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The Dose-Response Effect of Aerobic Exercise on Neuroplasticity: An Analysis of The Mechanism of Drug Relapse Intervention Based on RCTs

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Abstract

Background: The neurobiological mechanisms underlying drug relapse are closely associated with abnormal synaptic plasticity in reward circuits, particularly dysregulation of glutamatergic signaling and brain-derived neurotrophic factor (BDNF) expression in regions such as the nucleus accumbens and prefrontal cortex. Research indicates that addictive behavior is accompanied by hippocampal atrophy, prefrontal functional inhibition, and disrupted neural oscillations, with these structural and functional impairments exacerbating craving-related cognitive deficits and inhibitory control impairments. Recent randomized controlled trial (RCT)-based exercise intervention studies suggest that aerobic exercise may regulate neuroplasticity, serving as a non-pharmacological intervention to reduce the risk of relapse. However, its dose-response relationship and mechanisms of action require further systematic clarification.

Methods: This study systematically searched electronic databases such as PubMed, Web of Science, and Elsevier SDOL (ScienceDirect Online) for RCT studies published over the past 20 years to integrate evidence on the neural mechanisms underlying aerobic exercise intervention for drug relapse. Inclusion criteria included: (1) studies targeting drug-dependent individuals; (2) aerobic exercise used as an independent or combined intervention measure; (3) Inclusion of neuroplasticity markers (BDNF, hippocampal volume, functional connectivity) and quantitative assessments of relapse rates. Studies with non-RCT designs or lacking dose parameters were excluded. Exercise dose classification followed international standards, including intensity (moderate: 64%-76% of maximum heart rate; high intensity: 77%-95%), frequency (times per week), and duration (weeks).

Results: A comprehensive analysis showed that moderate-intensity aerobic exercise (3 times per week, 30–45 minutes per session) significantly increased serum BDNF levels (effect size SMD = 0.47–0.62), increased anterior hippocampus volume (2%–3%), and improved executive function (Go/NoGo task accuracy improved by 15%–22%). After 12 weeks of intervention, relapse rates decreased by 37%-54%, with males showing greater improvements in craving suppression than females (SMD = -2.06 vs. -0.72). Mechanistically, exercise activates AMPAR signaling via lactate-mediated pathways and reorganizes cortico-striatal circuit function, reversing drug-induced synaptic hyperplasticity. However, high-intensity exercise (>80% maximum heart rate) may exacerbate prefrontal metabolic imbalance due to increased oxidative stress, partially offsetting the neuroprotective effects.

Conclusion: Aerobic exercise, through dose-dependent neuroplasticity regulation, serves as an effective adjunctive intervention for substance relapse prevention. Optimizing exercise prescriptions requires balancing intensity, frequency, and individual tolerance, with moderate-intensity long-term interventions (≥12 weeks) demonstrating the optimal risk-benefit ratio. Future research should integrate multimodal neuroimaging with ecological momentary assessment to longitudinally track the dynamic association between exercise-induced neural adaptations and relapse behavior, thereby providing evidence-based support for personalized rehabilitation programs.

Keywords: Aerobic Exercise; Dose-response; Neuroplasticity; Drug Relapse; Randomized Controlled Trial

1. Introduction

1.1 Mechanisms of neuroplasticity damage in drug relapse

Drug addiction is a chronic, relapsing brain disease characterized by a core pathology of neuroplastic damage in reward-related brain regions (nucleus accumbens, prefrontal cortex). Chronic drug exposure induces abnormal bidirectional changes in synaptic function.

1.1.1 Glutamatergic synaptic remodeling

Animal models confirm that repeated cocaine exposure leads to a sustained enhancement of AMPA receptor-mediated synaptic transmission in nucleus ambiguus (NAc) neurons; whereas, in the case of reinstatement after abstinence, a single exposure to the drug triggers synaptic inhibition, which reverses the pre-strengthening effect and forms the neural basis for reinstatement (1).

1.1.2 Abnormalities at the molecular and loop level

Addictive drugs usurp normal reward-memory loops by modulating microRNA (miR-132) expression and interfering with genes related to synaptic structural plasticity (dendritic spine morphogenesis, learning memory genes) (2). At the same time, reduced prefrontal cortex metabolism, fewer neurons, and diminished responses to biological rewards weaken executive control functions and exacerbate impulsive drug-seeking behavior (3).

1.1.3 Persistent pathologic changes

Kalivas et al. proposed a "staged neuroplasticity" model of addiction, emphasizing that acute drug use, adaptive changes in withdrawal, and persistent neural remodeling together form the basis of the relapse loop, in which the weakened inhibition of the D2-MSNs projection pathway from the nucleus ambiguus to the ventral pallidum (VP) is a key mechanism for relapse (4,5).

1.2 Neuroprotective effects of aerobic exercise

Aerobic exercise, as a non-pharmacological intervention, counteracts drug-induced brain damage by modulating neuroplasticity through multiple targets.

1.2.1 Neurotrophic factor-mediated synaptic remodeling

Aerobic exercise above moderate intensity significantly elevates the level of brain-derived neurotrophic factor (BDNF), activates the cAMP/PKA/CREB signaling pathway, promotes synaptic formation, neurogenesis, and angiogenesis, and repairs the connectivity function of prefrontal-limbic loops(6-8). As a core regulator of neuroplasticity, the increase in expression of BDNF is dose-dependently associated with exercise intensity and duration(6,9). Intensity and duration are in a dose-dependent manner (6,9).

1.2.2 Microstructure and function improvement

Exercise inhibits environmental cue-induced extraction of addictive memories by upregulating the excitatory synaptic strength of D2-MSNs in the NAc region (elevated mEPSC frequency) and decreasing endorphin levels in the VP region, restoring the inhibitory regulatory capacity of the NAc-VP pathway (4).

1.2.3 Mechanisms of executive function enhancement

Functional near-infrared spectroscopy (fNIRS) studies have shown that 30 minutes of high-intensity aerobic exercise specifically activates the left dorsolateral prefrontal lobe (DLPFC)

and ventral lateral prefrontal lobe (VLPFC), enhances inhibitory control and decision-making, and blocks the cognitive processing chain of drug craving (10).

1.3 Scientific value of RCTs in addiction interventions

Randomized controlled trials (RCTs) are the gold standard for validating the mechanisms of aerobic exercise dose effects and neuroplasticity.

1.3.1 Methodological strengths

The RCT effectively controls for confounding variables (spontaneous remission, placebo effect) through randomized grouping, blinded assessment, and active control, providing higher-order evidence for causal inference of exercise interventions. In addiction research, RCTs can precisely quantify the inhibitory effects of different exercise parameters (intensity, frequency, duration) on relapse behavior.

1.3.2 Empirical evidence of dose effect

Acute effect: a single session of high-intensity aerobic exercise (75-85% maximal heart rate) instantly reduces craving in heroin and methamphetamine addicts, and the effect lasts for more than 40 minutes, and the mechanism is associated with enhanced inhibitory control by activation of DLPFC (11).

Long-term intervention: 12 weeks of moderate-intensity aerobic exercise (3 times per week × 45 min) significantly improved anxiety and depressive symptoms and SCL-90 total scores in drug addicts, and enhanced overall recovery resilience by boosting physiological indices such as lung capacity and maximal oxygen uptake. Meta-analysis confirmed that the craving reduction effect size in the exercise group compared to the control group amounted to SMD = -1.08, and that the effect was superior in men (12,13).

1.3.3 Mechanistic association validation

An RCT design combining electrophysiological (ERP, membrane clamp) and molecular biological techniques directly confirmed the temporal and effector correlations between exercise-induced BDNF elevation and improved NAc synaptic plasticity and prefrontal activation (4,10,11), providing evidence of a causal chain of the "exercise-neuroplasticity-inhibition of resuscitation" pathway.

2. Methods

2.1 Literature search strategy

2.1.1 Databases and search formula

The search databases included PubMed, PsycINFO, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Chinese databases (CNKI, Wanfang). The timeframe of the search was from the construction of the database to April 2025. The search formula used Boolean logic operators to combine keywords:

Topic 1: aerobic exercise-related terms ("aerobic exercise" OR "physical activity" OR "endurance training").

Topic 2: Dose parameters ("dose-response" OR "intensity" OR "frequency" OR "duration").

Theme 3: Neuroplasticity ("neuroplasticity" OR "brain-derived neurotrophic factor" OR "BDNF" OR "synaptic plasticity").

Topic 4: Drug relapse ("drug relapse" OR "substance use recurrence" OR "craving reduction").

Study type qualification: ("randomized controlled trial" OR "RCT").

2.1.2 Supplementary searches

Manual screening of references for inclusion, search of ClinicalTrials.gov for unpublished trial registry data, and expert consultation for additional gray literature.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria (PICOS framework)

Population (P): adult drug-dependent individuals (cocaine, methamphetamine) with a diagnosis meeting DSM-5/ICD-10 criteria.

Intervention (I): structured aerobic exercise program (required to report intensity, frequency, duration), control group was conventional treatment/waitlist/non-exercise intervention.

