Peripheral inflammatory biomarkers of methamphetamine withdrawal based on the neuro-inflammation hypothesis: the possible improvement effect of exercise

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Research Article

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Abstract

BackgroundInvestigate how exercise affects the desire for methamphetamine (MA) withdrawal and to explore the mechanisms of peripheral inflammation.

Methods Ninety methamphetamine withdrawal patients participated enrolled in the study. The subjects were grouped according to the degree of craving induced by the clues: non craving control group (NCC group), craving control group (CC group) and craving exercise group (CE group). The CE group performed aerobic combined resistance training. The ELISA method was then used to detect plasma IL-6, TNF-α and IL-1β concentrations, Visual Analogue Scale(VAS) measurement of cue-induced cravings under Virtual Reality(VR) exposure (VR-VAS) and the Desires for Drug Questionnaire (DDQ) were used to assess cravings.

ResultsPlasma IL-6, TNF-α, IL-1β, levels as well as the VR-VAS and DDQ scores of methamphetamine withdrawal patients were significantly reduced after exercise; The scores of VR-VAS were positively correlated with the plasma concentrations of IL-6, TNF-α and IL-1β.

ConclusionsThis study confirmed that plasma IL-6, TNF-α and IL-1β can be used as biomarkers of peripheral inflammation in methamphetamine withdrawal patients to predict the degree of craving. At the same time,eight weeks of incremental load aerobic combined with resistance training reduces peripheral inflammation, significantly reduces the level of craving for MA extraction.

Introduction

Methamphetamine (MA) is an addictive drug, and the abuse of MA can cause irreversible structural damage to the brain regions involved in regulating cognitive functions [1]. The current literature shows that the abuse of psychostimulant drugs can cause certain damage to the blood-brain barrier (BBB) and cause neurotoxicity [2]. Exposure of animals to methamphetamine induces neurotoxicity via several molecular and cellular mechanisms including various receptors, energy metabolism, inflammation and immune system activation [3].

The neuroinflammation hypothesis states that methamphetamine affects the activity of glial cells, which in turn triggers the addictive behavior and neurotoxicity of

methamphetamine. Microglia are immune cells in the brain. When activated, they can easily cause neuronal damage because they secrete some chemokines and cytokines. On the other hand, astrocytes are abundant in the central nervous system (CNS), which protect the brain and maintain brain homeostasis [3]. At the same time, astrocytes can also secrete a variety of cytokines such as tumor necrosis factor, interleukins and chemokines to activate methamphetamine-induced neurotoxicity [4]. A study reported that the activation of microglia and the proliferation of microglia in the CNS of MA addicts showed a proliferation trend for at least two years [5].

MA abusers seeking treatment usually suffer from serious neuropsychiatric complications (cognitive impairment, etc.), which are still observed after discontinuation of use thereby negatively affecting recovery outcomes [6-7]. A study on mice treated with MA showed that peripheral and central nervous system immune disorders and cytokines (IL-6, TNF-α and IL-β) showed specific changes in peripheral plasma and brain regions [8]. It has been shown that adults who recover from early MA dependence also exhibit peripheral immune deficiency, and the changes in immune cytokines activated by MA increase with the increase in cognitive impairment [8-9].

Another study show that moderate-intensity aerobic exercise reduces craving in MA- abuser individuals [9–11]. At the same time, aerobic combined resistance training can significantly reduce the anxiety and depression associated with MA withdrawal, improve aerobic capacity, muscle endurance and strength, improve heart rate variability, and promote the recovery of drug dependence [12-16]. In addition, long-term moderate-intensity exercise can reduce inflammation levels [17]. Some studies show that exercise does not have sufficient clinical benefits. Although exercise can relieve depression symptoms and improve physical fitness, it cannot reduce drug consumption [18]. This calls for further investigations into the mechanisms and methods. Based on the hypothesis of neuro-inflammation, this study hypothesized that levels of inflammation in the peripheral blood of patients with MA withdrawal can be used as plasma inflammatory markers for craving, and exercise can reduce MA-related pathology and show treatment efficacy. Therefore, the study is to test whether aerobic combined resistance training can reduce the cue-induced cravings of MA abstinence individuals, and to explore its peripheral inflammatory mechanisms. The overarching goal of the study is to provide a theoretical basis for reducing drug cravings during withdrawal, and provide protection for individuals withdrawing from drugs to better return to the society.

Subjects And Methods

Subjects

This study selected 765 male withdrawals from the Changsha Changqiao Rehabilitation and Addiction Treatment Center in Hunan Province. The selection criteria are as follows: (1) All participants are male MA abusers and it is not combined with other drugs; (2) More than two years of drug use; (3) Snorting as the method of taking drugs; (4) No obvious diseases such as systemic disease, metabolic diseases, autoimmune diseases, cerebrovascular diseases and family genetic diseases; (5) No anti-inflammatory drugs and β-blockers were taken within one month before and during the intervention; (6) All the participants filled in a Physical Activity Readiness Questionnaire+(PAR-Q+) to ensure that they were suitable for exercise. The investigation process is shown in **Figure 1.**

765 male drug addicts in the Changsha Changqiao Rehabilitation and Addiction Treatment Center

562 people were screened out according to the hospital physical examination report and the filled PAR-Q+ to ensure suitable exercise, the screening rate was 73.5% (562/765).

Filled in the basic situation questionnaire: Determine type of medication.Taking drugs for more than 5 years. The final number of people was 169,while the screening rate was 37.7%(169/562).

