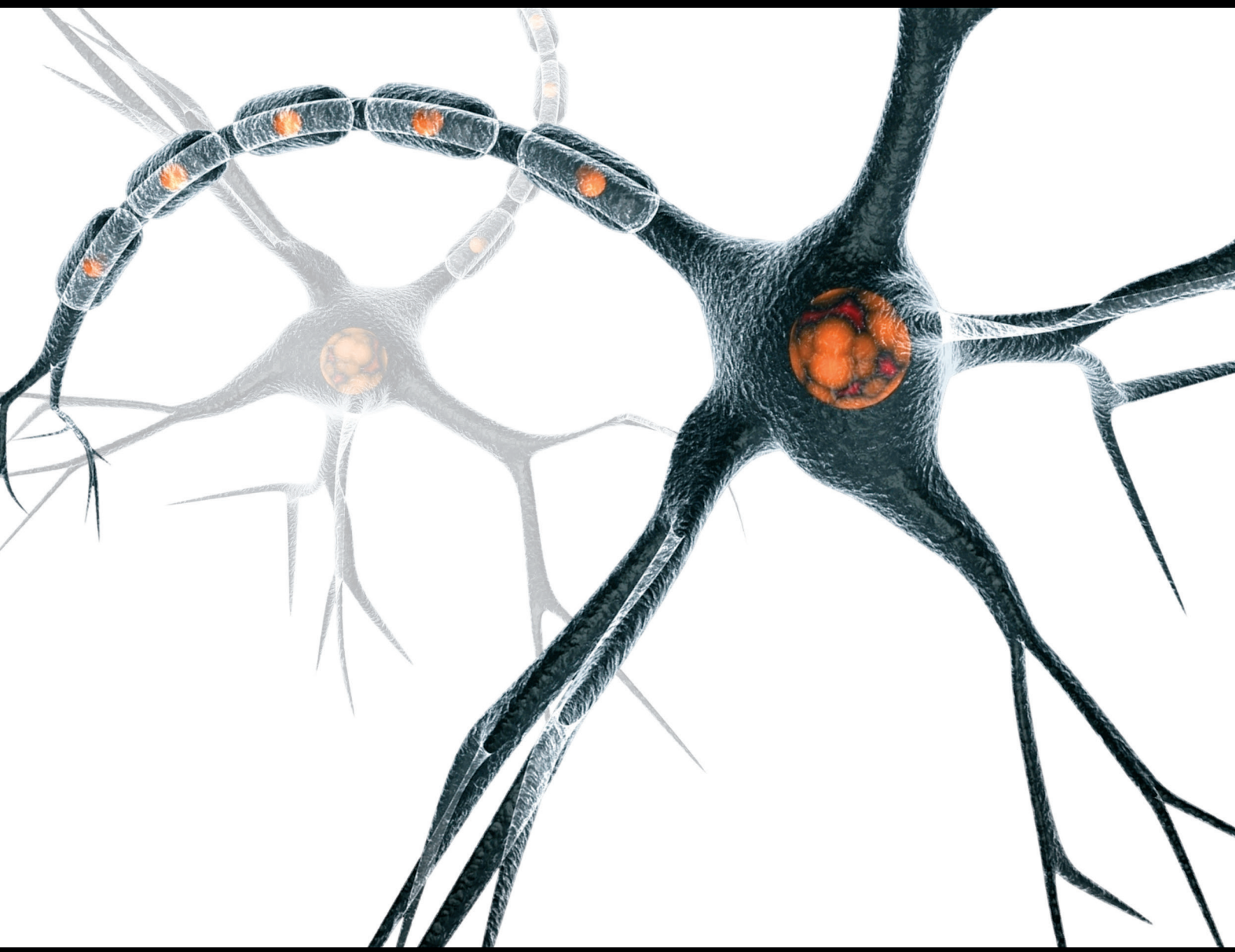
Neural Plasticity

Neuroplasticity and Healthy Lifestyle: How Can We Understand This Relationship?

Lead Guest Editor: Azucena B. Losa
Guest Editors: Luis J. Santín, Pablo Galeano, Debora Cutuli, and Patricia S. Piquero



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Editorial Board

Contents

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Editorial

Neuroplasticity and Healthy Lifestyle: How Can We Understand This Relationship?

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Our brain has this extraordinary ability to experience functional and structural changes before environmental stimuli, cognitive demand, or our experience itself. Exercise, diet, an appropriate sleep pattern, and reading habits are among those activities proposed to induce effects on cerebral architecture—an active lifestyle seems to induce changes in the brain function that favour welfare and better quality of life. This special issue is intended to extend the knowledge about the relationship between neuroplasticity and a healthy lifestyle.

L. Mandolesi et al. present a broad approach on environmental effects on neural plasticity in "Environmental Factors Promoting Neural Plasticity." Combining concepts such as brain reserve and cognitive reserve allows us to understand how different lifestyles impact both brain architecture and function. Therefore, physical activity, an appropriate sleep pattern, and certain diet are thought to promote better cognitive functioning, leading to a reduction of deficits such as those associated with ageing. In this sense, C. Phillips shows us how to achieve both physical and psychological health in her review "Lifestyle Modulators of Neuroplasticity: How Physical Activity, Mental Engagement, and Diet Promote Cognitive Health during Aging."

Physical activity has been proposed as a modulator of brain activity and cognition throughout the lifespan. Y.-K. Chang et al., in their study "Exercise Modality Is Differentially Associated with Neurocognition in Older Adults," conclude that both aerobic exercise and a programme of coordinated exercise have beneficial effects in the Stroop test for inhibitory control in individuals ranging from 55 to 70 years old—both groups exhibit lower reaction time in the Stroop test. After ERP (event-related potential) analysis, the authors highlight how N450 wave is reduced in exercised subjects, which could be reflected in the reduced activity in the anterior cingulate cortex, a brain area related to conflict resolution processes. The lower amplitude in N450 wave might indicate higher resolution capacity in the Stroop test. In line with this work, C.-H. Chu et al. in "Acute Exercise and Neurocognitive Development in Preadolescents and Young Adults: An ERP Study" propose that a simple exercise programme (20 mins) in preadolescent and young adults improves the performance in the Stroop test. The ERP technique showed an increase in P300 wave in every exercised group, accompanied by an improvement in control inhibition processes measured in the Stroop test.

