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Effects of treadmill exercise intensity on spatial working memory and long-term memory in rats

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ABSTRACT

Aims: Moderate exercise promotes learning and memory. Most studies mainly focused on memory exercise effects of in the ageing and patients. There is lack of quantitative research about effect of regular exercise intensity on different memory types in normal subjects. Present study investigated the effects of different intensities of treadmill exercise on working memory and long-term memory.

Main methods: Fifty female Wistar rats were trained by T-maze delayed spatial alternation (DSA) task with 3 delays (10 s, 60 s and 300 s). Then they got a 30 min treadmill exercise for 30 days in 4 intensities (control, 0 m/min; lower, 15 m/min; middle, 20 m/min, and higher, 30 m/min). Then animals were tested in DSA, passive avoidance and Morris water maze tasks.

Key findings: 1. Exercise increased the neuronal density of hippocampal subregions (CA1, CA3 and dentate gyrus) vs. naïve/control. 2. In DSA task, all groups have similar baseline, lower intensity improved 10 s delay accuracy vs. baseline/control; middle and higher intensities improved 300 s delay accuracy vs. baseline/control. 3. In water maze learning, all groups successfully found the platform, but middle intensity improved platform field crossing times vs. control in test phase.

Significance: Present results suggested that treadmill exercise can improve long-term spatial memory and working memory; lower intensity benefits to short-term delayed working memory, and middle or higher intensity benefits to long-term delayed working memory. There was an inverted U dose-effect relationship between exercise intensity and memory performance, but exercise -working memory effect was impacted by delay duration.

1. Introduction

Studies on patients with memory disorders [1–3], senior citizens [4,5] and animals [6] have shown that moderate exercise, especially aerobic exercise (e.g. jogging), improves learning and memory and other cognitive abilities [7]. And there were plenty of references investigated the effects and underlying mechanisms of aerobic exercise on learning and memory [7]. Memory can be classified into two basic forms: long-term memory and working memory [8]. Long-term memory, also known as reference memory, stores effective information for long period of time [8]. Whereas, as the basis of many higher brain functions, working memory is a kind of short-term memory with limited capacity responsible for transient holding and processing of newly acquired or already stored information [9,10]. These two kinds of memories have different neuroanatomical basis and molecular mechanisms [8]. Long-term memory, especially declarative or explicit memory, is hippocampus dependent [8]. Working memory is prefrontal cortex (PFC) dependent [10,11], and relying on the involvement of hippocampus in some cases [12–15]. It has been proven that aerobic exercise benefits long-term memory [16,17] and working memory [1–4] in human participants with or without memory impairment. Animal models experiments also proved that exercise can promote expression of brain derived neurotrophic factor (BDNF) [18–21], insulin-like growth factor-1 (IGF-1) [22,23], vascular endothelial growth factor (VEGF) [18], and many other molecules or neurotransmitters [19,24], which are the crucial to enhance synaptic plasticity, neurogenesis and cerebrovascular development, then to alleviate disorders or restore the impaired brain and cognitive functions [7,20,25,26]. Therefore, exercise may also affect working memory and long-term memory by altering the structure and physiological activity of the hippocampus and the PFC in a similar way [20,21,25,27–32].

However, there is an unsolved question on the relationship between the exercise style, intensities and memory. Firstly, acute and regular exercises have different effects on memory. Compared with acute exercise,

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regular exercise can produce long-lasting influence on the physiological activities and brain plasticity [33,34]. In most reports, moderate acute exercise improves working memory [32,35,36], long-term memory [16,17], but much higher intensity exercise would temporarily suppress or permanent impair cognitive performance [37–40] and cause excessive neuronal apoptosis [41–43]. Some researchers have reported an inverted U-relationship between the acute exercise intensity and cognitive performance, and proposed several hypotheses to interpret this effect [35, 44–46]. In consideration of the long-lasting positive/negative effects of moderate/excessive regular exercise to brain and cognition of normal human or patients, we paid more attention to regular exercise and its effect in memory. Quite naturally, we could imagine a similar inverted U relationship between regular exercise and memory. Moreover, some researches have indicated this possibility [26,40,47,48]. Two papers reported that 14 days lower but not higher intensity of treadmill exercise improved spatial memory in Morris water maze (MWM) and hippocampal dendritic complexity, BDNF, cyclic AMP response element binding protein (CREB) and postsynaptic density protein 95 (PSD-95) levels in rats with traumatic brain injury or cerebral ischemia [26,47]. However, compared with detailed researched acute exercise, there is lack of systemic studies on the effect of regular exercise intensity on memory. So the first aim of present study is to investigate the inverted U hypothesis on regular exercise intensity interacting with memory performance (including working memory and long-term memory).