169 people were evaluated using VR-VAS, and based on the comparison of heart rate, blood pressure, and VR-VAS score fluctuations. False fillings and wrong fillings were excluded. Finally, 90 drug addicts were enrollment in this study, with a screening rate of 53.3% (90/169).

90 drug addicts participated in the experiment, among them, 16 people dropped out, and the dropout rate of 16 cases was 17.8% (the dropout rate of the NCC group was 11.1%, and the dropout rate of the CC group and the CE group was 3%) (Table 1**).**

The grouping of 90 subjects is as follows: 30 people in the non-craving control group (NCC group), 30 people in the craving control group (CC group), and 30 people in the craving exercise group (CE group).Withdrawals in the craving group were assigned using simple random sampling.

FIGURE 1

Screening Flow Chart

The Ethics Committee of Hunan Normal University approved this study (Batch number: 16-2010). We completed the research in compliance with the ethical requirements of clinical trials. In addition, all subjects signed informed consent.

The dropout rate of 16 dropouts was 17.8% (the dropout rate for the NCC group was 11.1%, and the dropout rate for both the CC group and the CE group was 3%). The remaining 74 were excluded, namely:NCC group (20 people), CC group (27 people), CE group (27 people). The criteria for dividing the degree of craving are: abstinence with craving had increased heart rate and blood pressure during VR-VAS ($p<0.05$) with a score range of 11–100. The advantage of the method is that it can eliminate the possibility of subjectively selecting samples. Alternatively, abstinence with decreased heart rate and constant blood pressure were assigned to a group of patients ($p> 0.05$) with a score interval between 0~10 (Table 1).

Table 1
Basic information

Content	NCC group(n=20)	CC group(n=27)	CE group(n=27)
Age(year)	37.15±9.71	33.55±6.53	36.75±9.30
Height(cm)	166.0±5.59	166.4±5.78	167.95±4.45
Weight(kg)	66.50±8.96	61.45±8.01	65.95±7.32
History(month)	74.55±8.00	73.20±12.32	72.25±10.36
The length of withdrawal (week)	2.95±2.06	3.00±1.90	3.59±2.59

Methods

Exercise intervention

Aerobic combined resistance exercise is considered to be a good adjuvant treatment for methamphetamine withdrawal[12-16]. This exercise intervention program follows ACSM's recommendations[19]. In this study, 27 people in the exercise group received structured and progressive exercise intervention, while the control group received safety and health education. Each person's maximum heart rate (HR_{max} =206.9- 0.67×age) and maximum weight (1RM) were determined before exercise for one repetition. The specific content of the exercise intervention program was as follows: Each practice time is 60 min, 5 times a week, practice 8 weeks. The exercises for the muscle groups were divided into upper limb and lower limb muscle groups, strength resistance training is aimed at improving muscle strength and explosive power, with 8-12 times for each group, 2 sets for each device, 60s interval for each set. In addition, each equipment was used by the two groups, and each group had an interval of 60s (Figure 2).

PAR-Q+(Physical Activity Readiness Questionnaire+)

PAR-Q+ is an internationally recognized health risk assessment questionnaire. Exercise prescribers or qualified coaches can use it to understand the subjects' health history, symptoms and risk factors, and to understand possible risks and safety during exercise. At the same time, individualized, safe and effective exercise prescriptions can be designed for subjects based on the evaluation results. PAR-Q+ includes 7 general health problems and 10 supplementary problems for diseasesIf the answer is "no", then the subject is not allowed to participate in physical activities, which follows the general physical activity guidelines for healthy asymptomatic people [20]. The participant is only cleared for physical activity if he or she answers no to all of the follow-up questions on pages two and three. The survey conducted in this study found that 203 (26.5%) people were not suitable for exercise, while 562 (73.5%) people were suitable for exercise.

Measurement of craving

Desires for Drug Questionnaire (DDQ)

DDQ were originally used for self-evaluation of instant cravings for heroin withdrawals. However, recent studies have also applied it to evaluate the short-term craving process of METH withdrawals in clinical trials [21]. The questionnaire consists of three dimensions: desire and intention (the average of the sum of questions 1, 2, 4, 6, 9, 12, and 13), negative reinforcement (the average of the sum of questions 5, 8, 10, and 11), and control (the average of the sum of questions 3 and 7). DDQ can be used as a multidimensional scale to replace VAS, but at the same time, each dimension of DDQ has a high correlation with VAS. Therefore, the combination of DDQ and VAS used in this paper can better illustrate the problem.

Cue-induced craving during VR exposure(VR-VAS)

VAS used previously for heroin. The initial score of the scale is 10 where "0" represents no desire for heroin, while "10" represents a strong desire for heroin. In addition, "1-9" represents different levels of desire. However, scholars have different views on the severity of desire defined by VAS [22-27].

In this study, head-mounted VR devices (Pico Goblin A7215), headsets, and a 0-100mm VAS scale (0 means "no craving", while 100 means "extreme craving") were used to induce craving for methamphetamine cues during VR exposure. The DDQ score was then determined immediately after the evaluation. The VR-VAS and DDQ assessments were carried out on the same day as the blood draw, and the number of people assessed each time was 3 people. The test procedure was as follows: The participants were required to relax for 5 min, measure the baseline heart rate and blood pressure before the test. Next, they were asked to immediately wear the VR device to watch the neutral pictures (landscape, still life) for 5 min, immediately record VR-VAS and DDQ scores and measure the blood pressure and heart rate and rest for 5 min. After cue induction, the baseline blood pressure and heart rate were measured after which the VR device was put on to watch the meth equipment and objects, as well as the pictures and videos of meth inhaling ice for 5 min with sound effects. After completion of the prompt procedure, the VR-VAS and DDQ scores were immediately recorded, and the blood pressure and heart rate were measured (the heart rate measuring instrument was the Polar meter V800 made in Finland, while the sphygmomanometer was Omron T10).