On the other hand, M. Tajerian and J. D. Clark thoroughly review alternative medicine interventions in "Nonpharmacological Interventions in Targeting Pain-Related Brain Plasticity." Their analysis include a review of not only several of these interventions (distraction,

mindfulness and meditation, cognitive behaviour therapies, etc.) but also the plasticity mechanisms underlying each one of them. Although there are no conclusive data, it seems that alternative therapies could be a great complementary tool to classic pharmacological interventions.

Stressors are among the neuroplasticity-affecting agents that could disfavour welfare, as stressful events can induce negative effects on both cerebral and cognitive functioning. M. S. Henry et al. propose that higher resilience could reduce negative stress-related outcomes in their review "Enkephalins: Endogenous Analgesics with an Emerging Role in Stress Resilience." The concept of resilience is referred to as the ability an individual has to adapt to adverse conditions that could happen in life. It is a complex process combining coping abilities with neurobiological processes and the interaction between them. The study of resilience is likely to extend our understanding of affective disorders such as depression and anxiety.

In the past few years, it has been proposed that healthy habits (exercise, diet, etc.) could promote resilience. M. S. Henry et al. conclude that enkephalins (ENK) could play a relevant role in promoting resilience, increasing the subject's adaptability to the environment. Taking into account the distribution of enkephalins and their receptors in the hippocampus, the amygdala (AMG), the medial prefrontal cortex (mPFC), and the nucleus accumbens (NAc), these opioid neurotransmitters are proposed not only to exert analgesic effects but also to affect emotional responses; the level of anhedonia in rats, measured in the sucrose preference test, is increased when ENK transcripts show a reduction in the basolateral amygdala. M. S. Henry et al. show that resilience to social defeat and chronic unpredictable stress share common variations of expression among enkephalin systems within specific brain regions in rats. ENK mRNA (transcripts) were quantified in 23 nuclei of the mPFC, NAc, dorsal striatum, and AMG. Only one significant difference between control, resilient, and vulnerable individuals was found in the BLA of vulnerable individuals; ENK mRNA levels were decreased in vulnerable rats compared to control and resilient rats. This work extends the action of enkephalins to regions like the preoptic area and the bed nucleus of the stria terminalis (BST) with regard to stress resilience. Hence, modulating ENK or DOPr/MOPr expression within circumscribed regions or modulating selected neuronal circuits appears to be more appropriate.

Finally, X. Chen et al. analysed in their research "The Rapid Effect of Bisphenol-A on Long-Term Potentiation in Hippocampus Involves Estrogen Receptors and ERK Activation" the effects of bisphenol on memory-related processes such as long-term potentiation (LTP). Bisphenol-A (BPA) is a widely used synthetic compound included in polycarbonate plastics and epoxy resins, for example, in food and beverage containers, dental prostheses, compact discs, and baby bottles. Its action on the endocrine function has been assessed in numerous studies, showing that low doses can inhibit sexual differentiation and lead to relevant outcomes during adulthood. X. Chen et al. show that bisphenol-A exerts dose-dependent effects; that is, they observe biphasic effects of low-dose (100 nM) and high-dose (1000 nM) BPA on hippocampal LTP. The exposure to BPA at a low dose enhanced LTP, while exposure to a high dose inhibited LTP compared with vehicle controls. These effects require the participation of the membrane-associated estrogen receptor (ER).

We have tried to include in this special issue those studies analysing the role of healthy habits and how brain plasticity can be affected by them. The aim of this special issue was to give an insight into the current research of promoting quality of life.

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Research Article

Acute Exercise and Neurocognitive Development in Preadolescents and Young Adults: An ERP Study

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The purpose of this study was to examine the effect of a single bout of exercise on neurocognitive function in preadolescent children and young adults by determining the modulatory role of age and the neuroelectrical mechanism(s) underlying the association between acute exercise and executive function. Twenty preadolescents and 20 young adults completed the Stroop test, and neuroelectrical activity was recorded during two treatment sessions performed in a counterbalanced order. Exercise treatments involved moderate intensity aerobic exercise for 20 min as the main exercise and two 5 min periods of warm-up and cool-down. The control treatment participants read for a similar duration of time. Acute exercise improved participant reaction times on the Stroop test, regardless of Stroop congruency, and greater beneficial effects were observed in young adults compared to those in preadolescents. The P3 amplitudes increased after acute exercise in preadolescents and young adults, but acute exercise induced lower conflict sustained potential (conflict SP) amplitudes in preadolescent children. Based on these findings, age influences the beneficial effect of acute exercise on cognitive performance in general. Furthermore, the event-related brain potential differences attributed to acute exercise provide a potential clue to the mechanisms that differentiate the effects of acute exercise on individuals from preadolescence to young adulthood.

1. Introduction

The positive associations between exercise and a variety of psychological health outcomes, including reductions in anxiety and depression and improvements in emotion and mood, are well documented [1]. The beneficial effects of exercise on psychological health extend to cognition [2, 3], and even a single bout of aerobic exercise (i.e., acute exercise) has consistently been shown to positively influence cognitive function [4]. Specifically, the facilitation of cognitive performance by acute exercise of moderate intensity for 20 to 30 min has been reported in empirical studies (e.g., [5, 6]), qualitative reviews [7–9], and meta-analytical reviews [4, 10–12]. Notably, acute exercise is associated with improvements in a wide range of cognitive functions, including basic information processing, attention, crystallized intelligence, and executive function [4, 10], but a disproportionately larger benefit is observed for cognition related to executive function [13]. Studies of acute exercise and executive function typically emphasize effects on younger and/or older adult populations [5, 14–16], and only a few studies examined preadolescent children in a narrow age range (e.g., 9 to 10 years) [17, 18]. This research gap in children has generated several unanswered questions regarding executive function across childhood and adolescence [19] and how acute exercise affects executive function from the developmental

perspective; therefore, this issue is worthy of further investigation [20, 21].

Executive function is an essential cognitive process; this function includes a number of components of higher level cognition, and it controls and regulates other more basic cognitive processes to achieve purposeful or goal-directed behaviors [22, 23]. Executive function has also been shown to determine the appropriate decision in response to nonroutine or conflict situations [24, 25]. Maturation of executive function occurs during early childhood and continues during young adulthood [26]. For example, Velanova et al. [27] observed better executive function performance in young adults (older than 17 years), followed by adolescents (aged 13 to 17 years), and then children (aged 8 to 12 years). The developmental trend in executive function parallels the neuroanatomical changes in brain regions associated with executive function [28]. According to functional magnetic resonance imaging (fMRI) research, children exhibit higher activation in the anterior cingulate cortex (ACC) and right dorsolateral prefrontal cortex (DLPFC) than adolescents and adults, suggesting that children engage more effort for a given task. Adolescents also exhibit more behavioral errors [27]. Based on these findings, neurocognitive development appears to be incomplete in preadolescents, and the maturation of this circuitry continues into adulthood [27].

