The Cognitive Effectiveness of High-Intensity Interval Training (HIIT) for Individuals of Methamphetamine Dependent: A Study Protocol for a Randomized Controlled Trial

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Study protocol

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Abstract

Introduction

Cognitive deficit is a common syndrome of methamphetamine (MA) dependence, it relates to decision-making, control ability, and social functioning. High-Intensity Interval Training (HIIT) is a training technique that requests people to work out at full intensity during a short period. A number of studies have already shown the potential effects of HIIT on cognitive roles. A number of studies have already shown the potential effects of HIIT on cognitive function. The purpose of this trial is to evaluate the cognitive effects of HIIT on the individuals of MA dependent.

Methods and analysis

240 individuals of MA dependent are randomly assigned to High-intensity Interval Training group (HIIT), Moderate-intensity Continuous Training group (MICT) and Control group (CON) respectively. HIIT consists of a 24-minute exercise of high-intensity interval training on a treadmill. MICT consists of a 1-hour body-mind exercise. CON remains their traditional intervention. The experimental period will be 12 months, with 3 interventions weekly for the first 6 months and follow-up for the next 6 months. All subjects will be given both physical and cognitive tests at baseline, after intervention and follow-up. The cognitive performances will be compared by a mixed-model analysis for repeated-measures.

Discussion

HIIT training may reduce illicit drug cravings among individuals of MA dependent, it indicates that HIIT has better effect on cognitive functions such as memory and executive function for individuals of MA dependent.

Trial Registration

ChiCTR, ChiCTR2000032492, Registered on Aril 30, 2020, Prospective registration, http://www.chictr.org.cn/edit.aspx?pid=52127&htm=4.

Introduction

Substance abuse is a growing public health concern worldwide which not only causes negative influences to the health of abusers, but also leads to the occurrence of illegal and criminal behaviors. The consumption of the amphetamine type stimulant methamphetamine (MA) has risen rapidly in the past few years with an estimated annual prevalence of 0.7% worldwide (United Nations Office on Drugs and Crime, 2017). While in China by the end of 2018, there were 2.5 million drug dependents among whom 1.35 million were methamphetamine abusers, nearly half of the total according to the national anti-drug office (Office of China National Narcotics Control Commission Publication, 2018). Compared with traditional illicit drugs such as opium and heroin, MA causes greater harm to human body (Feil et al., 2010). Except arousing the strong mental dependence of users, MA also affect the central nervous

system directly and cause irreversible damage (LI, LI, ZHENG, & WANG, 2011; Zou, Guo, & Zheng, 2012). Numerous long-term users of MA suffer consequences such as physical illness, mental health, social adjustment, and poor mental symptoms (Iudicello et al., 2010; Scott et al., 2007). One study found this may result from long-term use of MA that disrupting the prefrontal striatum dopamine pathway, which involved in various cognitive and psychomotor processes including behavioral decision-making (Le et al., 2016). In fact, a number of examines have shown that long-term use of MA can lead to a series of cognitive deficits (Bernheim, See, & Reichel, 2016; Zhong et al., 2016), among which the most serious are related to reward or impulsiveness and social cognition (Potvin et al., 2018), such deficits are associated with decision-making disorders caused by drug addiction (Mizoguchi & Yamada, 2019). Different from normal subjects, those who had been using MA for more than five years had a defect in their decision-making ability among balancing reward and punishment (Le et al., 2016). MA using changed the decision-making of individuals by altering the value perception of reward and negative results (Mizoguchi et al., 2015) which could lead addicts continue to make negative decisions despite the potential hazard of the reward stimulus (Zhao, Huang, & He, 2016). This definitely means they get out of control on themselves towards drug-taking and drug-seeking behaviors (Mizoguchi, Wang, Kusaba, Fukumoto, & Yamada, 2019). Data from several Stroop tests including alcohol, cocaine, nicotine, internet addiction pointed out that compared with normal control group or light symptoms, addicts performed poor concentration, reaction time and accuracy under addiction-related stimulus, which represent their poor inhibitory control (Dong, Zhou, & Zhao, 2011; Fehr, Wiedenmann, & Herrmann, 2006; Field, Christiansen, Cole, & Goudie, 2007; Hester, Dixon, & Garavan, 2006; Lusher, Chandler, & Ball, 2004). Similarly, another research results showed MA dependents performed delay and misjudgment as well as poor cognitive control in a Stroop test using MA-related words as irrelevant stimuli (C. WANG, YUAN, LI, & SUI, 2015). Another drawback of long-term use MA was attention deficit (Baicy & London, 2007). It was identified MA and cocaine abusers performed worse on the Stroop test for attention than healthy control subjects (Kalechstein, Newton, & Green, 2003; Salo et al., 2002). In summary, extensive studies have shown that individuals who are chronically exposed to illicit drugs experience difficulties in execution, inhibition, and decision-making (Baicy & London, 2007).