Biochemical

The plasma concentration of IL-1β (Reagent test kit: ml058059-2;batch number LOT20181205A), TNF-α (Reagent test kit ml077385-2 batch number LOT20190207A) and IL-6 (Reagent test kit ml027379-2 batch number LOT20190508A) was measured by ELISA. The company name is Shanghai Enzyme Link Biotechnology Co., Ltd.

Statistical Methods

Mixed-effects analysis of variance was used to evaluate the differences in VR-VAS scores, blood pressure, heart rate, etc. between baseline and neutral induction, baseline and cue- induced NCC group, CC group, and CE group. Then use repeated measures analysis of variance to analyze the differences in different groups and time. Then assess the effect of the interaction on VR-VAS, DDQ scores, and plasma levels in patients with MA withdrawal. In the case of $p<0.05$, the Bonferroni method was used for post-test comparisons between groups. In addition, Pearson correlation analysis was used to evaluate the correlation between three groups of plasma and VR-VAS score, VR-VAS and DDQ three-dimensional score. Use SPSS

22.0 to perform statistical analysis on the acquired data.

Results

Results of VR-VAS, heart rate and blood pressure before and after elicited

The cue induction results show that group and time affect the changes in VR-VAS (F=146.87, $p<0.001$; F=0.032, $p<0.001$), heart rate (F=5.96, $p<0.001$; F=35.223, $p<0.001$), systolic blood pressure (F=9.782, $p<0.001$; F=95.314, $p<0.001$) and diastolic blood pressure(F=2.849, $p>0.05$; F=38.357, $p<0.001$) induced by cue, and there is an interaction between group and time (F=3.629, $p<0.05$; F=24.438, $p<0.001$; F=23.395, $p<0.001$; F=8.966, $p<0.000$). After

neutral induction, the VR-VAS score, heart rate, systolic blood pressure, and diastolic blood pressure in the NCC, CE, and CC groups did not change ($p>0.05$); after induction, the VR- VAS, heart rate, systolic and diastolic blood pressure in the NCC group did not change. VR- VAS, heart rate, systolic blood pressure and diastolic blood pressure increased in CC group ($p>0.05$) and CC group ($p<0.01$). (Figure 3).Each value in the figure is represented by Means

±SD.

VR-VAS and DDQ pre-exercise and post-exercise results

The obtained results indicated that both group and time affected the change of VR- VAS ($p<0.001$), and there is an interaction between them ($p<0.001$). The VR-VAS of the CC group and CE group was decreased after eight weeks when compared with pre- exercise ($p<0.01$) (Figure 4). Each value in the figure is represented by Means±SD.

The obtained results indicated that both group and time affected changes in the three dimensions($p<0.01$), and there is an interaction between them ($p<0.001$). The “desire and intention” and “negative reinforcement” of the CC group and the CE group post- exercise were significantly reduced when compared with pre-exercise ($p<0.01$), but in contrast the CE group decreased significantly. At the same time, the “control” of the CE group was significantly increased post-exercise ($p<0.01$), but there is no change in the CC group (Figure 5). Each value in the figure is represented by Means ± SD.

Measurement results of plasma IL-1β, TNF-α, and IL-6 concentration pre- exercise and post-exercise

The obtained results indicated that the concentration of IL-1 β, TNF - α, and IL-6 were affected by group and time ($p<0.001$), and there is an interaction between them($p< 0.001$). A comparison of week zero and week eight indicated that the plasma concentrations of IL-1 β, TNF - α, and IL-6 in the CC group and CE group were significantly lower than those in the CC group ($p<0.01$), but the decrease was more obvious in the CE group (Figure 6). Each value in the figure is represented by means± SD.

Correlation analysis results of plasma IL-1β, TNF-α, IL-6, and VR-VAS scores The obtained results indicated that the plasma IL-1β concentration was positively correlated with the VR-VAS score (r=0.717, p<0.001), plasma TNF-α concentration was positively correlated with VR-VAS score (r=0.628, p<0.001), and plasma IL-6 concentration was positively correlated with VR-VAS score (r=0.570, p<0.001) (**Figure 7**).

Correlation analysis results of VR-VAS scores and DDQ

The obtained results indicated that the VR-VAS score was positively correlated with the "desire and intention" (r=0.702, p<0.001) and "negative reinforcement" (r=0.688, p<0.001). The VR-VAS score was negatively correlated with "control" (r=-0.419, p<0.001), while the "desire and intention" was positively correlated with "negative reinforcement" (r=0.690, p<0.001) and negatively correlated with "control" (r=-0.507, p<0.001). In addition, "negative reinforcement" was negatively correlated with "control" (r=-0.538, p<0.001) (Table 2).