Executive function constitutes distinct and multifaceted subcognitive processes, including the inhibition of prepotent responses, shifting between multiple sets, and updating working memory [29]. Previous acute exercise studies in healthy children predominantly explored the inhibitory aspect of executive function [17, 30, 31], and no consensus has been reached. For example, acute exercise facilitated inhibitory performance in some studies [30, 31] but failed to influence inhibition in other studies [17, 32]. Inhibition is associated with academic achievement [33], analogical reasoning [34], and emotional regulation [35] and is therefore particularly important in children.

Researchers have not yet conclusively determined whether age moderates the effect of acute exercise on executive function. According to meta-analytic reviews, acute exercise positively influences both high school-aged and young adults (i.e., 14 to 30 years) but not elementary-aged children (i.e., 6 to 13 years) [4]; however, the positive effect elicited by acute exercise was not different among preadolescents, adolescents, and young adults [36]. As shown in the study by Best [21], both age and the nature of executive function may be moderated by the relationship between acute exercise and executive function. For instance, prior research indicated significant influence of acute exercise on task-switching performance among young adults [37, 38], but not among children [39]. On the other hand, improved performance in the flanker task was reported among fit children [40], but not among young adults [41, 42]. However, to date, no acute exercise study has simultaneously examined inhibitory function among different age groups. Because the maturation of several cortex regions (i.e., ACC and DLPFC) occurs during neurocognitive development [27, 28, 43], as well as the association between neurotrophic factors (e.g., serum brain-derived neurotrophic factor, which plays a significant role in executive function) and increased brain volume [27, 28], age might differentially impact the cognitive performance of children and young adults in response to acute exercise. As a result, more research on the effects of acute exercise on inhibition in children and across the age spectrum is required to improve our understanding of this topic.

Exercise-induced arousal has frequently been proposed as a potential mechanism for the beneficial effect of acute exercise on executive function [10]. Specifically, the inverted U-trend of the arousal-performance relationship indicates that the optimal effect of acute exercise on cognitive performance is obtained when arousal is induced by moderate intensity exercise [4, 9, 10, 12]. Studies utilizing electrophysiological techniques, such as event-related potentials (ERPs), have provided additional insights into the mechanisms connecting acute exercise and cognition. An ERP is the pattern of neuroelectrical activation in response to, or in preparation for, an event (e.g., a stimulus). ERPs are recorded with high temporal resolution and reflect distinct cognitive processing between stimulus engagement and response execution [44]. P3 or the P300 component is an endogenous and positive stimulus-locked ERP component that occurs approximately 300 to 800 ms after a deviant event (e.g., a stimulus), and the maximal amplitude of P3 is observed over parietal electrode sites [45]. The P3 amplitude reflects the allocation of attentional resources during stimulus engagement [31, 45] and the level of physiological arousal [46]. P3 is also linked to developmental age, as an increased P3 amplitude has been documented to follow a maturational path from young children to adolescent children, reaches a peak value at approximately the age of 20, and then gradually declines with age [47].

Empirical studies have examined variations in P3 associated with acute exercise and observed that an increased P3 amplitude corresponded with improved behavioral performance, particularly for tasks that required inhibition following an acute bout of exercise [17, 31, 48]. Based on these findings, acute bouts of exercise benefit inhibitory performance by increasing the allocation of attentional resources during task performance. However, most previous studies of the associations of acute exercise with inhibition relied exclusively on P3, and fewer efforts have been focused on other ERP components. The current study examined P3 and the conflict sustained potential (conflict SP) component, which is a tonic, sustained, and conflict-sensitive slow potential that is frequently observed in the Stroop Task [49–51]. The polarity of the conflict SP is a region-dependent component that occurs approximately 500 ms after stimulus onset, with greater positivity over the central-parietal region and greater negativity over frontal regions following incongruent trials than after congruent trials [50, 52]. The conflict SP over the central-parietal regions likely reflects neural activity that responds to the presence of conflict [50, 52] or response selection [53]. Notably, the conflict SP during the Stroop test is more sensitive to conflict than P3 [54, 55], suggesting that this component is appropriate for examining the neurocognitive effects of acute exercise in the current study.

The current study examined the effects of acute exercise on the neurocognitive function of preadolescents and adults

Table 1: Participant demographic characteristics (mean ± 1 SD; range).

Variable	Group	
	Preadolescent children	Young adults
Sample size	20	20
Gender (female: male)	0 : 20	2 : 18
Age (yrs)	10.50 ±. 53; 10-11	20.42 ± 1.16; 19–23
Education (yrs)	4.40 ± .52; 4-5	14.33 ± 1.37; 13–18
Height (cm)	146.30 ± 8.79; 138.00–167.00	169.75 ± 5.82; 156.00–178.00
Weight (kg)	40.00 ± 6.13; 30.00–50.00	66.25 ± 10.80; 48.00–80.00
BMI ($kg{\cdot}m^{-2}$)	18.65 ± 2.14; 15.11–22.32	22.92 ± 3.13; 19.15–27.68
Digit span forward	14.30 ± 1.49; 11–16	14.50 ± 1.31; 12–16
Digit span backward	8.70 ± 2.40; 5–12	10.58 ± 2.97; 5–14
VO_{2peak} ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$)	50.60 ± 8.24; 46.43–68.07	49.18 ± 7.57; 44.16–65.43
Resting heart rate	70.20 ± 6.78; 59.00–86.00	65.50 ± 5.27; 56.00–73.00

using the Stroop test. Specifically, the influence of age on the effect of acute exercise on executive function was elucidated. Furthermore, the neuroelectrical measures P3 and conflict SP were investigated to examine the potential mechanisms connecting acute exercise to neurocognitive function. We hypothesized that acute exercise would facilitate interference suppression in both populations, but young adults would show a larger beneficial effect. Similar patterns of larger P3 and conflict SP amplitudes would also be expected following the acute exercise intervention, with young adults exhibiting greater activation, suggesting that acute exercise differentially impacts cognitive function during the different stages of neurocognitive development.