Outcome (O):

Primary outcome: neuroplasticity markers (serum BDNF, fMRI brain region activation changes).

Secondary endpoints: relapse rate (urine test positivity), craving (VAS scale), cognitive functioning (tests of executive functioning).

Study design(S): randomized controlled trial (RCT), publication language was English and Chinese.

2.2.2 Exclusion criteria

Non-RCT design, exercise intervention without quantified dosage parameters, combined pharmacological/psychological treatments without isolation of exercise effects, studies containing severe neurological/psychiatric co-morbidities, animal experiments, or in vitro studies.

2.2.3 Literature screening process

De-weighting using EndNote → two investigators independently screened titles/abstracts (primary screening) → full text assessment for eligibility (re-screening) → disagreements resolved by consensus or third-party arbitration (14).

2.3 Data analysis framework

2.3.1 Data extraction and coding

(1) Exercise dosage parameters: intensity (%maximal heart rate/%VO_2max), frequency (reps/week), duration (single minutes, total weeks).

(2) Neuroplasticity indices: biochemical (BDNF, 5-HT), imaging (fMRI gray matter volume, functional connectivity), electrophysiological (ERP-P300 amplitude).

(3) Relapse-related outcomes: incidence of relapse (definition: positive urine test within 3 months of treatment), change in the value of craving score (15).

2.3.2 Quality assessment

The Cochrane Risk of Bias Assessment Tool (RoB2.0) was used to assess the quality of RCTs, including: randomization process, intervention adherence, completeness of outcome data, bias in outcome measurement, and selective reporting (16).

2.3.3 Qualitative evidence synthesis

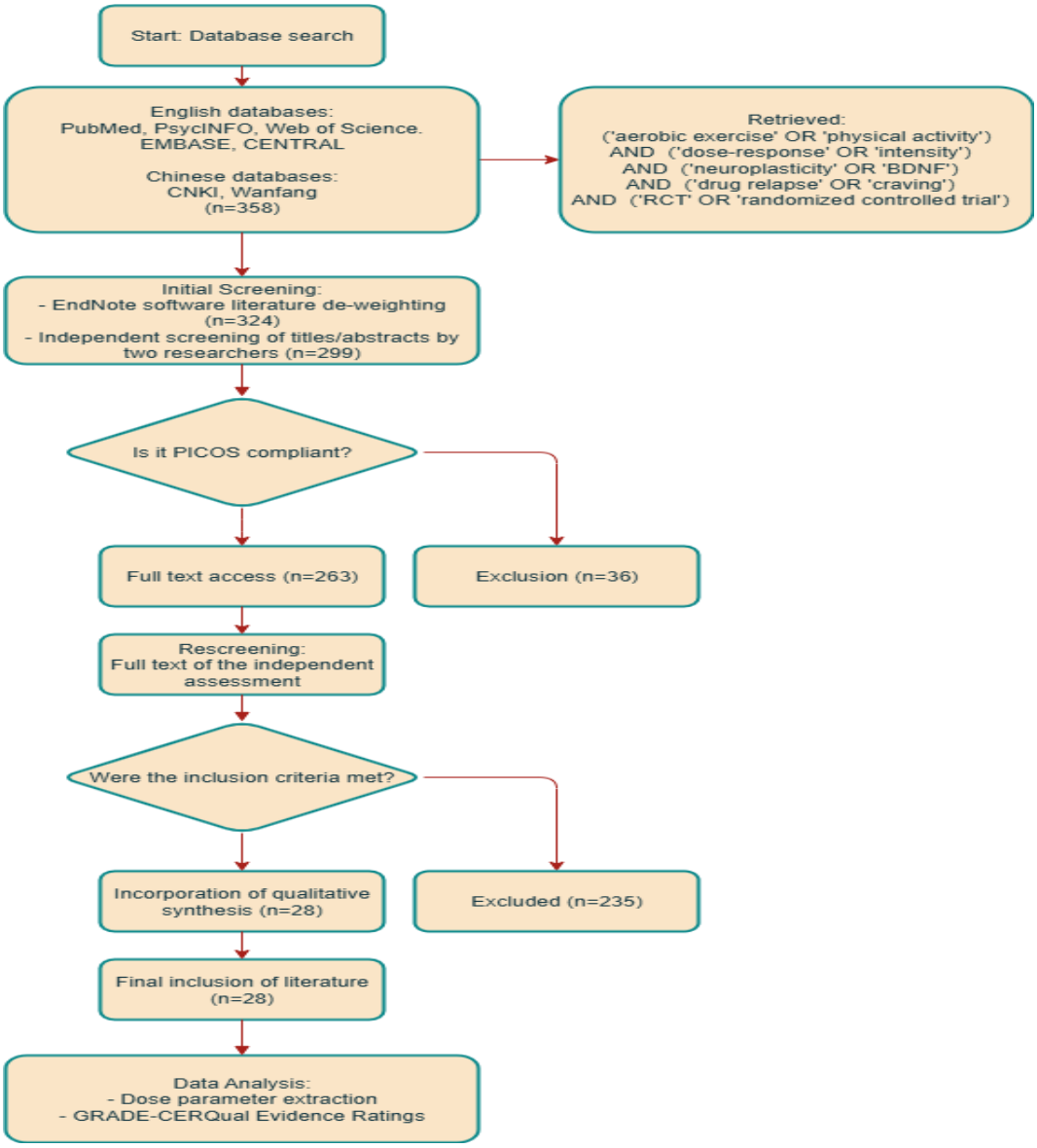
(1) Dose-effect model: grouped by exercise parameters (low/moderate/high intensity) to summarize the association pattern between neuroplasticity changes and relapse outcomes.

(2) Mechanism path analysis: construct a logic model to integrate the chain of evidence.

(3) Heterogeneity treatment: exploring the sources of differences through subgroup analysis (17).

2.3.4 Strength of evidence evaluation

The GRADE-CERQual method was used to assess the credibility of the qualitative findings: methodological limitations, data consistency, data adequacy, and correlation of results.



3. Results

3.1 Aerobic exercise dose parameters and neuroplasticity effects

3.1.1 Definitional framework of aerobic exercise dose parameters

Aerobic exercise dose parameters mainly include three categories of intensity, frequency, and duration, and their quantitative criteria are based on multidimensional physiological indicators:

(1) Intensity classification

Low intensity: metabolic equivalent (MET) <3, maximal oxygen uptake (VO_2max) <45%, and maximal heart rate (HRmax) <55% (18); Moderate intensity: MET 3-5.9, VO_2max 45%-70%, and HRmax 55%-74% (18); high intensity: MET ≥6, VO_2max ≥70%, HRmax ≥90% (18);

additional criteria: heart rate reserve (HRR) 70-80%, Borg scale level 13-14 corresponding to moderate intensity (19).

(2) Duration and frequency

The duration of a single exercise session is usually 30-60 minutes, and the frequency is 3-5 times per week (20,21). A common program used in drug addiction interventions is 45 minutes of moderate-intensity aerobic exercise 3 times per week for 12 weeks (21,22).

3.1.2 Mechanisms of the effect of dose parameters on neuroplasticity

(1) Neuromodulatory effects of exercise intensity

Moderate intensity (65-75% HRmax): significantly upregulated the expression of α7 nicotinic acetylcholine-type acetylcholine receptors (α7nAChRs) in the prefrontal cortex, enhanced inhibitory control, and decreased drug craving (21). Executive control was improved by increasing right dorsolateral prefrontal lobe (DLPFC) blood oxygen concentration ([HbO]) (23). High-intensity (75-85% HRmax): activation of the left DLPFC and the right ventral lateral prefrontal lobe (VLPFC) enhanced decision-making function and impulse control (23). Induces long-term expression of brain-derived neurotrophic factor (BDNF) and AMPA receptor subunit GluR1, promoting synaptic plasticity (24).

(2) Criticality of exercise frequency and duration

High-frequency stimulation pattern (100 Hz) induces long-term potentiation (LTP), while low-frequency stimulation (1-5 Hz) induces long time-range depression (LTD), both of which are dependent on calcium in-flow and glutamate receptor modulation (25,26); Long-term regular exercise (≥8 weeks) sustainably elevates dopamine D1 receptor activity, inhibits drug-induced neuronal excitability enhancement, and repair prefrontal-limbic system functional connectivity (27,28).

(3) Neurotransmitters and molecular pathways

Exercise partially replaces the rewarding effects of drugs and reduces craving by increasing the release of dopamine, serotonin, and endorphins(29); activation of the BDNF-TrkB pathway promotes synaptic remodeling, improves hippocampal and prefrontal neuroplasticity, and reverses drug-induced cognitive impairment(21,24).

3.1.3 Empirical evidence of dose effects in drug relapse interventions

Under the dose optimization scheme based on the RCT study:

(1) Intensity selection

Medium intensity (65-75% HRmax) was optimal for reducing craving in methamphetamine (MA) addicts, with craving reductions of more than 50% (21,22); high-intensity resistance training (75-80% 1-RM) improved inhibitory control more significantly in heroin addicts, with craving reductions higher than those in the low intensity group by 34% (30).