Table 2
Correlation analysis results of various dimensions between VR-VAS and DDQ

Dimension	VR-VAS	Desire and intention	Negative reinforcement	Control
VR-VAS	r=1	r=0.702**	r=0.688**	r=-0.419**
Desire and intention		r=1	r=0.690**	r=-0.507**
Negative reinforcement			r=1	r=-0.538**
Control				r=1

Discussion

The effect of aerobic combined resistance training on the levels of plasma IL-1β, TNF-α, and IL-6

A previous study reported that exercise protects an individual against the MA-induced systemic increase of pro-inflammatory cytokines levels. In addition, exercise can

prevent BBB destruction and improve related microenvironmental changes to reduce MA-induced neurotoxicity [28]. Our research found that eight weeks of aerobic combined resistance training can significantly reduce the levels of IL-1β, TNF-α, and IL-6 in peripheral blood. There was a slight decrease in the plasma level of IL-1β in the CC group on the 8th weeks, but the decline is not obvious. On the other hand, the CE group had a smaller decrease after eight weeks. Given that the degree of craving was not different, we infer that exercise had superior effects to conventional nursing in rehabilitation centers. In addition, the plasma TNF-α levels of the CC and CE groups showed significant differences at week eight, but in contrast, the CE group decreased significantly. This indicates that the effect of exercise on the improvement of plasma TNF-α levels is relatively obvious. The plasma IL-6 levels of the CC group and the CE group both decreased after 8 weeks, but the CE group had more changes than the CC group. This

indicates that aerobic combined resistance training has a significant anti-inflammatory effect in individuals with MA withdrawal. The slight decrease in inflammation levels in the CC group may be caused by the environment of the rehabilitation treatment center due to the influence of environmental regulation and the adjustment of self-cognition. This is also an interesting finding of this research. It was found that the level of inflammation in the peripheral system can be improved. At the same time, the blood-brain barrier protects the flow of central inflammatory factors to the periphery.

The change of aerobic combined resistance training on the degree of cue-induced craving under VR exposure

Cue-induced cravings are part of addiction and can easily lead to relapse [29-30]. Exposure to drug-related clues during the withdrawal period can easily cause cravings and lead to relapse [31-33]. VR is a group of seemingly real virtual worlds composed of images and sounds. It is a simulation environment generated by the computer, so that the user is immersed in the environment. It can be delivered to users through visual and auditory senses, making them feel immersive [34]. The immersive nature of VR can be used to modulate various sensory stimuli to evaluate and induce related pathological behaviors and feelings (for example, cravings), and to evaluate possible behavioral responses. The subjects can learn how to better deal with their problems. Park et al. (2019) reported that in addition to addictive psychopathology, VR can also be used for other mental illnesses [36]. Therefore, the VR equipment is widely used in the field of medical treatment and psychological treatment of China's judicial administration drug treatment system, where it is used to diagnose or evaluate the degree of craving, isolate the interference of internal and external environmental factors to a certain extent, and create real experience and feelings for patients. This study also used DDQ as a supplementary scale to supplement VR-VAS evaluation in order to increase its accuracy by incorporating the correlation analysis results of the two scales. The correlation analysis of the three dimensions in VR-VAS and DDQ indicated that the correlation between the two scales was relatively high, and the consistency of internal dimensions was also relatively high. This is similar to the results of the study by Frank *et al.*, (2002) [37].

Cravings caused by clues can increase blood pressure, heart rate, and skin temperature [38]. This theory is consistent with psychobiological activation. Moreover, grouping is based on the degree of cue-induced cravings, and there are corresponding group differences in blood pressure and heart rate, which also explains the principle of

psychobiological activation and the rationality of grouping to some extent. However, it was difficult to screen personnel in the NCC group because the rehabilitation center was isolated from the external environment decreasing accessibility and cravings. This may be because the reason for their drug use is the influence of the surrounding environment, but they cannot get rid of the drug use environment. However, the rehabilitation center plays a role of isolation and insulation at this time. Therefore, after a period of environmental isolation in the NCC group, a smaller heart rate and blood pressure response will occur when the cue is exposed, and this is also related to the individual's sensitivity to the cue exposure. Considering that addiction mental scales are different from objective indicators such as blood, repeated

measurements can be taken within a short period of time to enhance the sensitivity and accuracy of the true results of the craving assessment. Therefore, the psychological scales were only collected at two measurement points, at week zero and week eight. The obtained results indicate that there was a certain "ceiling effect" between baseline craving and cue-induced craving in the pre-test, and the VR-VAS score of the NCC group also had a "floor effect" after cue-induced exposure. However, it is undeniable that a consistently high craving score can accurately reflect the "true" high level [39]. According to the severity of cravings in the pre-test of this study, it was found that the CC group and the CE group also showed higher levels of cravings at baseline and after cue-induced exposure.

Previous clinical studies have shown that minocycline, and indomethacin, Ibudilast, and AV1013 anti-inflammatory drugs can reduce the reward effect of methamphetamine on mice, excessive exercise and behavioral sensitization [40]. In addition, minocycline can also reduce self-administration of methamphetamine in rats and relapse of addiction [40]. These drugs are to some extent considered to be drug targets that can treat methamphetamine addiction. Another study reported that short- term aerobic exercise can reduce the cravings of MA addicts and increase their inhibitory capacity [41]. The results obtained in this study also show that aerobic combined resistance training can significantly reduce the cue-induced cravings of methamphetamine withdrawal, and the effect is obvious. This indicates that fighting inflammation and reducing craving through exercise has the same good therapeutic effect as anti-inflammatory drugs.