2. Methods

2.1. Participants. Forty participants ($n = 20$ preadolescent male children; $n = 20$ young adults, 18 males and two females) were recruited through flyers posted in primary schools or universities in Taoyuan County, Taiwan. All participants were initially screened using the Physical Activity Readiness Questionnaire (PAR-Q) and Health Screening Questionnaire (HSQ) to ensure their safety prior to engaging in our fitness test and a single bout of moderate exercise [56]. Participants were also required to meet the following inclusion criteria: (a) right-handedness; (b) no history of psychological disorders, psychosis, neurological disorders, or head trauma; (c) no first-degree relatives with a history of psychosis; (d) not currently using any medications that may affect central nervous system function or cognitive performance; and (e) normal or corrected-to-normal vision and normal color vision. Demographic measures (e.g., age, body mass index, and education level) and working memory, which may influence performance on the Stroop test, were assessed [57]. Specifically, the Digit Span Forwards and Backwards tests of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) and Wechsler Intelligence Scale for Children (WISC-R) [58] were administered to young adults and preadolescents, respectively. These tests have high test-retest reliability [59]. Participants and their legal guardians provided written informed consent, as indicated in the study protocol approved by the National Taiwan Sport University committee for institutional review. Table 1 presents the demographic data for the young adult and preadolescent groups.

2.2. Cardiovascular Fitness Assessment. The cardiovascular fitness of the preadolescents and young adults was estimated using the single-stage submaximal treadmill walking test (SSTWT) developed by Ebbeling et al. [60]. The SSTWT is a convenient protocol for estimating the VO_2 peak (VO_{2peak}) in individuals of various ages and fitness levels [61], and it has been used previously [61–63]. The SSTWT includes two 4 min stages. Participants warmed-up on the treadmill at a comfortable speed between 2.0 and 4.5 mph at a 0% grade during the first 4 min stage, and the treadmill speed increased gradually until the participant's heart rate (HR) reached 60% to 70% of the maximum heart rate (HRmax). The estimated HRmax was calculated using the formula "$208 - (0.78 \times \text{age})$" for preadolescents [64, 65] and "$207 - (0.67 \times \text{age})$" for young adults [66, 67]. Following the 4 min warm-up stage, participants were asked to maintain the same speed for an additional 4 min while the treadmill inclined to 5%. The steady-state heart rate (SSHR) was recorded as the moment when the HR did not differ by more than 5 bpm during the final two minutes of the second 4 min period. VO_{2peak} was computed from the following formula: $VO_{2peak} = 15.1 + 21.8 \times \text{speed (mph at 5\% grade)} - 0.327 \times \text{HR (bpm at 5\% grade)} - 0.263 - \text{speed} \times \text{age (year)} + 0.00504 \times \text{HR} \times \text{age} + 5.96 \times \text{gender}$ (0 = female; 1 = male).

2.3. Stroop Color-Word Test. A modified computerized Stroop color-word test (Stroop test) developed by Stroop [68] was used in this study. The Stroop test consists of congruent trials, in which three color words (i.e., red, blue, and green in Chinese) are presented in the ink of the color indicated by the word, and incongruent trials, in which the three color words are presented in ink of a nonmatching color. The three color words, each 2 cm^2 in size, were displayed in the center of a 15-inch screen with horizontal and vertical angles of 28.14° and 1.40°, respectively, using the Neuroscan Stim2 software (Neurosoft Labs Inc., Sterling, VA, USA). The

distance between the screen and participant was approximately 70 cm. Participants were required to complete 6 blocks of 60 trials, in which the congruent and incongruent trials in each block were arranged in a random order at a ratio of 2 : 1. The total length of the Stroop task was approximately 25 min. A fixed cross first appeared in the center of the screen for 506 ms, and stimuli were shown for 500 ms each. Participants were instructed to respond to the ink color according to the color on a response pane ($10 \times 8 \times 2$ cm box) by pressing one of the three colored buttons with their right thumb as quickly and accurately as possible. Responses were accepted between 200 ms and 1000 ms following the stimulus presentation. Responses outside the acceptable time window or with the wrong key were considered inaccurate responses. The reaction times and accuracies of the participants were recorded and analyzed as the primary indices.

2.4. ERP Assessment. Electroencephalography (EEG) was performed using an elastic cap (Quick-Cap, NeuroScan Inc., El Paso, TX, USA) with 32 Ag/AgCl electrodes that were mounted and arranged in accordance with the International 10–20 system [69]. All EEG recordings were referenced to the average of the right and left mastoid, and the ground electrode was placed on the AFz electrode site. The electrooculogram (EOG) activity was recorded from electrodes attached below and above the left eye (VEOG) and electrodes located at the outer canthi of both eyes (HEOG). Electrode impedance was maintained at or below 10 kΩ prior to testing. Continuous EEG data were amplified using a SynAmps EEG amplifier and the Scan 4.5 package (NeuroScan Inc., El Paso, TX, USA), with digitization at a 500 Hz sampling rate and an amplification of 500 times. A 60 Hz notch filter was also applied to remove potential artifacts.

Offline individual EEG data from correct trials were segmented into epochs from 200 ms prestimulus to 1000 ms poststimulus. Baseline correction was performed using the 100 ms period prior to stimulus onset, and the data were filtered using a 30 Hz zero phase shift (12 dB/octave, low-pass cutoff). The horizontal and vertical eye movement artifacts and blinks were corrected using Semlitsch et al.'s [70] algorithm. Amplitude excursions of $\pm 100\,\mu$V were rejected. The ERP waveform analysis focused on P3 and conflict SP. The final remaining correct trial numbers from the control and exercise conditions for both groups were recorded. P3 was calculated separately at the Fz, Cz, and Pz sites from the mean voltage from 300 to 450 ms after stimulus onset. The conflict SP component was quantified as the mean amplitude from 600 to 800 ms following stimulus onset, and the average conflict SP amplitudes of the right and left hemispheres were calculated separately (left central-parietal hemisphere: CP3 and P3; right central-parietal hemisphere: CP4 and P4).

2.5. Experimental Procedure. Participants visited the laboratory three times at least 24 hours apart at approximately the same time of day. The legal guardians of the preadolescents and the young adults were briefly introduced to the study during the first visit and completed the informed consent form, a demographic questionnaire, IPAQ, and PAR-Q to screen for inclusion status. Eligible participants were subjected to the SSTWT to estimate their cardiovascular fitness. Instructions and practice for the Stroop test (i.e., 15 trials) were given, and all participants reached the 85% accuracy rate before further assessment. This accuracy criterion was employed to limit the learning effect.