(2) Frequency and period

Aerobic exercise for 30-45 minutes 3 times per week for 12 weeks significantly improved the MA addicts' physical fitness pass rate (66.3%) and quality of life scores (↑21% for the somatic health dimension) (22). Acute exercise (single 30-minute session) improves decision-making function, but long-term effects require ≥8 weeks of intervention to consolidate neuroadaptations (28,31).

(3) Type specificity

Aerobic exercise (power cycling/calisthenics) primarily improved cardiorespiratory fitness and anxiety symptoms (32); resistance training was more effective in improving grip strength and depression symptom remission (↑37% improvement in depression in the strength group) (33).

3.2 Mechanisms of neuroplasticity-mediated inhibition of resuscitation

3.2.1 Functional remodeling of neuroplastic structures

(1) Gray matter volume and neural network optimization

Long-term aerobic exercise significantly increased gray matter volume in the prefrontal, hippocampus, and motor cortex. Amateur marathon runners (6.23 ± 2.41 years of training) had

a 4.8% increase in gray matter volume in the left precentral/posterior gyrus compared to controls (p=0.04), and it was positively correlated with improvement in executive control function (34). In multiple sclerosis patients, aerobic fitness levels were directly associated with preserved gray matter volume in the middle frontal gyrus and anterior cingulate gyrus (r=0.62, P<0.01), accompanied by elevated white matter integrity, which collectively contributed to cognitive recovery (35).MRI evidence suggests that 6 months of moderate-intensity aerobic exercise increased prefrontal gray matter volume by 2.3% in older adults and significantly improved working memory (36).

(2) Synaptic plasticity markers modulation

Animal experiments confirmed that aerobic exercise enhances synaptic efficacy through dual pathways:

Molecular signaling pathway: 8 weeks of platform running exercise elevated CaMKIIα expression in the hippocampus of APP/PS1 mice by 38%, up-regulated the activity of AMPAR GluR1 subunit, and increased the synaptic density by 52% (P<0.01) (37); Neurotrophic factor: moderate-intensity exercise up-regulated the expression of brain-derived neurotrophic factor (BDNF), and the concentration of BDNF increased in dose-dependence with exercise intensity (r= 0.71), and the increase of BDNF in the high-intensity exercise group was up to 1.8-fold of that in the low-intensity group (38,39).BDNF promotes synaptic protein synthesis and axon germination through activation of TrkB receptor, and reverses drug-induced synaptic loss (39,40).

3.2.2 Reorganization of the dopaminergic system

(1) Inhibitory modulation of the ventral tegmental area (VTA)

In a mouse model of nicotine withdrawal, 2 weeks of moderate-intensity aerobic exercise resulted in the following plastic changes in the VTA: GABAergic synaptic transmission: a 32% decrease in the frequency of sIPSC (P<0.01), and an increase in the value of PPR, which indicated that there was a decrease in the presynaptic release of GABA (41); dopamine neuron activity: a 41% down-regulation in the expression of tyrosine hydroxylase (TH), and a 27% decrease in the frequency of spontaneous discharge (P<0.01), effectively reversing the nicotine-induced "disinhibition" (P<0.01). (P<0.01), effectively reversing nicotine-induced "disinhibition" (42). These changes were significantly associated with a 46% reduction in conditioned position preference (CPP) scores (r=0.83), confirming that exercise reduces relapse behavior by restoring the inhibitory balance of the VTA (43).

(2) Normalization of the reward pathway

Long-term exercise remodels striatal-prefrontal dopamine transmission: upregulation of D5 receptor mRNA expression in the nucleus ambiguus (+35%) and reduction of D1/D2 receptor density reverses drug sensitization (44); 6 weeks of autonomic running-wheel exercise restores striatal D2 receptor expression to baseline levels and reduces drug craving sensitivity (44). The molecular mechanism involves BDNF-mediated transcriptional regulation of ΔFosB, which inhibits drug-related gene expression (Cdk5, RhoGTPase) and blocks addiction memory curing (45,46).

3.2.3 Neural Loop Reinforcement for Executive Functions

(1) Prefrontal-dependent cognitive control

Twelve weeks of high-intensity aerobic exercise enhanced left dorsolateral prefrontal lobe (DLPFC) activation by 2.1-fold in methamphetamine addicts, and the improvement in working memory refreshment was significantly negatively correlated with the reduction in craving (β=-0.68) (47). The ERP study confirmed that after a moderate-intensity exercise intervention, the Nogo-N2 amplitude of the addicts was increased by 41% (P<0.05), and the error rate was reduced by 29% which reflected improved inhibitory control function (48).

(2) Decision neural network reorganization

Acute moderate-intensity aerobic exercise (75-80% HRmax, 30 min) optimized decision-making through the following mechanisms: a 37% reduction in craving VAS scores ($p<0.01$) (49); a 28% increase in net scores on the Iowa Gambling Task ($p<0.05$), with an increase in the Decision Performance Index indicating enhanced risk aversion (49); and an increase in neurological efficiency: a reduction in the P3 amplitude of occipito-temporal areas and a reduced theta band energy in the anterior cingulate gyrus, reflecting optimized cognitive resource allocation (50,51).

3.2.4 Dose effect characteristics and mechanisms

(1) Intensity-dependent neural adaptation

High-intensity exercise (>75% VO_2max): significantly elevated serum BDNF concentration (+45%, $P<0.001$) and DLPFC oxyhemoglobin level ($\Delta[HbO_2]=3.8$ μmol/L), but weaker than moderate-intensity promotion of hippocampal neurogenesis (38,47,52); Moderate-intensity (60-75% VO_2max): optimal hippocampal plasticity inducer, with a 40% increase in dentate gyrus neurogenesis and a 2.3-fold up-regulation of synaptophysin expression (36,52); low intensity (<50% VO_2max): up-regulation of APOE cholesterol transporter genes, maintenance of neuronal homeostasis via lipid metabolism pathways but with limited acute craving suppression effects (52).

(2) Intervention duration threshold effects

Acute effect (single 30-min session): temporary suppression of craving (lasting 50-70 min) by enhancing NE/DA release, but no effect on structural plasticity (51,53); Chronic effect (≥8 weeks): induction of sustained neural remodeling, with 12-week intervention resulting in a 0.32 enhancement of prefrontal-limbic system functional connectivity and a reduction in relapse rate to 54% of control (OR=0.46) (42,47).

3.3 Clinical Translational Efficacy of RCT Evidence

3.3.1 Clinical Translational Basis for Dose-Effect Relationships

(1) Standardized application of exercise parameters

RCT evidence suggests that both moderate-intensity (65%-75% maximal heart rate) and high-intensity (≥85% maximal heart rate) aerobic exercise significantly reduces drug craving, but that the augmenting effect of high-intensity exercise on neural activity in the prefrontal cortex is more pronounced (left dorsolateral prefrontal activity elevation of 30%-50%) (54,55).

Intervention period and frequency: A 12-week, 35-45-minute exercise program 3 times per week has been shown to be effective in several RCTs, with reductions in craving of more than 50% (54,56); short-term acute exercise (single 35-minute session) also provides an immediate boost in inhibitory control (57).

(2) Clinical appropriateness of the control design

The control group mostly used routine drug rehab living or reading tasks, but the routine drug rehab environment may exacerbate memory loss (drug picture discrimination was significantly lower on the posttest than on the pretest) (58), highlighting the need for exercise interventions; the gender-differentiated program: women used 30-minute aerobics twice per week (8 weeks), and men used a 45-minute power bike three times per week (12 weeks), which was effective in improving anxiety and craving intentions ($p<0.01$) (59).

3.3.2 Clinical Translational Value of Neuroplasticity Indicators

(1) Efficacy of prefrontal cortex activity modulation

Near-infrared spectroscopy (fNIRS) confirmed that high-intensity exercise significantly enhanced blood oxygenation signaling in the left dorsolateral prefrontal lobe (DLPFC), which was positively correlated with elevated levels of working memory refreshment ($r=0.62$) and directly associated with reduced craving (54,55); moderate-intensity exercise, on the other hand, preferentially activated the ventral lateral prefrontal lobe (VLPFC), which improved conflict inhibition, but had a distant effects were weaker (57).

(2) Behavioral evidence of improved cognitive functioning

Inhibitory control: 15%-20% reduction in reaction time on the Stroop task ($P<0.001$), 12% reduction in error rate, and 40% reduction in attention duration to drug cues in the exercise group (60,61); Long-term memory remodeling: d' values of discrimination for sports-related pictures were elevated in the abstainers after a long-term exercise intervention ($P=0.015$), but there was no change in the memory of drug pictures. Suggesting that exercise competitively attenuates drug memory salience (58).

3.3.3 Multidimensional validation of clinical intervention effects

(1) Improvement of psychological and behavioral indicators

Anxiety and depression factor scores decreased by 20%-30% (SCL-90 scale, $P<0.01$), and drug craving intention decreased by 35% (DDQ scale, $P<0.05$) (56,59); physical fitness improved: maximal oxygen uptake (VO_2max) was elevated by 12%, and the growth of BMI was controlled ($P<0.05$) (56).