Exploration of the relationship between plasma IL-1β, TNF-α, and IL-6 levels and the degree of cue-induced craving

Previous studies have confirmed that the inflammation indicators after methamphetamine abuse have significant therapeutic significance. Chronic methamphetamine exposure leads to increased BBB permeability and increases hippocampal IL-1β levels [28]. The level of IL-1β also increased significantly in the analysis of the sample [28]. Abuse of methamphetamine can increase the level of TNF-α in the central nervous system of the brain, and the nucleus accumbens, which is closely related to drug dependence, highly expresses TNF-α mRNA and protein [42]. A previous study reported that deleting the TNF-α gene affects addictive behaviors in wild-type mice, including automatic methamphetamine seeking, motivation to take methamphetamine, and prompting induced cravings and drug-seeking behaviors [3]. IL-6 can participate in neuroinflammatory response [43] and brain pathological changes [44], and enter the functional areas of the brain related to various diseases. This indicates that peripheral inflammatory factors are closely related to central

nervous system damage and drug seeking.

This study showed that the plasma inflammation levels in the CC group and the CE group were similar. Interestingly, when the craving degree is significantly different between the NCC group and the CC group, the plasma inflammation level is also different. In addition, the correlation analysis between the predicted VR-VAS score and the plasma inflammation level shows that they are both positively correlated. This indicates that plasma inflammation levels in methamphetamine withdrawal patients are significantly

related to drug cravings caused by brain inflammation. This may be similar to the results of previous studies on the damage of peripheral and central nervous system structures and mental disorders.

Conclusions

Plasma IL-1 β, TNF- α, and IL-6 as peripheral inflammatory markers of methamphetamine withdrawal have a high correlation with cue-induced cravings. In addition, this study confirms that 8 weeks of incremental load aerobic combined resistance training can reduce plasma IL-1β, TNF-α, and IL-6 levels, and improve the craving degree after MA withdrawal.

Deficiencies And Future Prospects

The main purpose of this study was to explore the relationship between plasma IL-1β, TNF- α and IL-6 levels and cue-induced cravings. We also studied whether 8 weeks of aerobic combined resistance training can reduce the levels of IL-1 β, TNF – α, and IL- 6 during MA extraction, and improve the cravings induced by cue. This will lay the foundation for further research on whether inflammatory factors such as IL-1 β, TNF – α, and IL-6 can be used as plasma markers of craving during the withdrawal period. However, this study has some limitations. Although the effect of exercise intervention for eight weeks is similar to that in previous studies, the 8-week exercise intervention time is relatively short and cannot predict the subtle changes of various indicators after a long time. At the same time, this article only conducted research on men, and did not explore the differences between men and women. Although VR-VAS and DDQ combined with objective indicators can accurately reflect the physiological response in the induction process, the number of objective indicators is small. The experimental group in future studies should increase skin resistance, eye movement, near-infrared and other tests to enhance the examples of objective indicators. The studies should also use FMRI to analyze the neuro-toxic inflammatory injury in the reward area of the central nervous system, and then observe the improvement effect of craving degree. In addition, they should use multiple indicators and multiple dimensions to explore the correlation between the degree of inflammation and craving of methamphetamine during long-term withdrawal, and verify whether exercise can improve the effect.

Declarations

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article.

ETHICS STATEMENT

The Ethics Committee of Hunan Normal University approved this study. All participants signed an informed consent form before conducting the experiment, which was to participate in the training voluntarily.

FUNDING

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We declare that this work was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

CONEST FOR PUBLICATION

All authors agree to publish in this journal.

COMPETING INTEREST

No authors note any direct competing interest.

AUTHERS' CONTRIBUTION

Jing song Wang, Jun Zhang, Lan Zheng, Chunxia Lu conceived and designed the experiments. Jing song Wang screened experimental subjects, signed the informed consent process and conducted the exercise intervention.