In recent years, exercise as supplementary treatment for substance abuse has been favored and concerned by many countries (Abrantes & Blevins, 2019). Exercise can reduce withdrawal symptoms and the possibility of relapse (Bock, Marcus, King, Borrelli, & Roberts, 1999; Taylor, Ussher, & Faulkner, 2007). Theoretical and empirical studies have found both short and long term moderate intensity aerobic and resistance exercise may significantly improve the brain cognition, psychological behavior, physical function and quality of drug-dependent group, as well as ameliorate their life quality and drug craving (Lynch, Peterson, Sanchez, Abel, & Smith, 2013; D. Wang, Wang, Wang, Li, & Zhou, 2014). According to the research of Zhuang (Shumei, 2013), the mental health of heroin addicts in the experimental group was promoted after six months of aerobic exercise, comparing to yoga intervention, the effect of aerobic exercise intervention was shown at three months while yoga exercise needed 6 months. Another study (Dongshi Wang, Zhu, Zhou, & Chang, 2017) manifested that 50 individuals of MA dependent who underwent aerobic exercise three times a week for 12 weeks had lower levels of craving and greater

accuracy in behavioral inhibition control than the control group. Relevant Tai Chi intervention for amphetamine-type synthetic drug addicts found that after 6 months of intervention, the cardiovascular function and physical condition of experimental group were phenomenal improved, the nervous system tended to balance, and the inhibitory ability of MA as well as drug craving was ameliorated (Jingjing, 2016; Mingzhen, 2018; Zhu, Ding, Dai, & Jingjing, 2016).

High-intensity interval training (HIIT) is defined as relatively short repetitive training, performed in a 'all-out' manner at the intensity close to or causes VO_2 peak, and usually lasting from 10 seconds to 4 minutes with short intervals in between (Buchheit & Laursen, 2013; Gibala & McGee, 2008). As a popular form of full-body aerobic exercise in recent years, HIIT includes various exercises such as running, roping, it is able to achieve a certain physical activity level in a shorter time than traditional aerobic exercise or physical activity. Previous studies have established that aerobic exercise has preferable influence on cognitive function including memory, reaction time (Bahdur, Gilchrist, Park, Nina, & Pruna, 2019; Loprinzi, Frith, Edwards, Sng, & Ashpole, 2018), and the effect of HIIT on physical and mental health was more helpful than Moderate-intensity continuous training (MICT). Besides, different intensities of exercise have disparate effects on cognitive function, immediately after a high-intensity workout, cognitive function got enhanced (Bahdur et al., 2019). An up-to-date meta-analysis found that within a period of time after acute high intensity exercise, subjects' executive effect including inhibitory control and memory task tended to be improved during a series of cognitive task (Chang, Labban, Gapin, & Etnier, 2012). Also, the positive effect of acute high-intensity exercise on cognitive task performance was more persistent than that of MICT (Chang et al., 2012). Acute aerobic exercise also promotes a range of cognitive behaviors in Parkinson's patients with cognitive deficits, the research suggests that effects of aerobic exercise on cognition depend on exercise intensity (Fiorelli et al., 2019). Similar study considers as well there are positive correlation between exercise intensity and cognitive function (Etnier et al., 2016; Ferris, Williams, & Shen, 2007; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001). Notably, as an important cognitive mechanism, increasing researchers have linked inhibitory control with higher cognitive functions in recent years (Groman, James, & Jentsch, 2009; J. Wang & Chen, 2013), they believe that individuals' poor inhibition control are likely to be an element in the maintaining addiction (Volkow & Li, 2004), also a key factor in the prediction of successful recovery of addicts (Baler & Volkow, 2006; Feil et al., 2010; Field et al., 2007; Garavan & Weierstall, 2012).

As a popular form of full-body aerobic exercise in recent years, HIIT includes various exercises such as running, roping, and is able to achieve a certain physical activity level in a shorter time than traditional aerobic exercise or physical activity. Researches had already elucidated physical activity has a host of potential advantages in addiction treatment (Abrantes & Blevins, 2019; Weinstock, Farney, Elrod, Henderson, & Weiss, 2017). However, as for drug addicts, it's tough for them to stick to a certain type of exercise for long periods of time due to comorbid cognitive and mental health difficulties (Abrantes & Blevins, 2019). Together, these studies indicate that the results of exercise intervention will be affected and HIIT to some extent can solve this issue owing to its less time-taking.