Participants attended one of the two treatments (control or exercise session) in a counterbalanced order on the second and third visits to eliminate any potential learning or practice effects. During the exercise session, aerobic exercise was performed on a motor-driven treadmill in a temperature-controlled room (mean temperature 22°C). The exercise protocol consisted of a 5 min warm-up phase, a 20 min main exercise phase, and a 5 min cool-down phase. Participants were instructed to run at 2.5 mph on a motor-driven treadmill that gradually increased in speed to reach the target 65–75% heart rate reserve (HRR) during the 20 min main exercise phase. This target HR range is considered moderate intensity, which is suggested to benefit cognitive performance [6, 9]. Participants were instructed to read educational documents for 30 min in a quiet room during the control session. Participants were escorted to an adjacent soundproof room immediately after each intervention to record the EEGs elicited during the Stroop test.

A polar HR monitor (Sport Tester PE 3000, Polar Electro Oy, Kempele, Finland) was utilized throughout the experimental procedure, and three HR indices were identified: resting HR, HR after 10 min of rest, and treatment HR, which was the average HR recorded during the 20 min exercise phase. The rating of perceived exertion (RPE) on the Borg scale [71] was recorded every 2 min during the exercise session. Participants received $40 and a brief review of the study purpose after completion of the experiment.

2.6. Data Analysis. The protocol employed a mixed design with Group as a between-subjects factor and the Treatment and Stroop congruency as within-subjects factors. Behavioral data (i.e., reaction time and accuracy) were analyzed using a three-way repeated-measures analysis of variance (ANOVA): 2 (Treatment: exercise and control) × 2 (Group: preadolescents and young adults) × 2 (Stroop congruency: congruent and incongruent). The remaining correct trial numbers were analyzed using a two-way repeated-measures ANOVA: 2 (Treatment) × 2 (Group). The mean averaged P3 amplitude was analyzed using a four-way repeated-measures ANOVA: 2 (Treatment) × 2 (Group) × 2 (Stroop congruency) × 3 (Site: Fz, Cz, and Pz), and the mean averaged conflict SP amplitude was analyzed using a different four-way ANOVA: 2 (Treatment) × 2 (Group) × 2 (Stroop congruency) × 2 (Site: averaged C3 and CP3 and averaged C4 and CP4). A Greenhouse-Geisser correction was used to adjust for family-wise error when the sphericity assumption was violated. The subsequent analyses consisted of univariate ANOVA and paired t-tests with Bonferroni's correction when appropriate. A partial eta-squared (η^2) value for the effect size was reported and represented as small (i.e., 0.01 to 0.059), medium (i.e., 0.06 to 0.139), and large (i.e., >0.14) values [72]. SPSS versus 18 was used for the statistical analyses, and the significance level was set at alpha = 0.05.

3. Results

3.1. Exercise Manipulation Analysis. The average heart rates during the control session were 72.10 ± 9.94 and 68.67 ± 5.10 (bpm) for preadolescent children and young adults, respectively. Regarding the manipulation of the exercise intensity, the mean heart rates during exercise sessions were 157.77 ± 4.71 and 150.79 ± 7.65 (bpm) for preadolescent children and young adults, respectively; these values were within the range of 60% to 75% of the HRR. This range of HRR corresponds to the moderate intensity zone, suggesting that our procedure achieved an appropriate exercise intensity.

3.2. Behavioral Measures

3.2.1. Reaction Time. A three-way ANOVA revealed a main effect of Treatment, which was superseded by a Treatment × Group interaction (for detailed statistical values, see Table 2). Subsequent analyses revealed a significantly shorter reaction time in the exercise session compared to the control session for young adults (481.09 ms versus 536.57 ms), $F(1, 19 = 21.13, p < 0.0001, \eta^2 = 0.53)$. A marginally significantly shorter reaction time was observed in the exercise session compared to the control session for preadolescent children (500.80 ms versus 519.62 ms), $F(1, 19) = 4.12$, $p = 0.057$, $\eta^2 = 0.18$. No differences were observed in the control session or the exercise session between preadolescents and young adults (Figure 1(a)).

A three-way ANOVA revealed a main effect of congruency, which was superseded by a Stroop congruency × Group interaction (Table 2). Subsequent analyses revealed a significantly longer reaction time in the incongruent condition than in congruent sessions for young adults (542.52 ms versus 475.14 ms), $F(1, 19) = 674.83$, $p < 0.0001$, $\eta^2 = 0.97$ and for preadolescent children (529.33 ms versus 491.09 ms), $F(1, 19) = 517.48$, $p < 0.0001$, $\eta^2 = 0.97$. No differences were observed in the congruent condition or the incongruent condition between preadolescents and young adults (Figure 1(b)). No other significant effects were observed.

3.2.2. Accuracy. A three-way ANOVA revealed a main effect of Stroop congruency with higher accuracy in the congruent condition than the incongruent condition (87% versus 76%, $p < 0.0001$) (Table 2). A main effect of Group, which was superseded by a Treatment × Group interaction, did not reveal significant differences between preadolescents and young adults (78% versus 85%). No other significant effects were observed.

3.3. ERP Measurements. For the remaining correct trial numbers, the main effects of Treatment (exercise = 212.6 ± 54.36; control = 219.95 ± 29.98) or Group (preadolescents = 217.7 ± 27.68, young adults = 206.8 ± 50.93) or an interaction effect was not observed.

3.3.1. Mean Averaged P3. A four-way ANOVA revealed a main effect of Treatment (Table 2), with larger P3 amplitudes in the exercise session than the control session (9.84 μV versus 8.27 μV, $p = 0.04$) (Figure 2(a)).

Table 2: Summary of statistical analyses of behavioral and ERP measures.

Measure and effect	df	F	p	η^2
Stroop test reaction time				
Treatment	1, 38	23.83	<.0001	.39
Treatment × group	1, 38	5.80	=.021	.13
Congruency	1, 38	60.65	<.0001	.62
Congruency × group	1, 38	4.62	=.038	.11
Stroop test accuracy				
Treatment × group	1, 38	7.03	=.012	.16
Congruency	1, 38	56.31	<.0001	.60
Group	1, 38	5.24	=.028	.12
Mean averaged P3 amplitude				
Treatment	1, 36	4.65	=.038	.11
Congruency	1, 36	24.66	<.0001	.41
Congruency × group	1, 36	9.02	=.005	.20
Site	2, 72	71.08	<.0001	.66
Site × group	2, 72	14.51	<.0001	.29
Mean averaged SP amplitude				
Treatment × group	1, 36	7.00	=.012	.16
Congruency	1, 36	13.23	=.001	.27
Site × group	1, 36	4.61	=.039	.11

Note. Only significant effects were presented.