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Figures

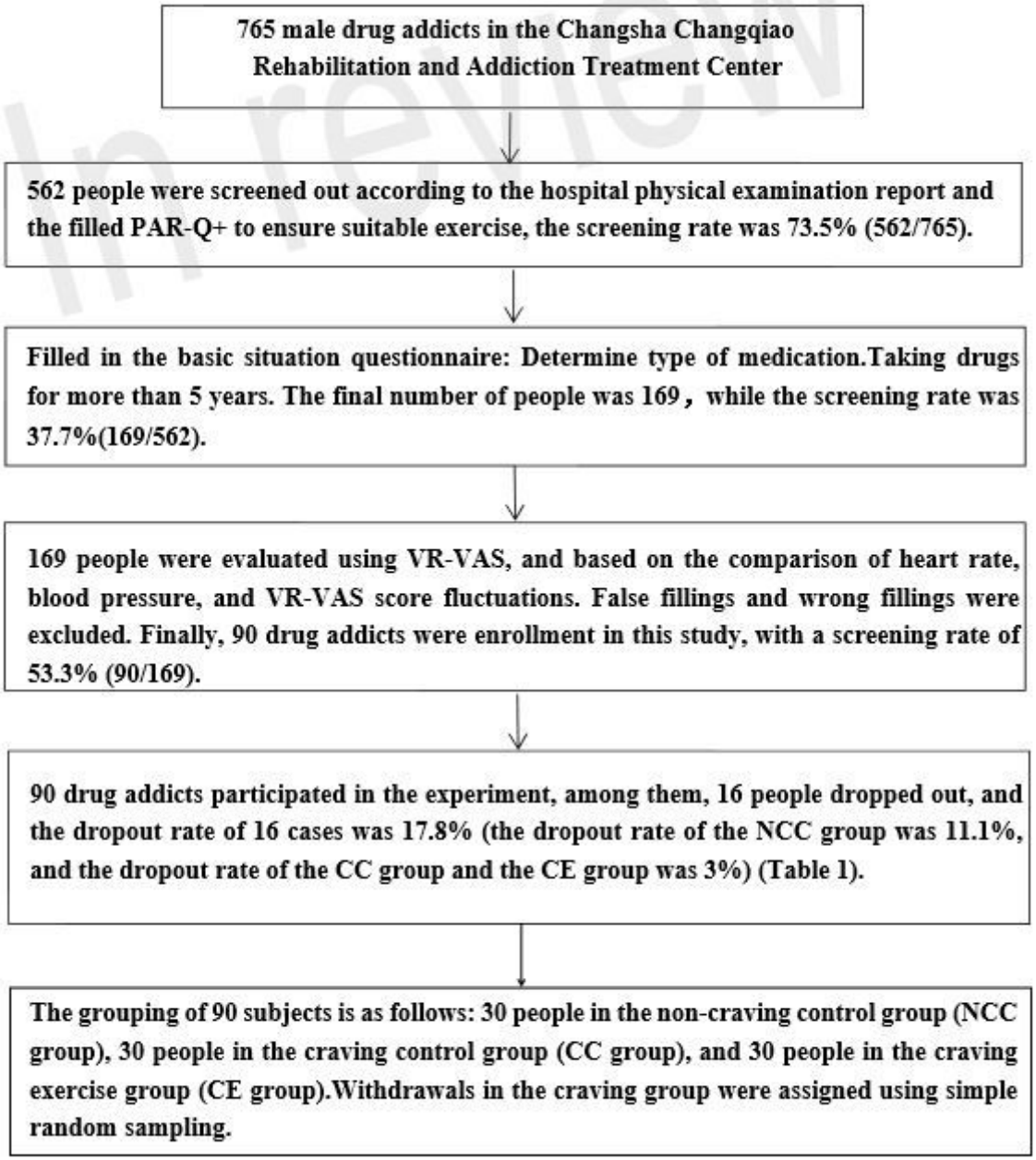

Figure 1

Screening Flow Chart

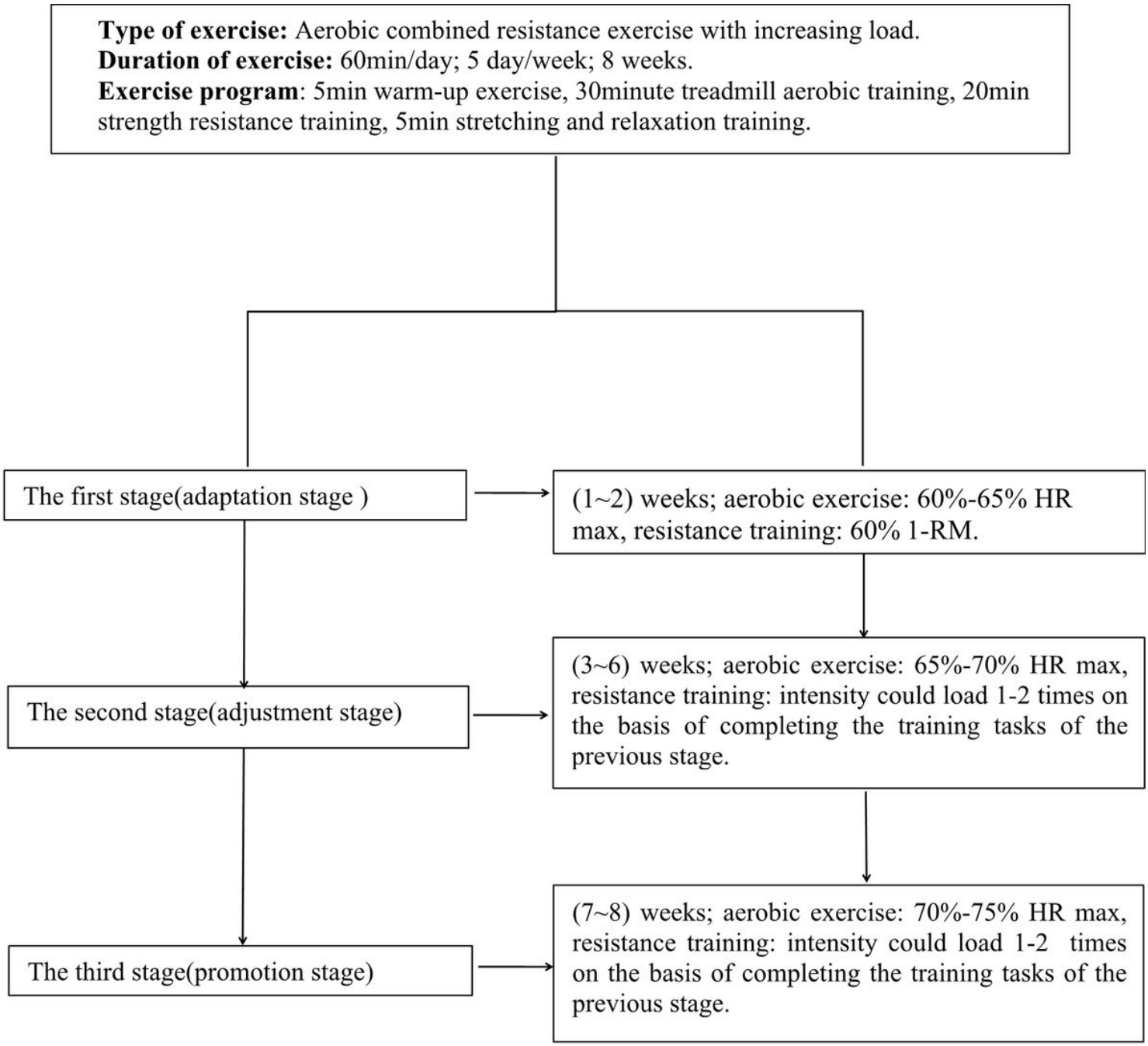

FIGURE 2: Exercise Intervention Flow Chart

