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Aerobic exercise training ameliorates craving and inhibitory control in methamphetamine dependencies: A randomized controlled trial and event-related potential study

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ABSTRACT

Objective: Methamphetamine (MA) usage has been recognized as a prominent substance-abuse issue. While exercise training reportedly improves fitness and mental status in the MA-dependent, how exercise training affects addiction and cognitive deficiency has yet to be established. The current study aimed to determine the effects of aerobic exercise training on both MA-associated cravings and inhibitory control among those with MA dependencies.
Design: A 12-week randomized controlled trial.
Method: Sixty-two people with MA dependencies recruited through the Drug Rehabilitation Bureau were assigned to either an aerobic exercise or attentional control group, with 50 participants completing the trial. The aerobic exercise program involved three 30-min sessions of moderate-intensity exercise per week. Along with a pre-test assessment, craving levels were evaluated every three weeks, and data on neutral and MA-related inhibitory control as well as its elicited neuroelectric activation were collected at the end of the intervention.
Results: Compared with the control group, the exercise group experienced attenuated MA craving levels after 6 weeks of the exercise program, and the decreased trend was maintained until the termination of treatment. In the post-test, the exercise group also demonstrated more accuracy in behavioral inhibitory control as well as greater N2 amplitude in the Nogo condition of both the standard and MA-related tasks than those in the control group or pre-test.
Conclusions: The current study provides the first evidence that aerobic exercise training may be efficacious for MA-associated cravings and inhibitory control from behavioral and neuroelectric perspectives among MA-dependent individuals.

Methamphetamine (MA) addiction is an emerging issue because of its high prevalence, affecting approximately 53.87 million people globally in 2013 and advancing to second place by outpacing opiates and cocaine (United Nations Office on Drugs and Crime, 2015). MA dependence is associated with increased violent behavior (McKetin et al., 2014), an elevated risk of human immunodeficiency virus infection (Colfax et al., 2010), and the development of psychiatric comorbidities (Salo et al., 2011). These burdens underscore the importance of developing effective therapeutic interventions for MA dependence. However, medication has yet to be approved for treating MA dependence, and behavioral treatments, including cognitive behavioral therapy and contingency management, have shown only modest success (Keoleian, Stalcup, Polcin, Brown, & Galloway, 2013; Roll, Chudzynski, Cameron, Howell, & McPherson, 2013).

Aerobic exercise is currently being recognized as a potential novel treatment for substance abuse (Linke & Ussher, 2014; Pareja-Galeano, Sanchis-Gomar, & Mayero, 2013; Wang, Wang, Wang, Li, &

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Zhou, 2014). The beneficial effects of aerobic exercise for addictions is speculated to work by attenuating physiological responses to stress during withdrawal symptoms and facilitating positive influences on depression and mood. While the majority of exercise studies emphasize cigarette smoking (Haasova et al., 2013; Ussher, Taylor, & Faulkner, 2014), few studies have assessed the effect of exercise on MA abusers (Chudzynski et al., 2014; Haglund et al., 2014). Aerobic exercise training for eight weeks has been demonstrated to improve fitness (Dolezal et al., 2013), affect heart rate variability associated with MA abstinence (Dolezal et al., 2014) and decrease depression and anxiety related to MA dependence (Haglund et al., 2014; Rawson et al., 2015b). Notably, acute exercise, i.e., a single bout of exercise, has recently been demonstrated to ameliorate cravings in MA dependence, where craving reduction was experienced immediately during and following exercise (Wang, Zhou, & Chang, 2015; Wang, Zhou, Zhao, Wu, & Chang, 2016). However, whether aerobic exercise training affects MA cravings has yet to be directly investigated.

Reward circuit and impulsiveness models of inhibition highlight the essential role of executive dysfunction, particularly inhibitory control, in drug addiction (Baler & Volkow, 2006; Feil et al., 2010; Goldstein & Volkow, 2011). Inhibitory control is believed to reflect the higher-order cognitive processes that adaptively suppress habitual or prepotent behaviors when environmental contingences demand it (Groman, James, & Jentsch, 2009). Drug abusers, including MA abusers, have an unrestrained motivation to take drugs without considering the catastrophic consequences, especially when exposed to salient substance-related cues (Baler & Volkow, 2006; Tolliver et al., 2012), suggesting a lack of inhibition. Additionally, MA abuses have been postulated to lead to functional and structural abnormalities in several brain regions that are associated with inhibitory control, including orbitofrontal areas, the anterior cingulate cortex (ACC), and the insula (Leland, Arce, Miller, & Paulus, 2008; Salo, Ursu, Buonocore, Leamon, & Carter, 2009).