A main effect of Stroop congruency was superseded by a Stroop congruency × Group interaction. Subsequent analyses revealed a significantly smaller P3 amplitude in the incongruent trials than in the congruent trials for young adults (8.28 μV versus 9.72 μV, $p = 0.02$), but not for preadolescent children (9.86 μV versus 10.81 μV, $p = 0.08$) (Table 2). No differences were observed in the congruent and incongruent conditions between preadolescent and young adult individuals (Figure 2(b)).

A main effect of Site was superseded by a Site × Group interaction. Subsequent analyses revealed that the P3 amplitude was largest at Pz, followed by Cz and Fz, in preadolescent children (ps < 0.0001) and young adults (ps < 0.0001). Only P3 at Pz exhibited significant differences between groups ($p = 0.02$) (Table 2). The topographic distribution of the grand mean P3 amplitude across the scalp for each group and treatment is illustrated in Figure 2(c). No other significant effects were observed.

3.3.2. Conflict SP. A Treatment × Group interaction was observed (Table 2), and subsequent analyses revealed that the conflict SP amplitude was significantly smaller in the exercise session than that in the control session for preadolescents (−1.63 μV versus 1.60 μV, $p = 0.03$), but not for young adults (4.54 μV versus 4.04 μV, $p = 0.51$). Additionally, a difference in the conflict SP amplitude between preadolescent children and young adults was observed for the exercise session ($p < 0.0001$) but not the control session ($p = 0.09$) (Figure 3(a)).

A four-way ANOVA revealed a main effect of Stroop congruency, with larger conflict SP amplitudes in the

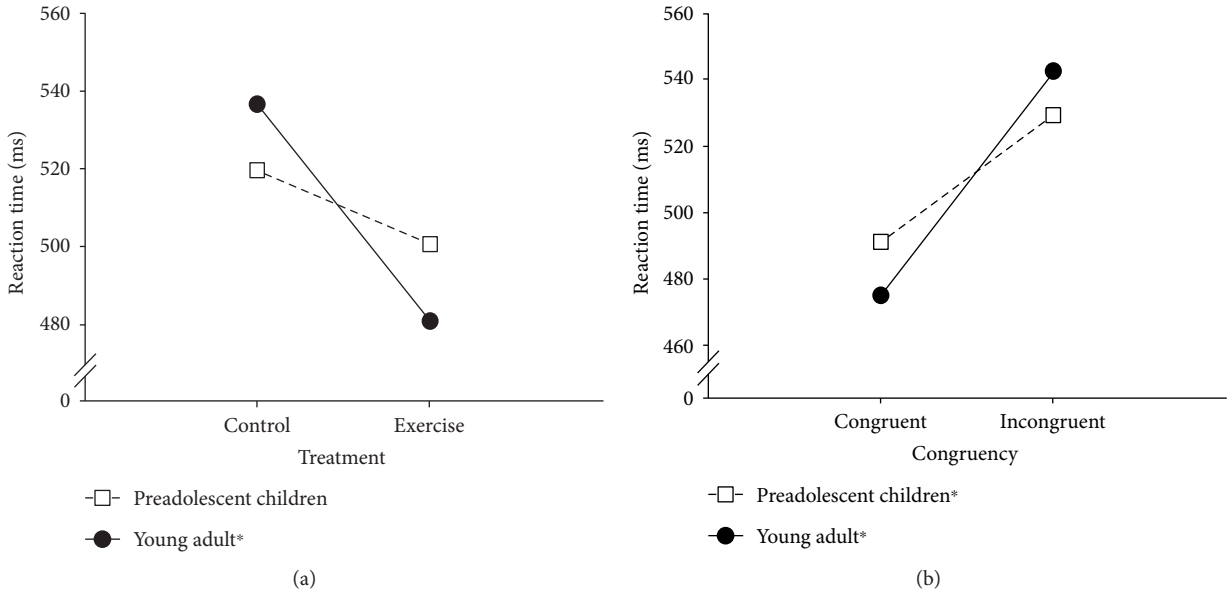

Figure 1: (a) Interaction effect of treatment and group. (b) Interaction effects of condition and group. *Significant difference ($p < 0.05$).

incongruent condition than in the congruent condition (2.81 μV versus 1.16 μV, $p < 0.001$).

A Site × Group interaction was observed (Table 2), and subsequent analyses revealed a significantly larger conflict SP amplitude in the right hemisphere than in the left hemisphere in young adults (4.91 μV versus 3.49 μV, $p = 0.004$), but this interaction was not observed in preadolescent children (−0.48 μV versus 0.30 μV, $p = 0.45$). Additionally, a difference in the conflict SP amplitudes was observed between preadolescent children and young adults in the right hemisphere ($p = 0.003$) and left hemisphere ($p = 0.0001$) (Figure 3(b)). No other significant effects were observed. The topographic distribution of the grand mean conflict SP amplitude across the scalp for each group and treatment is illustrated in Figure 3(c).

4. Discussion

The current study extended the literature on acute exercise and cognition by investigating the modulatory role of age during preadolescence and adulthood using the behavioral and neuroelectrical indices of the Stroop test. Based on our primary findings, moderate intensity acute exercise for 20 min improved cognitive performance on the Stroop test for both Stroop congruency conditions, and these beneficial effects were greater in young adults than in children. Specifically, young adults exhibited improved performance in reaction time after the cessation of the acute exercise, but preadolescent children exhibited only marginally improved performance following exercise. Acute exercise had also differential effects on ERP indices in preadolescent children and young adults. Specifically, larger P3 amplitudes were observed in preadolescent children and young adults following acute exercise. No differences were observed in the conflict SP amplitudes between the two treatments in young adults, but the conflict SP amplitudes in preadolescent children were significantly reduced following acute exercise.