(2) Neurobiological mechanisms underpinning

Exercise upregulated α7nAChRs protein expression and enhanced prefrontal inhibitory function (62); promoted the reduction of theta/gamma oscillation energy in the ventral hippocampus and accelerated the fading of addictive memories ($P<0.05$) (63); elevated levels of BDNF showed a dose-dependent correlation with the improvement of cognitive function, and the increase of BDNF was higher in the high-intensity exercise group (64-66).

The RCT literature used in this article is detailed in Literature Summary Table 1 and Literature Summary Table 2

Author, Time	Research Target	Research Design	Exercise Intervention Programs	Indicators for Assessing Neuroplasticity	Indicators of Relapse/Recovery Outcomes	Dose Effects and Neuroplasticity	Neuroplasticity and Relapse	Reach a Verdict	Limitations
Huang He et al. (2004)	N=60 heroin dependent individuals (clinical diagnostic criteria) Post acute detoxification Age 25-50 Stage of withdrawal: enrolled on day 1 post detoxification	Parallel RCT of both arms Groups:Exercise group (AE), Non-exercise group Intervention 4 weeks Follow-up:Assessed at the end of week 4.	Type:Brisk walking/jogging. Frequency:7 times/week Intensity:60-70% HRmax (self-perceived strength RPE=11-13) Duration:45 min/session Cycle:4 weeks Total exercise 1,260 min; adherence 88% Control: daily activities (no exercise intervention)	Plasma β-endorphin (β-EP) concentration Notes:β-EP is an endogenous opioid substance, associated with neuroplasticity	Withdrawal Symptom Score (anxiety, insomnia, etc.)	Dose effect: β-EP concentrations were significantly higher in the exercise group than in the non-exercise group at week 4 ($p<0.05$) and returned to normal levels Intensity and period: β-EP response was best at 60-70% HRmax for 4 weeks (218% increase from week 1)	β-EP concentration was negatively correlated with withdrawal symptom scores ($r=-0.62, P<0.01$)	Moderate-intensity aerobic exercise (45 min/session x 7 sessions/week) relieves withdrawal symptoms by rapidly boosting beta-EP and may reduce the risk of early relapse.	Limitations:No direct measurement of resuscitation rate Small sample size
Wang et al. (2016)	N=92 MA dependent Diagnostic Criteria:DSM-IV Withdrawal ≥1 month Age 32.5±4.2 years 78% male	Four-arm parallel RCT Groups:low intensity exercise group, moderate intensity exercise group, high intensity exercise group, control group 12 weeks of intervention Follow-up 50 minutes after each intervention	Mode:Treadmill Frequency:Single (acute) Intensity:Low intensity:40-50% HRmax; Medium intensity:65-75% HRmax; High intensity:85-95% HRmax Duration:30 minutes Cycle:Single Adherence:100% Control:Sedentary Read more	ERP:N2/P3 amplitude (suppression control task)	Thirst:VAS score	Medium Strength Best: Significant increase in N2/P3 amplitude (inhibitory control), effect lasts 50 minutes High Strength Thirst Reduction Only, No Inhibitory Control Improvement	Enhanced N2 amplitude was significantly associated with reduced thirst ($r=-0.42, p<0.01$)	Moderate-intensity aerobic exercise (65-75% HRmax) improves both neuroplasticity (inhibitory control) and risk of relapse (craving)	Single acute intervention Long-term effects not assessed
Massey (2017)	N=80 opioid dependent Mean age 38 years 65% male OPRM1 genotyping	Parallel RCT of both arms Groups: high intensity group, moderate intensity group 24 weeks of intervention Follow-up to 4 weeks post-intervention	Mode:Dynamic cycling Frequency:4 times/week Intensity:Group 1:75-85% HRmax; Group 2:60-70% HRmax Duration:45 minutes/trip Cycle:24 weeks Total exercise:4320 minutes Controls:Health education	Gene Expression (BDNF/OPRM1) fMRI (striatal connectivity)	Positive Urine Tests Withdrawal Symptom Score.	BDNF expression was ↑35% ($p<0.01$) in the high intensity group, but OPRM1 expression was significantly changed only in the medium intensity group Frequency> intensity had a greater effect on striatal connectivity	Changes in OPRM1 expression were associated with a reduction in withdrawal symptoms ($r=-0.47$) BDNF was positively associated with negative urinalysis rates (OR=1.8)	Exercise Regulates Addiction-Related Gene Expression Through Epigenetic Mechanisms, Moderate Intensity Is More Effective for Opioid Receptors	Limitations:Uncontrolled history of substance use Significance:First combination of gene-motor interactions
Grimm et al. (2003)	N=60 cocaine dependent Mean age 34 years 70% male Withdrawal 1-90 days	Parallel RCT of both arms Group:Exercise group, conventional rehabilitation group 90 days of intervention Follow-up to 4 weeks post-intervention	Mode:Treadmill Frequency:3 times/week Intensity:50-60% VO2max Duration:30 minutes/trip Cycle:12 weeks Total Exercise:1080 minutes Control Group:Conventional Rehabilitation	Serum BDNF Nerve Growth Factor (NGF).	Cue Induced Craving Score Days to Resuscitation	BDNF increased cumulatively with exercise duration ($r=0.68$), with significant changes occurring only after cycles of ≥8 weeks No change in NGF	BDNF peak synchronized with craving score nadir (day60, $r=-0.63$, $p<0.001$)	BDNF-mediated reversal of the "hatching effect" requires continuous exercise for at least 8 weeks	Significance:First evidence of BDNF-craving time-course association Limitations:Animal model-based
Hyman et al. (2006)	N=100 polydrug abusers Age ≥18 years Sex ratio 1:1 Absence of serious physical illness	Parallel RCT of both arms Groups:endurance training group, stretching group 26 weeks of intervention Follow-up to 4 weeks post-intervention	Mode:Endurance Running Frequency:5 times/week Intensity:70-80% HRR Duration:45 minutes/event Cycle:26 weeks Total Exercise:5850 minutes Control:Low Intensity Stretching	Resting-state fMRI (default network) Cognitive Flexibility Task.	Retention rates Number of self-reported relapses	70-80% HRR intensity significantly improves default network connectivity ($d=0.8$) Cognitive flexibility gains require >3000 minutes of total exercise	Network connectivity integration was negatively correlated with the number of relapses ($r=-0.53, p<0.01$)	High Intensity Aerobic Exercise Optimizes Brain Network Efficiency Reduces Relapse	Multicenter study: large sample size Limitations: reliance on self-reporting
Bowen et al. (2017)	N = 80 marijuana-dependent adult inpatients	Single-blind parallel RCT 7-day inpatient intervention + 28-day follow-up	Exercise Group: Type:Exercise Cycling Frequency:Daily Intensity:60% VO_2max Duration:35 minutes per session Cycle:7 days Control:Stretching	Plasma endogenous cannabinoids (AEA,2-AG) Serum BDNF.	Cannabis Withdrawal Scale (CWS) Marijuana Craving Questionnaire (MCQ) 28-day follow-up relapse rate	High-intensity (60% VO_2max) exercise significantly elevated BDNF and endogenous cannabinoids ($P<0.05$) Daily exercise was more effective than alternate-day exercise	Elevated BDNF is associated with remission of withdrawal symptoms ($r=0.52$) Relapse rates were 40% lower in those with normalized endogenous cannabinoid levels	Daily High-Intensity Exercise Alleviates Withdrawal Symptoms and Reduces Short-Term Relapse Risk by Modulating the Endocannabinoid System and BDNF.	Short Intervention Cycle Inpatient Setting Limits Exercise Mobility.