Delayed response task and delayed spatial alternation (DSA) task are the frequently used working memory tasks in animal research [12,49, 50]. And "delay" is an important control variable in these tasks, on behalf of relevant information is holding in working memory to direct the forthcoming behavior [10,51]. And the working memory performance often negatively correlates with the delay duration [12,49]. According to Yerkes–Dodson law [52,53], the effect of exercise intensity on working memory should be influenced by delays. Therefore, our second aim was to verify the role of delay in the exercise effect on working memory. To address these questions, we designed treadmill exercise with lower-, middle- and higher-intensities, and used spatial T-maze DSA task, MWM task and passive avoidance (PA) task to explore the effects of regular exercise intensities on (1) spatial working memory with three kinds of delays (10 s, 60 s and 300 s), (2) long-term spatial memory, (3) passive avoidance memory and (4) hippocampal neuronal density. Present study will provide first hand animal experimental data to shed some light on regular exercise intensity effect on memory.

2. Materials and methods

2.1. Animal subjects

Fifty adult female Wistar rats (8 weeks, 186–225 g, purchased from Dashuo Experimental Animal Co. Ltd., Chengdu, China; license number, SCXK (Chuan) 2014-002) were allowed to accommodate for a week before experiments. Rats were housed in an environment with 12 h/12 h dark/light cycle and at a temperature of 22 ± 1 °C. Experiments started at 09: 00. All experimental procedures were in accordance with *the Regulations of Laboratory Animals Care of Yunnan Province*, *China*. Animals were randomly divided into five groups with 10 rats in each group: naïve (only used for histological examination), control, lower, middle, and higher groups (Fig. 1A).

2.2. Methods

2.2.1. DSA task

2.2.1.1. Appliance. A black wooden T-maze was placed in the middle of a room on a shelf 60 cm elevated from the floor. Three sides of the room had a chest, bookshelf, etc. against the walls and one side had a window. The T-maze consisted of a major arm (90 cm × 13 cm × 20 cm) and two perpendicular side arms (65 cm × 13 cm × 20 cm). A food container (depth: 1 cm, diameter: 3 cm) was fastened at a point 2.5 cm away from the end of each side arm, respectively. An initial compartment (length: 25 cm) on the major arm was partitioned by a dodge gate. Two fluorescent lamps (40 W) were hung over the maze to illuminate and avoid casting shadows.

2.2.1.2. Experimental procedures. Discrete DSA task was applied and the procedures in reference of [12,13,49] were followed with some modification. All animals were trained by an appointed experimenter and were fed with restriction to control body weight gains. Animals were trained for 5–7 days per week and training was done before feeding. Animals were allowed to accommodate with the maze for 5 days until they could feed from the food container. During the accommodation phase, animals were allowed to explore the maze freely and the rewarding food (sunflower seed kernels) was initially scattered on all three arms, then on the two side arms, and finally placed only in the food containers. The training was started right after accommodation and each trial included one sample choice and one test choice. During the sample choice, one side arm was closed; the animal was rewarded if it enters the opened arm. After a delay with the animal in the initial compartment, the dodge gate and both of the side arms were opened, then, if the animal chose the closed arm earlier, it was rewarded for 3 s; otherwise, it was retained without reward for 3 s. The time from the opening of the dodge gate to the animal reaching the food container was recorded as the response time. The animal was placed back in the initial compartment, the dodge gate closed, and the junctions of major arm to side arms were wiped with alcohol to eliminate odors. The delay of initial training was 10 s, and 10 trials were performed per day as a session. The order of closed side arm in sample choice was arranged semi-randomly. After the average accuracy of the four groups reached 80%

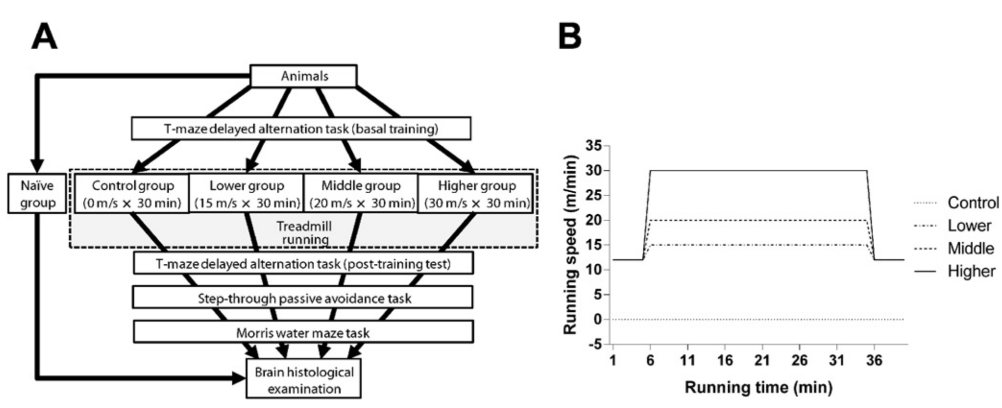

Fig. 1. Schematic diagram of animal groups and experimental timeline (A) and treadmill running speeds plan in a training phase (B) Animals in each group (n = 10) were trained by treadmill and three behavioral tasks except the naïve only for histological examination. In treadmill exercise, the running process included three processes: the first is warm-up (12 m/min for 5 min), then high speed running (30 min), and cool-down (12 m/min for 5 min) at last.