4.1. Acute Exercise and Behavioral Performance. Acute exercise improved the cognitive performance of young adults, regardless of Stroop congruency. Additionally, the longer reaction time and lower accuracy in incongruent trials compared to those in congruent trials reflected a robust "Stroop effect," which is the response in incongruent trials which involves greater executive control because of competition between the stimulus-response translations that are introduced by task-relevant (i.e., ink color) and task-irrelevant (i.e., word meaning) stimuli [5, 13, 73, 74]. A selective improvement in the Stroop incongruent condition was reported after acute exercise [75], but our findings of improvements in the Stroop incongruent and congruent trials are partially consistent with recent studies in adults [5, 6, 13]. For example, Chang et al. [13] assessed the influence of acute exercise on five conditions of the Stroop test (i.e., congruent, word, square, neutral, and incongruent conditions) and observed that acute exercise had the largest positive effect on Stroop incongruent trials, but performance was enhanced for all five Stroop test conditions, which appears to reflect selective and general improvements. Alternatively, the enhanced behavioral performances induced by acute exercise may be due to more general effects on perception or response preparation. Although the statement may require further examination, acute exercise generally enhanced cognitive functions associated with the Stroop test in an adult population in our study.

Interestingly, the acute exercise-related improvements in Stroop test performance were significant in young adults, but only a positive trend was observed in preadolescent children. These results indicate a modulatory role of age on the interaction between acute exercise and cognition. Compared to young adults, children experienced a smaller beneficial effect

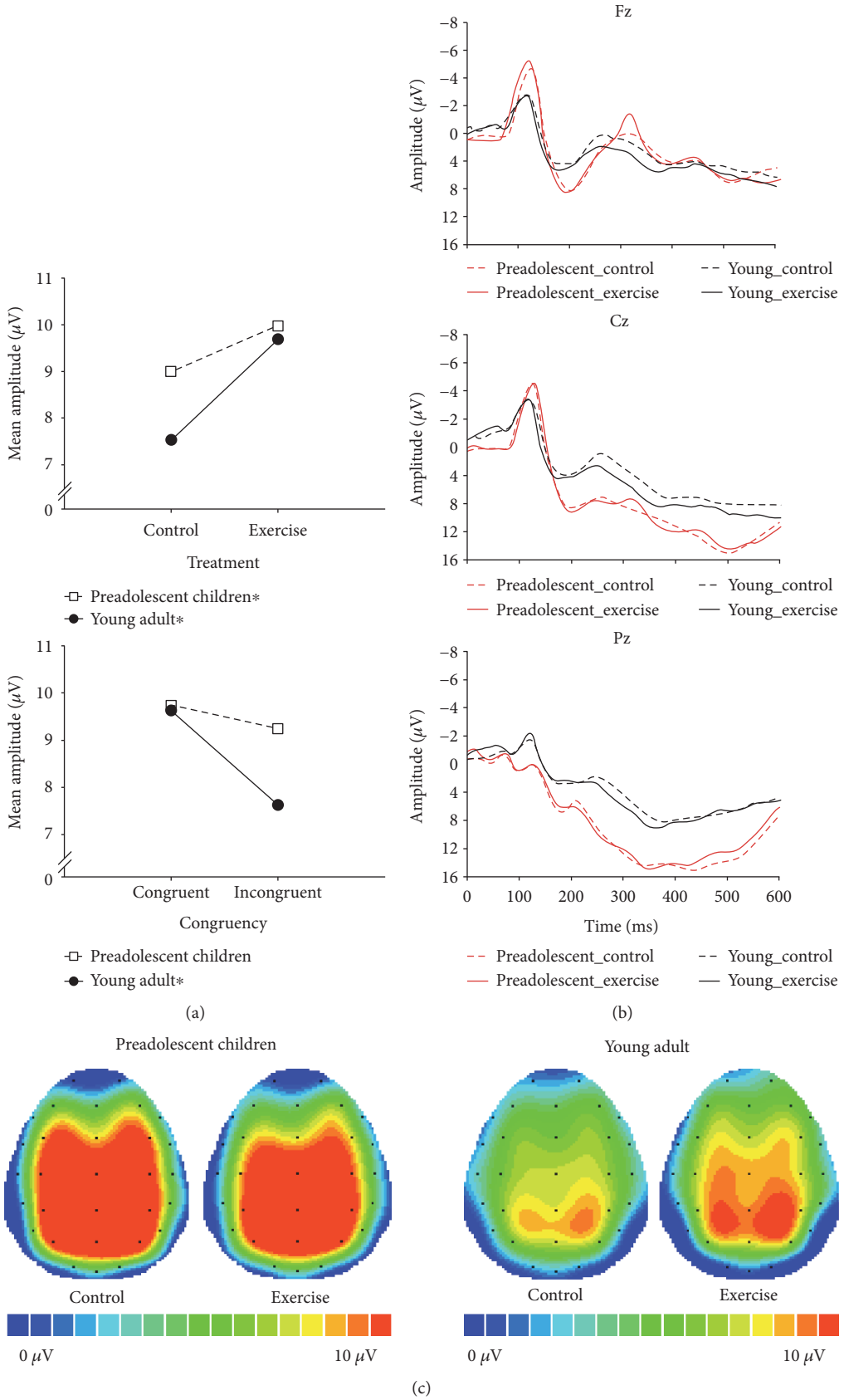

Figure 2: (a) Main effect of treatment and the interaction effect of congruency and group. (b) Stimulus-locked grand-average waveform at Fz, Cz, and Pz, collapsed across congruency in treatments and groups. (c) Topographic scalp distribution of the P3 amplitude collapsed across congruency in treatments and groups. *Significant difference within a group ($p < 0.05$).