Investigations on MICT and HIIT to improve cognitive function have been attached much concentration of researchers at present. Although individual studies explored the effects of HIIT on drug-dependent animals (Huang et al., 2004), there is a lack of research of HIIT on cognitive effects of drug dependence. This paper describes the trial protocol of HIIT intervention for individuals of MA dependence. Specifically, we aim to determine the cognitive effect of the HIIT intervention on MA dependents. We hypothesize that, compared with control group, both HIIT and MICT intervention will be effective in improving the cognitive functions of MA dependents while HIIT will be more effective than the other two interventions.

Methods

Study design

This study is designed as a prospective, single-blind randomized controlled trial (RCT).

Design and procedures

We will recruit subjects of amphetamine-type dependent in the Mandatory Detoxification and Rehabilitation Center in Shanghai (MDRCS). Participants will be randomly assigned to three groups. Participants in the HIIT group will run 24 minutes on a treadmill with HIIT program, participants in the MICT group will practice body-mind exercise in a fixed, quiet site while participants in control group will keep their ordinary daily intervention including health knowledge education, recreational aerobics exercise. Experimental groups receive professional guide and control group conduct intervention under the guidance of MDRCS. The total experimental period will be 12 months. First 6-months is exercising intervention under the frequency of 3 times a week, total 72 times. All the interventions will be conducted simultaneously, subjects who completed 80% of the total intervention times are eligible to participate in the subsequent evaluation. During the last 6-month follow-up observation,subjects continue to carry out the traditional daily intervention according to the general practice of the rehabilitation in MDRCS. All subjects voluntarily participate in this experiment, they signed the informed consent prior to study begins.

Participants

Inclusion criteria

1) Age between 18and 40; 2)Patients diagnosed according Chinese criteria for classification and diagnosis of mental disorders in diagnostic criteria for drug dependence; 3) Patients' remaining withdrawal time more than 1 year; 4)Patients without serious medical or mental illness; 5) Primary school education or above; 6) Compulsory drug treatment personnel who volunteered to participate in this study.

Exclusion criteria

1) Participation in high-intensity interval training before; 2) Other diseases that may interfere with the implementation of the research program, such as heart and lung diseases, liver and kidney diseases,

musculoskeletal dysfunction or cancer; 3) Antisocial personality disorder and borderline personality disorder; 4) Severe cognitive, visual or auditory impairment; 5) Unstable medication.

Participants' characteristics

Demographic and health characteristics of subjects will be collected at baseline (Table 1) to describe the sample, comparison conditions, and investigate characteristics associated with outcomes. These characteristics included age, gender, education, marital status, drug abuse years, type of drug use, whether exercise, weight (kg), height (cm), body mass index, blood pressure (mmHg), and lung capacity (ml).Automatic equipment (Omron blood pressure meter), electronic digital scales, electronic lung capacity tester will be used to measure blood pressure, weight, height and lung capacity.

Table 1
Demographic and characteristics of participants

	HIIT(n)	MICT(n)	CON(n)
Age			
Gender			
Education			
Marital Status			
Drug Abuse Years			
Types of Drug Use			
Whether exercise			
Weight (kg)			
Height (cm)			
BMI			
Hypertension (mmHg)			
Pulmonary (ml)			

Sample size calculation

A statistical analysis was conducted for sample size estimation using G*power V.3.1 (Franz Faul, Universitat Kiel, Germany). The purpose of this study was to examine the effects of high-intensity interval training on major cognitive functions in individuals of MA dependent. However, due to the lack of informed preliminary data and empirical evidence on the effects of HIIT, we estimated the effect size in this power calculations using estimated sample from the published studies that compared the effects of HIIT and continuous training on cognitive function in healthy adults (Mekari et al., 2020). Specifically, we

used the values of some variables within the analysis of variance (ANOVA) framework in this essay to obtain an effect size of 0.28 through t test, then according to the F test, set α = 0.05, power = 0.95, we calculated the required sample size of 223 subjects. With an anticipated 10% attrition rate, a final average enrolment number of 240 (80 in each group) was set for the study to detect the difference in cognitive outcomes between HIIT and MICT relative to the control group.

Randomization and blinding

The study was designed as a single-blind RCT. Two trained assessors will be blinded to group allocation and will not participate in the intervention. We set a 1:1:1 ratio and generated a sequence of random numbers by computer (STATA v. 12.0, StataCorp, Texas, USA). The random numbers were placed in a sealed envelope and participants will be allocated randomly assigned to HIIT group, MICT group and control group by randomly selecting the numbers in the envelope (Fig. 1).