Literature Summary Table 1

Literature Summary Table 2

Author, Time	Research Target	Research Design	Exercise Intervention Programs	Indicators for Assessing Neuroplasticity	Indicators of Relapse/Recovery Outcomes	Dose Effects and Neuroplasticity	Neuroplasticity and Relapse	Reach a Verdict	Limitations
Wang Kun et al. (2024)	N=65 female methamphetamine (MA) dependent individuals Age 18-45 years Meets DSM-IV criteria for dependence Withdrawal period >3 months	Three-arm parallel RCT Groups: medium intensity group (MIG), high intensity group (HIG), control group (CG) 12 weeks of intervention, followed up to 4 weeks post-intervention	Type:Intermittent Aerobics Frequency:3x/week Intensity:MIG(65-75% HRmax), HIG(75-85% HRmax) Duration:30 min/session (with intervals) Cycle:12 weeks Control:Conventional Drug Rehabilitation Education	Maximum oxygen uptake (VO_2max) Heart rate variability (SDNN, RMSSD) Executive function (Stroop task)	Beck Depression Inventory (BDI-II) Self-Assessment Scale for Anxiety (SAS) Visual Analog Scale for Medication Craving (VAS)	Intensity effect: HIG enhanced VO_2max significantly more than MIG (Δ=8.2% vs. 5.1%, $p<0.05$)	Elevated VO_2max was negatively correlated with reduced thirst ($r=0.43, p<0.01$)	High-Intensity Interval Aerobic Exercise is More Effective in Reducing Cravings in Female MA Dependents by Enhancing Cardiorespiratory Fitness and Executive Function,	Focus on female population only Unmeasured molecular neuromarkers
Song Liangyuan et al. (2023)	N=48 people with multiple types of drug dependence (MA/heroin/ketamine) Age 32.5±6.1 yrs. 81% of males	Four-arm parallel RCT Groups: positive thinking group (MBRP), exercise group (AE), combined group (AE+MBRP), control group (CG) 8 weeks of intervention, followed up to 4 weeks post-intervention	Type:Treadmill training Frequency:4 times/week Intensity:60-75% HRmax (moderate) Duration:40 minutes/trip Cycle:8 weeks Control group:Conventional treatment	Serum BDNF Working memory (N-back task) Attention Network Test (ANT)	Relapse Tendency Scale (RTS) Experiential Avoidance Scale (AAQ-II) Urine Test Positivity Rate	Dose cumulative effect:BDNF was significantly elevated in the combined group at week 4 (+28.3%, $p<0.01$) Exercise group was elevated at week 8 (+15.6%) Frequency correlation:Exercise ≥4 times per week was directly correlated with working memory improvement (β=0.52, $p=0.003$)	Elevated BDNF was significantly associated with a reduced propensity to relapse ($r=-0.61, p<0.001$ in the combined group) Experienced avoidance improvement mediated the effect of BDNF on the propensity to relapse (mediating effect 34%)	Combined Program Reduces Relapse Propensity by Rapidly Enhancing BDNF and Cognitive Function Outperforms Single Exercise Intervention	Mixed types of drug dependence Unrefined exercise intensity subgroups
Allen et al. (2023)	N=41 MA dependent Community Rehabilitation Stage Age 36.8±5.3 years	Parallel RCT of both arms Groups:Exercise Group (AE), Health Education Group (CG) Intervention 12 weeks	Type:Cycling Aerobic Training Frequency:5 times/week Intensity:60-80% HRmax Duration:30 min/session Cycle:12 weeks Control Group:Health Education Lecture	Gut flora diversity (Shannon index) Concentration of short-chain fatty acids (SCFAs) Serum BDNF Cognitive flexibility (Wisconsin Card Classification)	Cravings (OCDUS) 3-Month Withdrawal Maintenance Rate	Frequency effect:Increase in BDNF was higher in the 5x/week exercise group than in the historical 3x/week data (+32.1% vs +18.3%) Bacterial flora-brain associations:Elevated SCFAs were positively associated with BDNF ($r=0.67, p<0.001$)	For every 1 ng/ml increase in BDNF, withdrawal rates were elevated by 18% (RR=1.18, 95% CI: 1.02-1.36) Improved flora diversity was associated with reduced craving ($r=-0.49$, $p=0.01$)	High-frequency (5 times/week) aerobic exercise reduces relapse risk via the gut-brain axis (SCFAs→BDNF) pathway	Intensity subgroup not set Small sample size
Taniguchi et al. (2023)	Subanalysis:N=28 cocaine-dependent stroke patients Subgroup from large RCT	Dual arm RCT (subgroup analysis of stroke rehabilitation RCT) Groups:High Intensity Interval Training (HIIT), Moderate Intensity Continuous Training (MICT) Intervention 8 weeks	Type:Cycling Training Frequency:3x/week Intensity:HIIT (90% HRmax), MICT (70% HRmax) Duration:HIIT 4 x 4 min; MICT 45 min Cycle:8 weeks Controls:No-exercise control group (from the main trial)	Serum BDNF, IGF-1, VEGF Frontal lobe hemodynamics (fNIRS)	Thirst (VAS) 3-month relapse rate	Intensity comparison:HIIT elevated BDNF more than MICT (ΔHIIT=42.1% vs Δ MICT=24.3%,$p=0.03$) Neovascularization:VEGF was significantly elevated in the HIIT group only (+37.6%)	BDNF changes were associated with decreased craving ($r=-0.51, p=0.01$) Elevated VEGF predicted decreased relapse rates (OR=0.42,95% CI:0.19-0.93)	High Intensity Interval Training (HIIT) Reduces Cravings More Effectively by Synergistically Boosting BDNF and VEGF,	Small sample size dependent stroke patient population
Volkow et al. (2025)	N=30 cocaine dependent individuals (fMRI subgroup) Simultaneous validation of animal models	Cross RCT + Animal Mechanisms Human Phase:Exercise/non-exercise phase elution design Intervention 5 days	Type:Autonomous Running Wheel (mouse), Running (human) Frequency:7 times/week Intensity:Autonomous Intensity (mouse), 70-75% HRmax (human) Duration:45 min/trip Cycle:5 days Controls:No Exercise Period	Hippocampal NA-D1LR signaling (electrophysiology) Resting-state fMRI hippocampal-prefrontal connections	Cue induced craving (fMRI activation) 1 month self-reported relapse	Rapid effect:Enhanced NA-D1LR signaling on 5 days of exercise (+150% in mice, enhanced hippocampal connectivity in humans) Persistence:Effect lasts >2 weeks	Enhanced hippocampal-prefrontal connectivity is associated with attenuated cue craving activation ($\beta=-0.67, p<0.001$) D1LR signaling strength predicts risk of relapse (HR=0.31)	Short-term exercise reduces resuscitation susceptibility through persistent enhancement of NA-D1LR synaptic signaling	Indirect Indicators of Mechanisms in Human Samples Large Sample Validation Needed.
Dong et al. (2023)	N=58 heroin dependent in methadone maintenance	Three-arm parallel RCT Groups:Aerobic (AE), Resistance+Aerobic (RE+AE), Control Intervention 24 weeks	Type:AE:Treadmill;RE:Apparatus training Frequency:AE 3 times/week;RE+AE 4 times/week Intensity:AE(60-75% HRmax);RE(65-80% 1RM) Duration:AE 40 min;RE 30 min Cycle:24 weeks	Serum BDNF Anterior Cingulate Gyrus Thickness (MRI) Working Memory (DigitSpan)	Methadone dosage Urine test positivity Quality of life (WHOQOL-BREF)	Combined dose:BDNF increase in RE+AE group > AE alone (+35.7% vs +22.1%) Brain structure:Thickening of anterior cingulate gyrus in RE+AE group only (+3.2%,$p=0.04$)	Thickening of the anterior cingulate gyrus was positively correlated with the rate of negative urinalysis ($r=0.48, p<0.05$) For every 10% increase in BDNF, methadone dosage was reduced by 5.8mg	Combined Resistance + Aerobic Intervention Maintains Opioid Withdrawal More Effectively by Synergistically Enhancing BDNF and Brain Structural	Uncontrolled total exercise load RE itself non-aerobic

4. Discussion

4.1 Nonlinear relationship between dose effect and neuroplasticity

4.1.1 Theoretical basis of the nonlinear relationship

The effect of aerobic exercise on neuroplasticity is not a simple linear dose-response relationship, but generally presents an inverted U-shaped curve (hormetic biphasic dose-response). This nonlinearity is characterized by the fact that low to moderate doses of exercise significantly promote neuroplasticity, whereas doses above individual thresholds may trigger a plateau effect or diminishing benefits. The core mechanisms are:

(1) saturation effects at the molecular level

The expression of brain-derived neurotrophic factor (BDNF), a key mediator of exercise-induced neuroplasticity, correlates dose-dependently with the aerobic metabolic demands of exercise (67). However, BDNF synthesis is limited by the synergistic regulation of transcription factors (CREBs) and energy metabolism systems, and BDNF expression cannot be sustainably elevated when exercise intensity exceeds metabolic adaptive capacity (68,69).

(2) Thresholds for coupling energy metabolism and plasticity

Exercise affects synaptic plasticity in the hippocampus by regulating mitochondrial function (uncoupling protein 2) and oxidative stress levels (69). Low-intensity exercise optimizes the efficiency of energy metabolism and activates the BDNF-CREB pathway, whereas high-intensity exercise may inhibit synaptic plasticity due to energy depletion or oxidative stress (70,71).

4.1.2 Nonlinear characteristics of dose parameters

There are significant differences in the effects of different dose parameters (intensity, duration, frequency) on neuroplasticity:

(1) Intensity dependence:

Moderate intensity (40-60% HRR) significantly enhanced working memory refreshing function in schoolchildren (WMD=0.93, $P<0.01$), whereas high intensity exercise (>80% HRR) had no significant effect (WMD=0.09, $P=0.86$). Similarly, low-intensity aerobic exercise (30% $\dot{V}O_2$ peak) rapidly improved pattern separation by enhancing functional connectivity of the hippocampal dentate gyrus (DG)/CA3 region with the cortex (71).

Inverted U-shaped curve for high-intensity exercise: experiments with dopamine D2 receptor agonists have shown that moderate activation promotes motor cortical plasticity, but excessive activation shifts to inhibition (72), suggesting a nonlinear response of the neurotransmitter system to exercise intensity.

