., 2009). Therefore, high-frequency rTMS of the left DLPFC may enhance the attention bias to salient information by increasing the dopamine release in this region. This possibility, postulated by Dommett et al. (2005), needs to be examined in future studies.

Although we found an improvement in RTs to negative conditions after high-frequency, but not after sham intervention, we did not find a similar effect in ACCs. It is worth noting that in ACCs we only observed a significant effect on Time by Emotion interaction, which was unaffected by the rTMS treatment. Thus, the rTMS intervention modulated, as indicated by our RT data, response speed but not response accuracy. On the other hand, the experimental task required participants to react primarily as accurately and only secondarily as quickly as possible. ACC values were on average greater than 90% in all groups for all stimuli and approached the ceiling effect, suggesting that participants performed the task with diligence in both pretest and post-test. Therefore, the lack of differences in accuracy between the 10 Hz and sham groups suggests that the improvement of reaction speed to negative stimuli after 10-Hz intervention cannot be explained by a trade-off between speed and accuracy.

Our results have some limitations that should be considered and resolved in future studies. First, although an abundance of studies demonstrates impaired cognitive functions in different domains caused by meth addiction (Kalechstein et al., 2003; Salo et al., 2002; Ezzatpanah et al., 2014), there remain some controversies regarding this issue (Hart et al., 2012). These controversies may be associated with the dose and duration of meth intake. In meth addicts, low-dose meth intake may improve attention processing speed and working memory in comparison to abstinence (Mahoney et al., 2011). While short-term meth intake increases spatial working memory, long-term meth intake not only decreases spatial working memory but also affects protein kinase M zeta, dopamine, and glutamate receptors in rats (Braren et al., 2014). However, these studies did not compare the performance of a low-dose meth use group with that of healthy participants. Hence, it is unclear, whether low-dose meth use enhances or reduces attention and working memory Dose and duration effects of meth intake should be examined in future studies.

Second, the effect of rTMS of the left DLPFC should be discussed. In this study, we did not work with neuroimaging methods to test the excitability of the left DLPFC and its connected brain regions. Maeda et al. (2000a) applied rTMS to the motor cortex of participants at different frequencies (1, 10, 15, and 20 Hz) to examine its effects on motor evoked potentials (frequency tuning curve). They demonstrate a frequency-dependent increase in cortical excitability. But De et al. (2010) find that high-frequency rTMS of the left DLPFC is associated with increased activity within the right DLPFC, dorsal anterior cingulate cortex (dACC), right superior parietal gyrus and left orbitofrontal cortex. When rTMS is applied over the right DLPFC, it is linked to decreased activation within the right DLPFC, dACC, and left superior parietal gyrus and to increased activity within the right amygdala. Whether rTMS exhibits inhibitory or excitatory effects, seemingly depends not only on the frequency but also on the intensity, duration and intertrain interval of the stimulation. Although we applied high-frequency rTMS of the left DLPFC, the magnetic stimulation of this region may also evoke activations in adjacent cortical and subcortical regions (Speer et al., 2000). Neural mechanisms underlying cognitive plasticity effects induced by the rTMS protocol in this study remain unclear. Future studies, combining rTMS with neuroimaging techniques like fMRI, should clarify this point.

Third, previous studies show that non-invasive brain stimulation applied over the DLPFC modulates emotional processing without influencing mood (Marine et al., 2015; Vanderhasselt et al., 2009a, 2009b). We controlled for neuroticism traits across sample groups, but we have to acknowledge the limitation that we did not measure mood states and its potential modulation by rTMS intervention in this study. Though we observed a long-term effect of high-frequency rTMS on emotional attention, we cannot exclude a practice effect within the 10 Hz group. Because the sham group did not show any practice or placebo effect in the second compared to the first test, this possibility is probably small and may not constitute a major confounding factor. Although studies have shown that rTMS is accompanied by non-significant side effects (Kleinjung et al., 2005; Slotema et al., 2010), a limitation of this study is the lack of assessment of rTMS side effects. We will address this problem in our future work.

Lastly, although we considered several basic emotions that are common in daily life, the current study did not consider anger because it is difficult to be induced by pictures. Anger induction has been suggested to be induced by self-relevant situations (Arslan, 2009; Leonard et al., 2011). However, anger is closely related to aggressive behavior and hostility, which are common in meth addicts (Payer et al., 2011). In this regard, future studies need to consider the role of anger in meth addicts and how rTMS may help them with anger processing and regulation.

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Declarations of interest

None.

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Authors' contributions

Each of the authors participated in this research by contributing to designing the study (L.Z., X.L., J.M.Y.), conducting experiments (L.Z., Q.L., X.C.), analyzing data (L.Z.), and writing the manuscript (L.Z. and J.J.Y.).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.04.039.

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