Intervention

HIIT group

The HIIT group will conduct 3 interventions per week for 6 whole months on a treadmill. Total exercise time is 24 minutes including a 3-minute warm-up with low intensity (walking or jogging), 18-minute of high intensity training and moderate intensity intervals, then 3-minute of relaxation (walking or jogging). The 18-minute HIIT process will consist six groups of 2-minute high-intensity exercises and 1-minute moderate intensity intervals. Training will be conducted under the supervision of professional instructors. During the supervised intervention, Heart Rate (HR) will be recorded using a Polar Heart Rate Monitor (model FT4; Polar Electro, Finland) to encourage or ensure them maintaining appropriate exercise intensity according to their measured maximum HR. In addition, each subject will be able to observe their exercise intensity and real-time heart rate from a 6 × 3 meter projector curtain.

Exercise intensity will be divided depend on separate part during the intervention. Warm-up will be 50%-65% of maximum HR and the 2-min high-intensity training will be 80–90%.The 1-min moderate intermittent will be 70–80% of maximum HR. The target intensity of relaxation will be 50–65% of maximum HR in theory (Romain et al., 2019). Exercise intensity will be controlled by regulating the speed of the treadmill. All intervention will be implemented in the afternoon, except the different intervention parts, each participant' daily rehabilitation staying the same carrying out by the administrators and will instructed to remain their usual lifestyle (such as diet and medication).

MICT group

The MICT protocol will consist of Tai Chi rehabilitation exercises and self-designed body-mind exercises. 24-styles Tai Chi movements including 'Part the wild horse's mane on both side, Hold the lute, Forearm on both sides, Grasp the bird's tail, Brush knee and twist step on both side, Golden rooster standing on one leg' will be reserved in the Tai Chi rehabilitation exercise and the entire exercise duration will be nearly 4–5 minutes;The self-designed body-mind intervention will consist 9 forms of exercise, which is tailored to

the physical and mental characteristics of illicit drug users. These movements combine Tai Chi, Qigong and Yoga, emphasizing dynamic postural control and body weight shift stepping with lateral-medial and anterior-posterior movements, body symmetry pulling across up-down and left-right axes, and hand-eye coordination movement. The duration of each session is one hour, the frequency of intervention in the MICT group will be the same as the HIIT and control group. Exercise intensity will be achieved via adjusting movements range and squat height under the guidance of the instructor.

Control group

The control group will be instructed to their normal intervention including lectures of relevant health education and daily activities such as reading books and watching news. Participants can withdraw from the study at any time according to their subjective feelings.

Incremental exercise test

The primary purpose of this test is to obtain maximum HR of HIIT group in order to minimize or avoid the risk that may occur during formal intervention. Participants will be tested on a power bike following the cardiopulmonary test guidelines of the American Heart Association (Balady et al., 2010) after knowing the procedure of the experiment. Borg6-20 scale will be used to measure motion perception every two minutes (Borg, 1982). The test will stop when the subjects reached maximum voluntary fatigue index of 18 to 20 as determined by the scale, i.e. they are unable to reach the established rhythm (< 5 RPM) for five seconds or show signs of extreme fatigue.

Primary outcome assessment

Stroop test

Stroop is one of the most widely used neurocognitive tasks (Mitchell & Potenza, 2017) as well as a tool to assess the efficiency of inhibition mechanisms and explore the relationship between inhibition and impulsivity (Portugal et al., 2018). Individuals with substance use disorders have lower baseline metabolic activity in the prefrontal cortex (PFC), which is associated with impaired cognitive function in decision-making and inhibitory control (Alizadehgoradel et al., 2020; Bechara, Tranel, & Damasio, 2000). The cognitive portion of the Stroop test has been used as a psychometric test to assess cognition as it relates to executive function in decision making and inhibitory control related to prefrontal cortex exercise.

Experimental materials are RED, GREEN, BLUE characters written in Chinese ‘□, □,□’ and conditions are classified as congruent and incongruent. Congruent condition means the font color in line with its literal meaning. For instance, the word "□" written in red; incongruent condition means the font color disagree with its literal meaning;For example,the word "□" written in green. Participants will be asked to respond to the color of the word with the following instructions: Press ‘J’ key if the color of the Chinese character is red, press ‘K’ if it’s green, press ‘L’ if it’s blue. Key ‘J,K,L’ corresponds to the index finger, middle finger and ring finger of the right hand respectively. At the beginning of the experiment, the fixation point "+" 500 ms

will be presented in the center of the screen then the experimental stimulus is presented. Participants will be required to identify the color of the stimulus on the premise of ensuring correct reflection then use the right finger to make correspondent response. Stimulus words last for 1000 ms or disappear after pressing the button then entered the next test after 500 ms.