Figure 2

Exercise Intervention Flow Chart

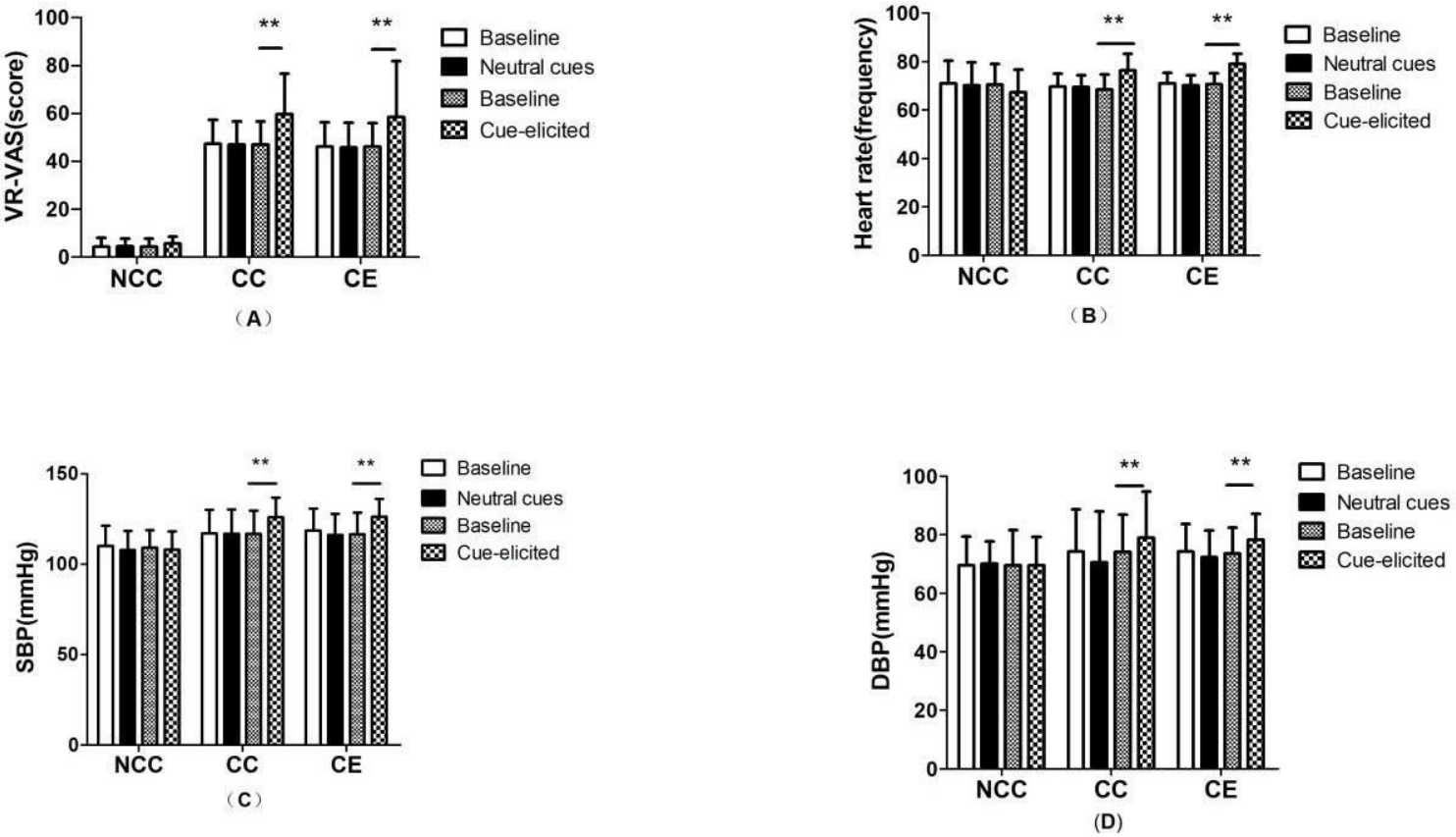

Figure 3

VR-VAS scores, blood pressure and heart rate measurement results before and after elicited (**p<0.01)