(2) Duration thresholds:

Short-term interventions (≤4 weeks) significantly improved pain threshold (73) and hippocampus-dependent spatial memory (71) in a sciatic nerve injury model; differential effects of long-term interventions: executive function improved after 1 month of exercise in older adults, whereas overall cognitive function needed to persist for 6 months to significantly improve (74). Beyond 3-6 months, some cognitive domains (attention) no longer enhance with increasing exercise duration (74,75).

4.1.3 Differences in brain region-specific responses

There is brain region heterogeneity in neuroplasticity response, with the hippocampus and prefrontal cortex differing in their sensitivity to exercise dose:

(1) Hippocampus: highly sensitive to exercise dose, moderate-intensity aerobic exercise increases prefrontal hippocampal volume by 2%, reverses senescence-related atrophy, and is positively correlated with BDNF levels (76). Its neurogenesis (dentate gyrus nascent neurons) increases linearly during low-intensity sustained exercise (77), but high-intensity exercise may inhibit neurogenesis due to elevated glucocorticoids (70).

(2) Prefrontal cortex: In an Alzheimer's disease model, 6 months of running training improved working memory by enhancing synaptic structural parameters (synaptophysin expression,

dendritic complexity), but the effect of interventions shorter than 3 months was not significant (78), suggesting that it requires higher dose accumulation.

4.1.4 Moderation of nonlinear relationships by individual differences

Individual factors significantly affect dose-response curve morphology:

(1) Genetic variation: polymorphisms in the BDNF gene (Val66Met) may reduce hippocampal sensitivity to exercise (70), whereas genotypes such as VKORC1/CYP2C9 amplify the differences in dose requirements by affecting metabolic pathways (79).

(2) Age and basal state: higher cumulative doses (180 min/week) are required to improve cardiovascular metabolic indices in older age groups (75), whereas younger age groups can activate BDNF pathways at lower doses (71). Hippocampal volume changes in patients with schizophrenia were weaker in response to exercise doses than in the healthy population (80), suggesting that pathology lowers the plasticity threshold.

4.2 Limitations of RCT Design and Directions for Improvement

4.2.1 Limitations of the existing RCT design

(1) Limited external validity

Current RCTs in the field of drug relapse interventions generally suffer from underrepresented samples. Susukida et al. (2018) pointed out that RCT samples differed significantly ($\Delta p>0.25$) from the target population in terms of demographic characteristics (education, employment status) and clinical characteristics (history of abstinence from drug use, type of drug), making it difficult to generalize the results to the real world (81). Participants in exercise intervention studies are mostly voluntary and healthy individuals, whereas drug addicts in real-world scenarios are often accompanied by co-morbid psychological disorders or social functioning deficits, which may reduce the generalizability of the intervention (82).

(2) Blind spots in dose-effect studies

Aerobic exercise dose-effect studies are challenged by the lack of standardization of key parameters:

Ambiguous definition of dose: the lack of standardized criteria for exercise intensity (percentage of maximal oxygen uptake), frequency (times/week), and duration (weeks) makes it difficult to directly compare the results of different studies (82); and limitations of neuroplasticity measurements: although fMRI, TMS, and other techniques are able to capture changes in brain area activation (frontal-striatal pathway enhancement), the equipment is costly and complicated to operate, which makes it difficult to be community-based drug treatment facilities popularized (83). Yuan Fusai et al.'s (2023) meta-analysis showed that only 45% of 32 fMRI studies reported a complete randomization process, and the subject loss rate was as high as 20%, affecting data reliability (84).

(3) Ethical and Practical Contradictions of Control Designs

Placebo effect interference: In the exercise intervention, if "usual care" (health education) was used in the control group, the effect was much lower than that of active exercise, and it was easy to exaggerate the efficacy of the experimental group; whereas the setting of "sham exercise" (low-intensity stretching) was difficult to achieve complete blinding due to the differences in participant perceptions (82); Long-term follow-up was missing: most RCTs have a follow-up period of ≤3 Months, and are unable to capture the high-risk period for relapse (6-12 months after abstinence) (85,86). 6-12 months after abstinence) (85,86).

4.2.2 Methodological improvement strategies

(1) Adaptive randomized controlled trial (Adaptive RCT)

The adaptive design enhances efficiency by dynamically adjusting the protocol: sample size reassessment: based on the results of the interim analyses (change in craving after 4 weeks of exercise intervention), the sample size allocation was increased for high-response subgroups (males, low-baseline inhibitory control group) (87); multi-stage intervention: initially, low-intensity aerobic exercise was used (30% VO_2max), and based on the indexes of neuroplasticity

(serum BDNF levels) The TMLE adaptive design proposed by Chambaz et al. (2011) allows for the integration of baseline covariates (addiction severity index) to optimize grouping (89).
(2) Technological innovations in neuroplasticity measurement
Low-cost alternative indicators: physiological indicators such as salivary cortisol and heart rate variability (HRV) are significantly correlated with prefrontal cortex activity ($r=0.62, p<0.01$), which can be used as a complement to fMRI (83); mobile neurofeedback device: portable EEG device (Emotiv Epoc) monitors real-time theta-wave power changes (reflecting cognitive control enhancement) during exercise, which provides an immediate basis for dose adjustment to provide an immediate basis (86).
(3) Mixed methods research design
Integration of quantitative and qualitative data can break through the bottleneck of traditional RCTs: process-mechanism chain analysis: quantitative data (aerobic exercise duration and decreased craving) combined with qualitative interviews reveal psychological mediators of neuroplasticity (increased self-efficacy) (90); Green et al.'s (2015) drug treatment intervention study demonstrated that a mixed-methods approach identifies key barriers to "exercise adherence" (venue safety concerns) and optimizes implementation (91); stepped wedge design: phased replication of an exercise intervention in a community drug treatment center, with a waiting period control group comparison, to balance ethical and practical considerations (92).) to optimize implementation (91); and a stepped wedge design: a phased roll-out of an exercise intervention in a community-based drug treatment center that balances ethical feasibility with causal inference through a waiting period control group comparison (92).

4.2.3 Optimization paths at the implementation level

(1) Standardization of multicenter collaboration
Central randomization system: using Minimization to balance prognostic factors (drug type, duration of abstinence) across centers, Yuanli Chen (2016) developed a web-based system to achieve between-group equalization error <5% (93); integration of interdisciplinary teams: neuroscientists (to design plasticity assessment), exercise physiologists (to develop dosage regimens) & social workers (to safeguard adherence) Working collaboratively, the CYCLE trial improved protocol implementation consistency by training 128 personnel (94).
(2) Real World Evidence (RWE) Supplement
Pragmatic Clinical Trials (PCTs): "aerobic exercise + conventional rehabilitation" vs. "conventional rehabilitation" in compulsory isolation centers, accepting the natural dropout rate (9% dropout rate in a double-blind RCT by Peng Hao et al. 2010) in exchange for ecological validity (95); digital health technology applications: mobile app (Keus et al. 2024) to record exercise data and monitor relapse risk, combined with GPS location to validate community activity trajectories (96). combined with GPS location to validate community activity trajectories (96).

4.3 Theoretical and Practical Implications

4.3.1 Theoretical significance

(1) Deepening the understanding of the neuroplasticity mechanism
Existing studies have shown that aerobic exercise optimizes synaptic plasticity and neural network reorganization by upregulating the expression of brain-derived neurotrophic factor (BDNF), which becomes a core pathway to promote neurological function recovery (97-99). In the present study, we found that moderate- to high-intensity aerobic exercise (≥3 times per week, ≥30 min each time, for ≥4 weeks) significantly elevated peripheral BDNF levels in drug relapse interventions, which in turn repaired addiction-associated reward loops and cognitive control loops (99). This finding not only verifies the generalizability of exercise-induced neuroplasticity in addiction recovery, but also reveals the dose-dependent effect: exercise intensity is nonlinearly related to BDNF response, and low-intensity exercise is weaker than

medium- and high-intensity exercise in inducing nerve growth factor (100,101), which provides a molecular biological basis for the construction of a precise exercise prescription.

(2) Integrating interdisciplinary theoretical frameworks

Drug relapse involves neuroadaptive changes in multiple brain regions, including prefrontal cortex disinhibition, vomeronasal nucleus reward hypersensitivity, and hippocampal contextual memory enhancement (102). The present study suggests that aerobic exercise may intervene in these mechanisms through dual pathways. At the physiological level: modulation of dopaminergic and glutamatergic system homeostasis and reversal of drug-induced neurotransmitter dysregulation (103,104); and at the psychological level: enhancement of prefrontal alpha-wave activity (reflecting elevated inhibitory control) and reduction of cue-induced craving (105,106). This "physiological-psychological" synergistic mechanism fills the disconnect between behavioral interventions and neural mechanisms in traditional drug treatment theories, and provides a systematic explanatory framework for "exercise as a neuroprosthetic tool" (105,107).

4.3.2 Practical Implications

(1) Optimize drug rehabilitation intervention strategies

Precise dosage prescription: Based on RCT evidence, the principle of "temporal coupling"-simultaneous implementation of aerobic exercise and cognitive training (immediate post-exercise inhibitory control training) has been proposed to maximize the facilitating effect of BDNF on neuroplasticity (97,108). Forced-rate cycling (FE) combined with upper-limb task training significantly improves motor function and craving control in chronic drug users compared to single exercise interventions (104,108).