The whole task will be divided into two parts and the former has feedback while the latter not. There are four stages each consisting of 40 trials in formal trials with 30-second break between. The three color words are presented to the participants for 24 times and the symbols of red, green and blue are presented for 16 times. Each subject will receive a total of 120 tests. Sequence of presenting is randomly. Response time (RT) and accuracy are recorded at each stage. Accuracy represents individual's inhibition control ability. Average RT (ms) of HIIT group will be compared to the MICT group and the control group (Fig. 2).

Wechsler Adult Intelligence Scale-III

The Wechsler Adult Intelligence Scale is the most commonly used test for assessing intelligence in various settings including clinical practice (Wechsler, 2008). Two tests of the Wechsler Adult Intelligence Scale-III—Digit Span and Symbol Search will be used to evaluate the following cognitive aspects: attention, working memory, processing speed, executive functions and cognitive flexibility.

1. Digit Span

Digit span is a sub test comprised in the WISC-III constituting an attention and working memory measure. The examiner pronounces a list of digits at a rate of approximately one digit per second, and the patients are required to repeat the list in the same order immediately. If they succeed, a list one digit longer is presented; if they fail, a second list of the same length is presented. If participants are successful on the second list, a list one digit longer is given as before. However, if they also fail on the second list, the test is ended. The length of the digit sequences increases gradually, starting with a sequence of 3 numbers (e.g.: 5, 8, 2) to a sequence of maximum 9 items (e.g.: 7, 1, 3, 9, 4, 2, 5, 6, 8). The span is established as the length of the most extended list recalled correctly.

2. Symbol Search

This test evaluates attention, speed of mental processing, short-term visual memory, visual-motor coordination, cognitive flexibility, visual discrimination, psycho-motor speed, and speed of mental operation. It consists of 60 items. The task is to identify whether the symbols displayed in the target group (left) are present in the hunt group (right). Working within a specific time limit (120 s).

Table 2
Primary outcome of baseline measurements

	HIIT	MICT	CON
Stroop			
Accuracy(%)			
Mean reaction time (ms)			
Congruent RT (ms)			
Incongruent RT (ms)			
Interference Cost (ms)			
Digit Span			
Attention			
Working Memory			
Symbol Search			
Attention			

Secondary outcome assessment

Cognitive function test

Eight aspects of cognitive function will be examined using the CogState assessment tool: Speech learning and memory (International Shopping List Task, ISLT), processing speed (Detection Task, DET), Attention and vigilance (Identification Task,IDN), Visual learning and memory (One Card Learning Task, OCL), working memory (Two Back Task, TWOB), spatial working memory (Continuous Paired Association Learning Task), Problem solving and wrong supervision (Groton Maze Learning Task, GML), social cognition (Social Emotional Cognition Task, SEC). All the tests will be conducted in a quiet room, the questions will be presented to the participants in a fixed order fora computer to reduce distractions, and each test will be scored automatically.

Craving Automated Scale for Substances (CAS-S)

Chinese version of the addictive substance craving and automated behavioral response scale (CAS-S) will be adopted revised from English version. The scale is a self-rating scale consisting of 15 items in total, each item values 6 points, 0 = never; 1 = hardly; 2 = occasionally; 3 = frequently; 4 = very frequently; 5 = always. Use of addictive substance will be asked at the end of the questionnaire. This scale shows a good reliability and validity in the measurement of craving and automatic behavior characteristics of drug addicts (Rui-ting, Peng-fei, Wen-jun, Zhi-ling, & Hong, 2019).

Mental health characteristics

Mental health characteristics will be collected by Symptom Check List90 (SCL-90). SCL-90 mainly measures 10 kinds of mental symptoms, including somatization, depression, anxiety, fear, compulsive symptoms and other factors. Each measurement item adopts a five-level grading system: (1) Not at all; (2) Minimal; (3) Moderate; (4) Severe; (5) Extreme. The checklist will be used to assess how you actually feel “now” or “in the last week”.

Statistical analysis

SPSS25.0 (IBM) will be used for statistical analysis. When the data meets normal distribution, The repeated-measures (ANOVA)will be applied to analyze the data of within groups (time), between groups (HIIT, MICT, CON) and time (pre-test, pro-test) × groups (HIIT, MICT, CON). For the Stroop test, a 2 × 3 repeated-measures (ANOVA) will be conducted to test (time × groups). Independent sample t-test will be applied to test the continuity variables in the baseline of the subjects. Classification variables will be tested by Chi-square. All post-hoc tests are corrected by Bonferroni for multiple comparisons. Intention-to-treat analysis will be used to process the missing data. The linear mixed model method will be applied to analyze all continuous variables with random missing values. The magnitude of the difference between fitness levels will be assessed by the Hedges’ g (g), as presented elsewhere (Dupuy et al., 2014). The magnitude of the difference will be considered either small ($0.2 < ES < 0.5$), moderate ($0.5 < ES < 0.8$), or large ($ES > 0.8$). The significance level is set at $p < 0.05$ for all analyses. The descriptive outcomes are displayed as mean ± standard deviation (Mean ± SD).