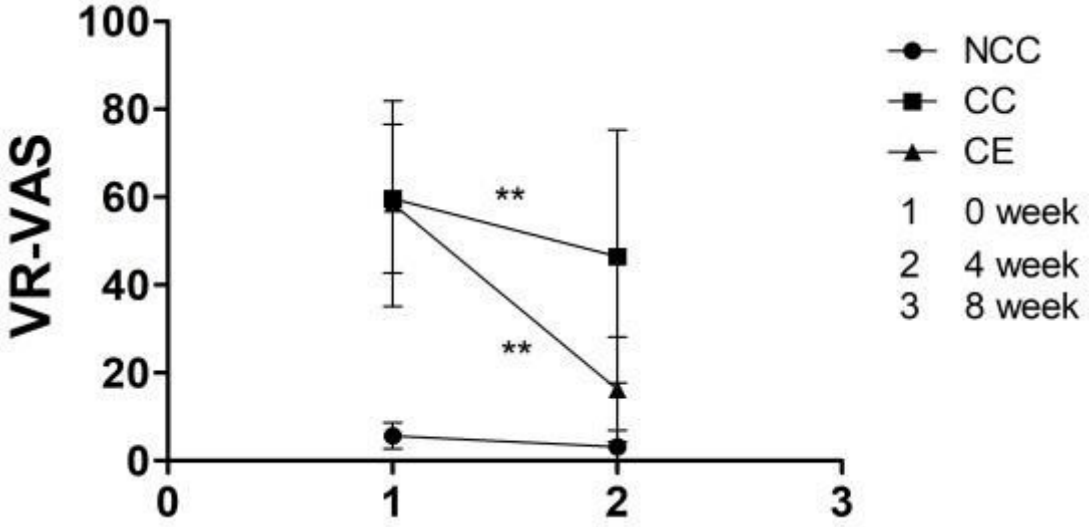

Figure 4

Comparison of VR-VAS scores pre-exercise and post-exercise.

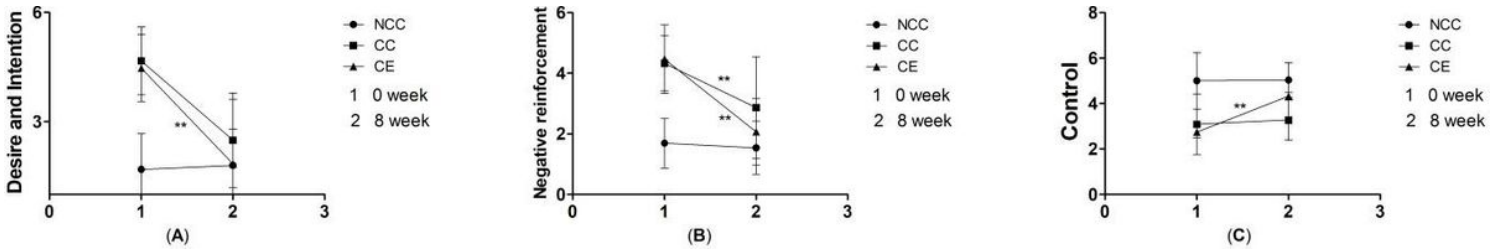

Figure 5

Comparison of DDQ scores pre-exercise and post-exercise.

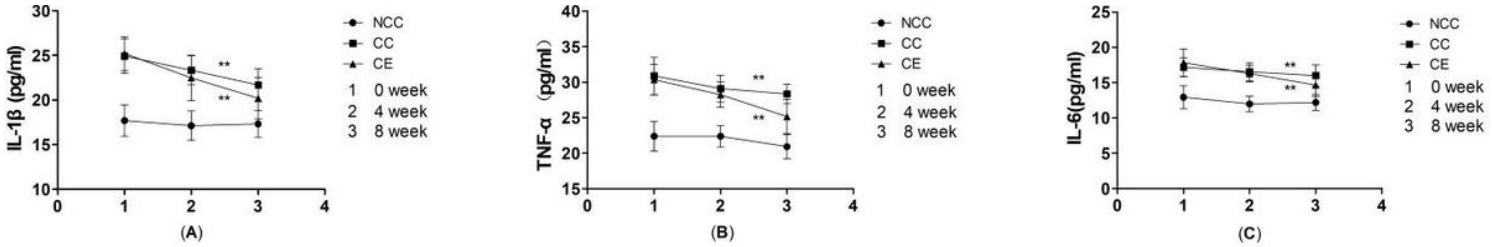

Figure 6

The effect of exercise on plasma IL-1β, TNF-α, IL-6 concentration.

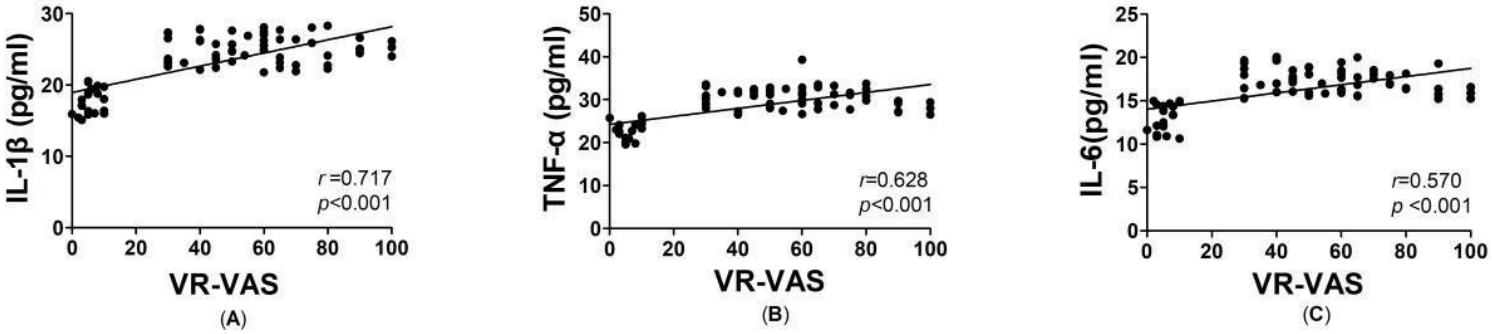

Figure 7

Correlation analysis results of plasma IL-1β, TNF-α, IL-6, and VR-VAS scores

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- DATA.xlsx