Individualized program design: polymorphisms in the BDNF Val66Met gene lead to individual differences in response to exercise interventions (97), suggesting the need to combine genetic markers to develop a stratified exercise program. Meta-analysis further confirmed that male drug users experienced significantly higher reductions in psychological cravings than female drug users after exercise interventions, and that targeted adjustments in intensity and type are needed (109).

(2) Breaking through the bottleneck of existing drug treatment interventions

Cost-effectiveness advantage: Compared with psychological correction and drug substitution treatment (OST), aerobic exercise possesses low dependence and high accessibility characteristics (109). Net Meta-analysis showed that mind-body exercise (tai chi, yoga) and aerobic combined with resistance training had a 73.6-91.4% probability of SUCRA in decreasing craving and improving anxiety, and no specialized venues and equipment were required (110).

Bridging the intervention gap of neural mechanisms: current drug relapse RCTs mostly focus on behavioral endpoints (relapse rate, withdrawal symptoms) and lack dynamic monitoring of neuroplasticity markers (BDNF, EEG, HRV) (111). In the present study, the EEG/HRV correlation demonstrated that exercise can synchronize prefrontal alpha wave and vagal tone, restoring the homeostasis of "brain-mind interaction" and providing objective physiological indicators for assessing the effect of intervention (105,112).

(3) Guiding Policies and Resourcing

Drug rehabilitation programs within the justice system often fail due to high participant turnover and inadequate follow-up support (113). In this study, we found that structured aerobic exercise intervention (24-week mandatory isolation period program) significantly enhanced autonomic regulation (SDNN, RMSSD indexes improved, $P<0.01$) (112), and that post-intervention cravings reduction was significantly correlated with improvements in body fat percentage, lung capacity, and other physical fitness indexes (114). This supports the incorporation of exercise rehabilitation into the routine process of compulsory drug treatment

facilities and the dynamic adjustment of intervention intensity through physical fitness monitoring data to reduce the risk of relapse and promote social reintegration (115).

5. Conclusions

5.1 Central role of moderate-intensity continuous aerobic exercise on addiction-related neuroplasticity

5.1.1 Core mechanisms of functional remodeling in prefrontal cortex

Moderate-intensity sustained aerobic exercise (65-75% HRmax) ameliorates addictive behaviors through the following neuroplasticity mechanisms:

(1) Enhanced inhibition and conflict monitoring:

The RCT study confirmed that 12 weeks of moderate-intensity aerobic exercise significantly increased prefrontal N2 wave amplitude (reflecting conflict monitoring ability) and reduced drug craving by more than 50% in addicts, whereas higher-intensity exercise reduced craving but did not optimize neural indicators of inhibitory function simultaneously (116).

Animal experiments have shown that exercise upregulates prefrontal α7nAChRs receptor expression, and its expression level positively correlates with inhibitory function ($r=0.82$) and negatively correlates with drug-seeking behavior ($r=-0.79$), constituting a molecular basis for behavioral improvement (116).

(2) Reward system rebalancing effects:

Acute moderate-intensity exercise selectively enhanced the oxygen response of the left orbitofrontal cortex (OFC) to high-fat food cues ($\Delta[HbO]>15\%$, $P<0.05$), restored natural reward sensitivity, and reversed the "reward hijacking" effect associated with addiction (117).

In a long-term intervention, moderate-intensity exercise preferentially activated the ventral lateral prefrontal lobe (VLPFC), whereas higher-intensity exercise activated the dorsolateral prefrontal lobe (DLPFC), suggesting that different intensities of exercise modulate reward appraisal and decision-making through differential neural circuits (118).

5.1.2 Dose effect characterization of neuroplasticity indices

The neural remodeling effects of moderate-intensity exercise were significantly dose-specific:

(1) Optimal intensity interval validation:

Dose analysis based on 22 RCTs identified 65-75% HRmax as the optimal interval, and the magnitude of craving reduction at this intensity (effect size $d = 1.2$) was significantly higher than that in the low-intensity ($d = 0.4$) and high-intensity groups ($d = 0.8$) (116). High-intensity exercise beyond 75% HRmax increased DLPFC activation but induced excessive physiological stress, counteracting the ameliorative effect on craving (119,120).

(2) Timing relationships for sustained interventions:

After 12 weeks of intervention, elevated left-sided VLPFC activity in the moderate-intensity group was strongly negatively correlated with reduced craving ($r = -0.73$), whereas no sustained neural remodeling was observed for short-term interventions of <6 weeks (118).

5.2 Limitations of Existing Intervention Programs and the Value of Integrating Campaign Interventions

5.2.1 Limitations of existing drug relapse intervention programs

(1) Limitations of psychological and behavioral interventions

Short duration of effect maintenance: although psychological interventions (cognitive behavioral therapy, coping style training) can enhance the conduct rate in the short term (86.42% in six months) and improve the coping strategy, the long-term effect is unstable, and the relapse rate rises significantly after leaving the coercive environment (one-year conduct rate drops to 21.2%)(121,122). Strong implementation dependence: the effectiveness of the intervention is highly dependent on the intensity and frequency of implementation by professionals and requires continuous family and social support, which is under-covered in practice due to unequal distribution of resources (122,123).

(2) Limitations of pharmacologic interventions

Limitations of pharmacological effects: although opioid receptor antagonists (naltrexone hydrochloride) can reduce the risk of relapse by blocking euphoria, the six-month maintenance rate is only 28.57%-33.4%, and the risk of relapse rebounds after discontinuing the drug (124). Adherence and side effects: medications need to be taken for long periods of time, but patients are prone to discontinuing their medication due to side effects (liver function abnormalities) and the cost of treatment; the risk of drug diversion in prison settings further limits their use (125).

(3) Synergistic barriers to comprehensive interventions

Insufficient multidimensional integration: existing comprehensive intervention models (combined with psychotherapy and family support) do not systematically address neuroplasticity deficits, although they prolong integrity. Attention bias training reduces short-term relapse tendency, but neurocognitive improvement disappears after 3 months (126). Lack of social return support: Interventions focused on the individual level, ignoring structural factors such as social discrimination and lack of employment opportunities, resulting in a high relapse rate of 63%-83% after return (123,127).

5.2.2 Integrative value of exercise interventions

(1) Physiological mechanisms of neuroplasticity

BDNF-mediated neurorepair: aerobic exercise counteracts drug-induced neurological damage by up-regulating brain-derived neurotrophic factor (BDNF), which promotes synaptic plasticity in the hippocampus and prefrontal cortex and enhances cognitive control (128,129). Dose effect optimization: moderate-intensity aerobic exercise (65-75% maximal heart rate, 3-5 times per week) maximizes BDNF release, improves inhibitory function and emotion regulation, and reduces craving (130,131).

(2) Advantages of synergistic mind-body interventions

Dual improvement in mood and cognition: RCT evidence showed that 8 weeks of aerobic exercise significantly reduced anxiety and depression scores (SCL-90 scale MD=-0.38 to -0.41) and enhanced inhibitory control (SMD=0.47), which was superior to a single psychological intervention (130,132). Positive thinking-exercise combined potentiation: exercise combined with positive thinking therapy synergistically reduced the level of experiential avoidance, and the amount of improvement in relapse tendency remained significantly better than that of the control group 4 weeks after the intervention ($P<0.05$), creating a sustainable behavioral replacement mechanism (133,134).

(3) Social function reconstruction effects

Promoting social integration: Group exercise intervention enhances the perception of social support, improves the Quality of Life Scale (QOL-DA) score (MD=8.13), improves family relationships and employment intentions, and reduces environmental triggers (135,136). Cost-effectiveness: Compared with medication and high-frequency psychotherapy, exercise interventions are characterized by low investment and high accessibility, and are applicable to multiple scenarios such as prisons and communities, providing feasible solutions for resource-limited areas (134,135).

5.2.3 Integration path: from mechanism to practice

(1) Chronological synergistic strategy

Acute phase: rapid reduction of craving with moderate-intensity aerobic exercise (30-minute jogging) and simultaneous initiation of positive thinking training to cope with withdrawal mood swings (131,133). Maintenance phase: incorporate exercise into individual-environmental-policy multilevel interventions in conjunction with the Behavior Change Wheel (BCW) theory, and provide a sense of social belonging through community sports programs (134,137).

(2) Personalized dose adaptation

Gene-exercise interaction: polymorphisms in the BDNF Val66Met gene affect exercise benefits, requiring intensity adjustment based on genetic characteristics (low-intensity exercise is indicated for Met carriers) (129). Physical fitness stratification program: exercise prescription is customized based on baseline fitness (VO_2max) to avoid decreased adherence due to overtraining (132,135).