Ethics

This study has been approved by the Ethics Committee of Shanghai University of Sport and registered at China Clinical Trial Registry. Participants will sign informed consent prior to the participation of the trial. Only participants who sign the form will be included in the study. The results of the survey will be published anonymously, and subjects may immediately withdraw from the study if there is an unexpected worsening of motor or neuropsychiatric symptoms.

Discussion

The present study may find that, on the basis of traditional interventions, HIIT training may reduce illicit drug cravings among individuals of MA dependent, it indicates that HIIT has better effect on cognitive functions such as memory and executive function for individuals of MA dependent.

The conjunction of exercise and medicine therapy is still a vital means of drug withdrawal management for substance abuse (Ashdown-Franks et al., 2020; Linke & Ussher, 2015). Individuals of MA dependents demonstrate worse functional performance in several specific domains, including comprehension and planning, engaging in financial transactions, setting up travel arrangements, communication skills, and they often exhibit poor cognitive control, decision-making, and social adjustment (Dean, Groman, Morales, & London, 2013; Henry, Minassian, & Perry, 2010; Kim, Kwon, & Chang, 2011). However, this can be ameliorated by exercise training. Preliminary studies suggest that HIIT may be superior to low-intensity

exercise in improving and maintaining executive function (Cooper & Tomporowski, 2017; Kao, Westfall, Soneson, Gurd, & Hillman, 2017; Tsukamoto et al., 2016). A study proves that two weeks of HIIT had a mixed effect on adolescents' cognition (Stenman, Pesola, Laukkanen, & Haapala, 2017). HIIT can also improve the inhibition of mentally ill youth by improving the response efficiency of the Stroop test control (Lee, Boafo, Greenham, & Longmuir, 2019), evidence from a research showed that longer training time may have a stronger effect on cognitive function (Stenman et al., 2017). In addition, one research team (Drigny et al., 2014) conducted 6-month HIIT on 6 obese patients, the finding indicated that participants' cognitive functions such as short-term memory, verbal memory, processing speed and attention were significantly improved after intervention compared with those of before training. Moreover, studies reported that HIIT is more effective than continuous aerobic exercise for improving inhibit control task performance as a result of longer sustained benefits and increased neural efficiency for healthy adults (Kao et al., 2017; Tsukamoto et al., 2016).

The positive effect of HIIT on the improvement of cognitive function can be explained by the following mechanisms: The first is that exercise may increase cerebral blood flow. The cardiovascular hypothesis suggests that improvements in cardiovascular function (cardiac output, oxygen transport, and metabolism) can improve neurotransmitter function and brain health (Dustman et al., 1990). According to this hypothesis, the higher the cardiac output, the higher the cerebral blood flow, which means HIIT is more adaptable to the cardiovascular system and has a positive effect on the cognitive ability (Mekari et al., 2020). Study has proved HIIT induces a greater increase in cardiac output than MICT (Helgerud et al., 2007). Thus, this may be one cause that HIIT is better than MICT in improving cognitive function.

The second mechanism is in regards to BDNF increases in brain. Acute aerobic exercise increased levels of brain-derived neurotrophic factor (BDNF) which is a significant component of the brain's neuroplasticity (Ferris et al., 2007; Knaepen, Goekint, Heyman, & Meeusen, 2010). It is well known that physical activity can improve the circulation level of BDNF, which has beneficial properties of neurotrophic, neuroprotective and cognitive (Walsh, Smith, Northey, Rattray, & Cherbuin, 2020). The impact of physical exercise on BDNF has been well summarized by some published reviews. Current evidence supports that physical exercise may change the concentration of BDNF in the brain, acute and chronic aerobic exercise increases peripheral BDNF concentration (Coelho et al., 2013; Knaepen et al., 2010; Mang, Campbell, Ross, & Boyd, 2013). Specifically, several studies have shown that BDNF levels increased after short-term moderate-intensity exercise (Ferreira, Real, Rodrigues, Alves, & Britto, 2011). Mindfulness meditation, physical and mental exercises including yoga and Tai Chi can increase circulating BDNF in healthy and sick individuals as well (Cahn, Goodman, Peterson, Maturi, & Mills, 2017; You & Ogawa, 2020). In addition, a new study shows (Abbasian & Asghar Ravasi, 2020) that 3-week HIIT can bring about more expression and delivery of BDNF in brain and plasma. Similar study also demonstrated that HIIT can attenuate hippocampal oxidative damage likely by increasing the concentration of BDNF (Freitas et al., 2018).