There is promising behavioral and neurophysiological evidence regarding the relationship between aerobic exercise and inhibitory control across the lifespan (Kamijo, 2016). Specifically, individuals with higher levels of aerobic fitness demonstrate better task-irrelevant inhibition as well as altered neuroelectric activation (i.e., event-related potential, ERP) than those with lower fitness (Chu et al., 2016; Hillman et al., 2006; Kamijo, Takeda, Takai, & Haramura, 2015; Themanson, Pontifex, & Hillman, 2008). Given that better fitness may be a consequence of a greater amount of aerobic exercise training, these findings suggest that a greater amount of exercise is associated with greater inhibition control. Although research has primarily focused on healthy populations, the positive alterations in inhibition as assessed by behavioral and neuroelectric measures have been further extended to MA-dependent abusers after engaging in acute aerobic exercise (Wang et al., 2015, 2016), supporting the postulated association of aerobic exercise and inhibition control for MA-dependent individuals.

The current study applied a randomized controlled design to determine the effects of aerobic exercise training on craving and inhibition control among people with MA dependencies. Additionally, as substantial evidence indicates that the N2 component of ERP is a sensitive measure of impaired inhibitory control in people with substance dependence (Buzzell, Fedota, Roberts, & McDonald, 2014; Luijten et al., 2014) and as this index has been shown to be sensitive in exercise studies of MA abusers (Wang et al., 2015, 2016), the study employed this specific neuroelectric component of ERP. It was hypothesized that aerobic exercise training would ameliorate MA cravings and facilitate inhibition from both behavioral and neuroelectric perspectives among MA abusers.

1. Methods

1.1. Study design

The study utilized a randomized controlled design to determine the effect of aerobic exercise training on cravings and inhibition control in people with MA dependencies. The treatments were an aerobic exercise program or attentional control program administered over a period of 12 weeks. Participants' craving levels were assessed at baseline as well as at 3, 6, 9, and 12 weeks following the beginning of the treatment, and inhibition was assessed at baseline and at 12 weeks. The study protocol was approved by the Institutional Review Board of Shanghai University of Sport. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

1.2. Participants

People with MA dependencies who were incarcerated, aged between 18 and 40 and actively receiving detoxification treatment were enrolled through the Drug Rehabilitation Bureau of the Shanghai Police Department in China. Participants were excluded if they failed to meet the following criteria: (a) DSM-V criteria for drug dependence as assessed by the Structured Diagnostic Interview, (b) right-hand dominance, (c) intact color vision, (d) Raven's standard test of intelligence percentile rank greater than 5% (Raven, Raven, & Court, 2004), (e) history free of neurological disease or physical disability, and (f) no medical contraindications against exercise as assessed by the Physical Activity Readiness Questionnaire (PAR-Q) (American College of Sports Medicine, 2014). Sixty-three of 72 eligible participants were randomly assigned into either the aerobic exercise group or the attention control group, and 50 participants completed the entire trial ($n = 25$ for each group, Fig. 1). The sample size meet the criteria of a power analysis assuming a 2-by-2 mixed design, an alpha of 0.05, a power of 0.08, and an effect size of 0.33 (Etnier et al., 1997). Table 1 summarizes the analyzed participants' demographic characteristics, and no differences were detected between the two groups at baseline.

1.3. Intervention

Participants in both the exercise and attention control groups received routine care by staff at a rehabilitation center. This care included behavior management, nutritional support, physical examination, legal education, and discipline education at the Drug Rehabilitation Bureau of the Shanghai Police Department. Participants in the exercise group were engaged in an exercise program that involved three 30-min sessions per week of moderate-intensity aerobic exercise (i.e., cycling, jogging, or jump rope) for 12 weeks. The exercise protocol was created in accordance with the recommendations of the American College of Sports Medicine (ACSM) (American College of Sports Medicine, 2014). The intensity and duration were selected based upon our previous studies associated with acute exercise and MA. Moderate-intensity exercise [65–75% of the indirect maximum heart rate (HR max); the HR max is defined as $206.9 - 0.67 \times$ age] is beneficial for craving and inhibitory control in people with MA dependency (Wang et al., 2015, 2016). The exercise training program began at an intensity of 65–70% of the HR max for each MA-dependent individual. After the second week, the intensity was gradually increased to 70–75% of HR max, based on the participant's response. HR was monitored throughout the entire procedure using the Polar heart rate monitor (Polar RCX3, Polar Company, Finland). Each session of the program involved stretching the large muscle groups as a warm-up (5 min), performing the aerobic exercise as the main exercise stage