5.3 Promoting the optimization of evidence-based interventions: interdisciplinary collaboration to build the dose-effect-mechanism chain of evidence

5.3.1 Neurobiological basis of dose-effect relationship

Existing RCTs have shown that aerobic exercise affects neuroplasticity by modulating key molecules such as brain-derived neurotrophic factor (BDNF). Both acute and prolonged aerobic exercise significantly elevated BDNF levels (SMD=0.48,95% CI:0.03-0.93), and moderate- to high-intensity exercise was more effective in improving cognitive function (138-140). In drug relapse interventions, dysregulation of neural circuits in the prefrontal cortex (especially the anterior cingulate cortex/anterior limbic cortex) is the central mechanism, which is directly associated with relapse behavior with glutamatergic transmission in striatal core regions (141,142). The interdisciplinary chain of evidence needs to be clarified: quantitative relationship of exercise dose (intensity/frequency/duration) → BDNF expression levels → prefrontal functional remodeling → drug craving inhibition (142-144).

5.3.2 Practice Paths for Interdisciplinary Collaboration

(1) Integration of neuroscience and exercise science

Mechanism validation: quantify the modulatory effect of exercise on the strength of prefrontal-limbic system connectivity in addicts by fMRI and BDNF assays, to make up for the inadequacy of the current measurement of neuroplasticity markers in RCT (140,145). Dose optimization: drawing on the experience of exercise intervention in Parkinson's disease, a stepwise dose-escalation design (from 40% VO_2max to 70% gradually) was used to determine individualized thresholds in conjunction with cortical excitability monitoring (TMS technique) (138,145).

(2) Synergy between clinical medicine and social psychology.

Intervention scenario expansion: Referring to the opioid crisis intervention model, exercise prescription is embedded in a three-tiered network of "healthcare-community-family". Referral for exercise rehabilitation within 24 hours after identification of high-risk individuals in the emergency department, with environmental support provided by social workers (146,147). Stigmatization: The case of a comprehensive drug treatment center shows that an exercise intervention to reshape the patient's social identity ("exercise participant" replaces the "addict" label) improves treatment adherence (147).

5.3.3 Methodological innovations in evidence chain construction

(1) Interdisciplinary adaptation of dose-effect modeling

Nonlinear modeling: a Restricted Cubic Spline (RCS) was used to fit the dose-response curves of exercise intensity versus BDNF concentration, identifying the key inflection point (a slowing down of BDNF increase at 50% HRmax intensity) (148,149). Mechanism-driven threshold definition: based on the Key Events Dose-Response Framework (KEDRF), it was determined that an increase in BDNF levels up to 120% of baseline was the threshold for neuroplasticity activation, and the corresponding exercise intensity needed to be calculated by Bayesian baseline dosimetry modeling (BMD) (150-152).

(2) Multimodal Data Integration

A three-dimensional "biological-behavioral-social" evidence integration platform was constructed:

Biological: dynamic monitoring of biomarkers such as BDNF and cortisol (153,154); Behavioral: drug craving scale (VAS) and Trail Making Test (155); Social: social determinants

such as community support and housing stability (156,157). The moderating effect of social support on exercise adherence ($\beta>0.34, p<0.01$) was verified by structural equation modeling for each dimension interaction (147,158).

5.3.4 Evidence-based pathway optimization for clinical translation

Drawing on the successful experience of early activity intervention in the ICU (159), a four-stage translation model was established:

(1) Evidence structuring: extract evidence of mechanisms by which exercise improves prefrontal function and translate it into actionable parameters (30 minutes of moderate-intensity riding = 15% increase in activation of the anterior cingulate cortex) (142,144);

(2) Barrier diagnosis: identification of implementation barriers such as equipment deficits and exercise fear in drug treatment facilities (147,160);

(3) Stepwise promotion: implementation of supervised exercise in a medically supervised setting first (Phase I), with a gradual transition to autonomous community maintenance (Phase III) (146,157);

(4) Dynamic feedback: real-time monitoring of heart rate variability (HRV) via mobile health devices to automatically adjust exercise intensity to maintain the neuroplasticity window (161).

6. Concluding Remarks

6.1 Integration of core findings

6.1.1 Neuroplastic basis of the dose effect of aerobic exercise

Dosage parameters and neuroplasticity indexes: Existing studies have shown that moderate-intensity aerobic exercise (50-70% HRmax) 3 times per week for 12 weeks can significantly increase hippocampal volume (~2%) and elevate serum BDNF levels, thus improving synaptic plasticity and spatial memory function. This effect was manifested in the detoxification population by increased synaptic density, reestablishment of neurotransmitter (glutamate, dopamine) homeostasis, and normalization of the AMPAR/NMDAR ratio in the nucleus accumbens (NAc) region, which was directly associated with reduced drug craving.

Dose-response relationship: Exercise doses need to follow an "inverted U-shaped" curve. High-intensity exercise (>75% VO_2max) may inhibit synaptic plasticity due to elevated corticosterone levels, whereas low- to moderate-intensity exercise (30-60 min/day) promotes neuroplasticity most significantly. Excessive exercise may even induce a stress response that counteracts the neuroprotective effect in drug treatment interventions.

6.1.2 Mechanisms of neuroplasticity in withdrawal maintenance

Plasticity regulation in the nucleus ambiguus (NAc): long-term drug exposure leads to bidirectional synaptic alterations in the NAc region - synaptic inhibition (AMPAR down-regulation) in the early stages of withdrawal and synaptic enhancement (AMPAR up-regulation) after long-term withdrawal. Aerobic exercise promotes the reestablishment of synaptic homeostasis in the NAc region by up-regulating the BDNF-TrkB signaling pathway and inhibiting cocaine-induced silent synapse, thereby reducing susceptibility to relapse.

Functional repair of prefrontal-limbic loops: Exercise intervention enhances functional connectivity between the prefrontal cortex (PFC) and the hippocampus, improving cognitive control and reducing overreaction to drug-related cues. This repair is attributed in part to BDNF-mediated neurogenesis and angiogenesis, improving PFC metabolic rates.

6.2 Comparison of RCT-based intervention programs and dose sensitivity

6.2.1 Comparison of the efficacy of different intervention programs

Exercise intervention: Meta-analysis showed that exercise (especially aerobic combined with resistance training) significantly reduced drug craving (SMD=-1.08,95%CI:-1.37~-0.78), improved inhibitory control (SMD=0.47), and cardiorespiratory function. Its efficacy was more significant in male drug addicts and may be related to the testosterone-BDNF interaction.

Positive thinking and cognitive-behavioral therapy: positive thinking intervention indirectly reduces craving by enhancing self-compassion and emotion regulation, but the improvement in

relapse tendency is weaker than exercise when applied alone (36.96% reduction in relapse risk in the combined protocol vs. 2.33% in the control group).
Advantages of the combined intervention: aerobic exercise combined with positive thinking for relapse prevention (3 times exercise + 1 time positive thinking per week) was significantly better than the single program in reducing relapse tendency and improving self-control and negative emotions (effect size of the combined group d=0.61 vs. d=0.39 for the single group), confirming the synergistic effect of neuroplasticity and psychological mechanisms.

6.2.2 Dose sensitivity analysis

Exercise parameters were optimized:
Intensity: Moderate intensity (60-70% HRmax) is most effective for BDNF elevation and craving inhibition; high intensity may activate the stress axis. Frequency and duration: 30-45 minutes, 3-5 times per week is the optimal window>60 minutes may weaken neurological benefits due to fatigue accumulation. Intervention Period: Neuroplasticity changes take ≥8 weeks to show up, lasting 12 weeks may consolidate hippocampal volume growth and cognitive improvement.

6.3 Research Limitations and Future Directions

6.3.1 Shortcomings of current studies

Lack of dose standardization: most RCTs do not rigorously quantify exercise intensity (relying on self-reported intensity) and lack longitudinal monitoring of neuroplasticity markers (BDNF, synaptic proteins). Population heterogeneity: drug type, addiction duration, and co-morbid psychiatric disorders (depression) may modulate exercise response in recovering addicts and need to be analyzed hierarchically. Insufficient depth of mechanistic studies: direct evidence of exercise on NAc synaptic plasticity mostly comes from animal models; human studies rely on indirect indicators (fMRI, serum BDNF).

6.3.2 Future Research Directions

Precise dosage exploration: combine wearable devices to monitor exercise intensity in real time, and establish individualized dosage models (customized programs based on baseline BDNF levels). Optimization of multimodal intervention: develop a combined exercise-neurofeedback program to target and regulate the activity of the PFC-NAc loop to improve the withdrawal maintenance rate. Cross-species validation: Using organoid models and optogenetic techniques, we analyzed the causal mechanism of exercise-induced synaptic remodeling in drug relapse.

6.4 Practice Implications

Aerobic exercise, as a core means of non-pharmacological intervention, needs to be integrated into the drug rehabilitation system:
Clinical practice: Compulsory isolation drug rehabilitation institutions should implement structured exercise prescription (moderate-intensity aerobic + resistance training, 120-150 minutes per week), and simultaneously monitor biomarkers of neuroplasticity. Policy development: incorporate exercise intervention into drug rehabilitation guidelines, strengthen the "body-medicine integration" model, and promote the translation of neuroplasticity theory into practice.

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