Exercise-training interventions can increase basal BDNF of healthy adults (Abbasian & Asghar Ravasi, 2020; Dinoff, Herrmann, Swardfager, & Lanctôt, 2017), and BDNF has long been implicated in cognitive

benefits (Leckie et al., 2014). Training-induced changes in BDNF have also been found to mediate cognitive improvement through hippocampal and peripheral levels in animal models (Vaynman, Ying, & Gomez-Pinilla, 2004) and human models (Leckie et al., 2014). It is worth noting that a recent study examined the relationship between BDNF and cognition and found that the level of BDNF in the brain is related to the cognitive area (Hori et al., 2017). Another research on the relationship between BDNF levels, physical activity and cognition also believes that high-intensity short-term activities may effectively promote the BDNF response and extend brain health from a practical perspective (Walsh et al., 2020). Through these findings, we speculate the improvement of cognitive function in patients with cognitive deficits may be caused by exercise-induced increasing in BDNF levels, and high intensity aerobic exercise is able to increase the level of this substance in the brain.

Whether HIIT is a suitable exercise for MA dependents is controversial. Some researchers believe that interval training may be too arduous and may give participants a feeling of incompetence, failure, and inferiority, thereby reducing participants' motivation to participate in physical exercise (Hardcastle, Ray, Beale, & Hagger, 2014). However, some studies conducted on adults with mental illness have shown that HIIT is as feasible as continuous aerobic exercise in terms of withdrawal rate, self-determined exercise motivation, and emotional response after exercise (Bartlett et al., 2011; Gerber, Minghetti, Beck, Zahner, & Donath, 2018). HIIT consists of customized exercise prescriptions which are feasible to be used in most exercise environments (Ross, Porter, & Durstine, 2016). So far, the exercise intervention for substance abuse mostly concentrated in the low and moderate intensity, while these interventions may exert positive effect to cognitive function. However, the effectiveness brought by high intensity exercise is generally considered better than that of moderate intensity exercise n (CHEN, ZHOU, WANG, ZHOU, & LU, 2019) apart from some potential risks brought by HIIT (Quindry, Franklin, Chapman, Humphrey, & Mathis, 2019).

There are several limitations in this study. First, it is difficult to achieve a blinded intervention for this study because exercise that served as an intervention is widely open to the participants. Second, the subjects in this trial were restricted to MA use, therefore, the effect of HIIT on other types of substance use remains unknown. Third, function of cardiorespiratory and other organs of the body are highly required to be mobilized during the HIIT intervention. Hence, future research should be concentrated on how to reduce the risk of HIIT intervention on both healthy and disease subjects.

This trial will compare the effects of HIIT on the cognitive function of MA dependent individuals, the results may offer new evidences to the effects of HIIT for illicit drug abusers.

Trial Status

The study has been initiated as planned in April 2020. Recruitment is ongoing. The study will be completed in July2021. The protocol version number is 2020-4, Date: May-31-2020.

Abbreviations

Methamphetamine (MA)

High-Intensity Interval Training (HIIT)

Moderate-intensity Continuous Training (MICT)

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate will be obtained from all participants.

Consent for publication

Obtained.

Availability of data and material

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Sheng Menglu participated in the design of the study and drafted the manuscript. Zhu Dong participated in the design of this study, coordination of intervention conducted in Shanghai detoxification and rehabilitation center, and calculated the sample size. Yang Suyong participated in manuscript revision, study design. Lu Songting participated in exercise design and discussion related to Tai Chi. All authors read and approved the final manuscript.

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Figures

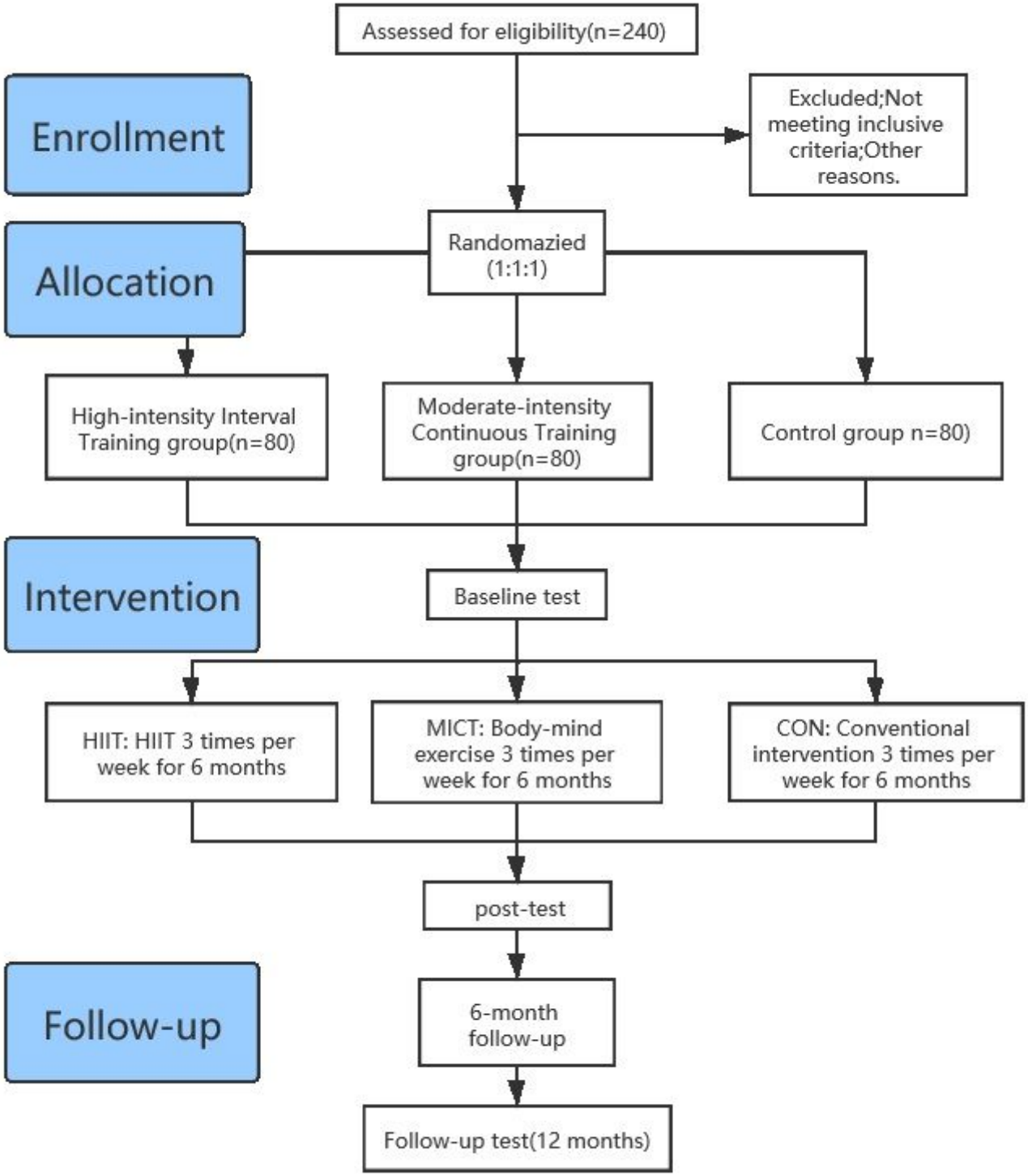

Figure 1

Flow Diagram of Study Design

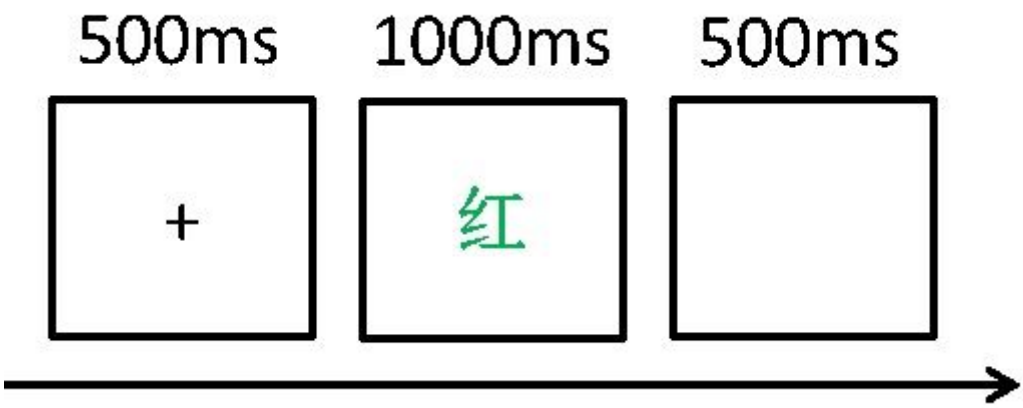

Figure 2

Stroop test

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