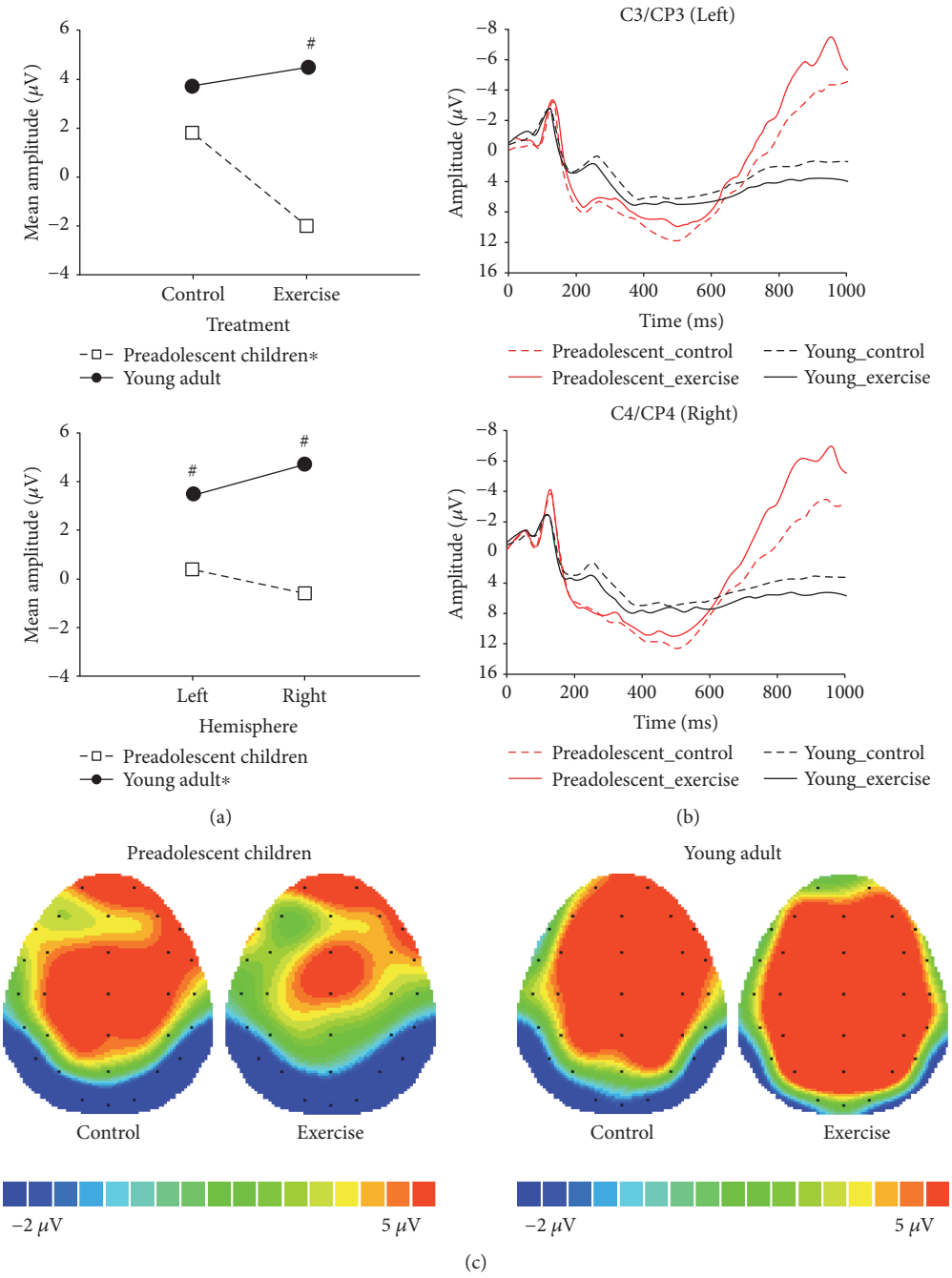

Figure 3: (a) Interaction effect of treatment and group and site and group. *Significant difference ($p < 0.05$). (b) Stimulus-locked grand-average waveform at the right and left central-parietal hemisphere collapsed across congruency in treatments and groups. (c) Topographic scalp distribution of the conflict SP amplitude collapsed across congruency in treatments and groups. *Significant difference within a group ($p < 0.05$); #Significant difference between groups ($p < 0.05$).

on cognitive function after exercise cessation. Executive function and the brain are still developing in children [27, 76], which may render children less susceptible to changes elicited by acute exercise than young adults. However, our findings are inconsistent with previous studies that show facilitated interference suppression in the flanker task after acute exercise in preadolescent children, but the heterogeneous designs used in these studies should be considered. For example, acute exercise improved the response accuracy on a modified flanker task, but the behavioral index of reaction time [30, 31] and higher accuracy were observed only in children who displayed a lower inhibitory control capacity but not in children with a higher capacity [17]. Furthermore, studies [18, 48] also reported an acute exercise-induced improvement in inhibitory performance in children with attention-deficit/hyperactivity disorder (ADHD), which is linked to inhibitory dysfunction. Based on these findings, the beneficial effect of acute exercise on

inhibition may be stronger in preadolescent children when inhibition is assessed using specific tasks and in children who are characterized by lower levels of or deficits in inhibitory capacity.

4.2. Acute Exercise and Neuroelectrical Activation. The larger P3 observed in adults and preadolescent children following exercise cessation is consistent with previous research using the flanker task in adults [77–79] and children [31, 48]. Our findings regarding acute exercise extended previous studies by revealing that neuroelectrical alterations might correspond to interference suppression during the Stroop test. The induction of a greater P3 amplitude by acute exercise regardless of Stroop congruency and age was also a novel finding. These results revealed a general rather than selective effect of acute exercise on the P3 amplitude for the different experiments in both age populations. The physiological arousal induced by acute exercise may be one of the primary mechanisms underlying improved cognitive function [80], and acute exercise-induced arousal and cognitive performance exhibit an inverted U-shaped correlation [77, 81–83]. Arousal induced by moderate intensity exercise leads to better performance compared to performances elicited by light or vigorous exercise. Arousal may be a potential mediator of the effects of acute exercise on cognition because of the positive relationship between arousal and P3 amplitude [45] and the similar inverted U-shape pattern for the correlation between exercise intensity and P3 amplitude [77, 81]. Additionally, the P3 amplitude is linked to the level of attentional allocation [45], and it is possible that our finding of a larger P3 amplitude after acute exercise might lead to an increase in arousal as well as in attention allocation, which might be used in the experimental task. Notably, acute exercise influenced cognitive processing in both age groups, as indicated by the neuroelectrical P3 index; this effect is unlike the modulatory role of age in the behavioral measurements, as preadolescent children received less of a positive effect of acute exercise than the benefit obtained by young adults. Thus, the effects of acute exercise are reflected by more sensitive indices at neuroelectrical levels, and these positive variations are similar in preadolescents and young adults.

Examination of the conflict SP provided another unique insight into the relationship between acute exercise and interference suppression and conflict resolution and conflict response selection. Young adults did not exhibit differences between the exercise and control sessions, and preadolescent children exhibited reduced conflict SP amplitudes following acute exercise, indicating that the modulatory role of age is illustrated by this specific ERP component. The current findings, which revealed a main effect of Stroop congruency on a greater conflict SP amplitude in incongruent trials than in congruent trials, are consistent with previous visual Stroop studies reporting that the conflict SP was proportional to the level of incongruence [50–52, 84]. Based on these results, the conflict SP reflects the cognitive resources that are recruited to resolve conflicts by selecting the proper response during the Stroop test [50, 85].

The maintenance of the conflict SP amplitudes between control and following acute exercise in young adults might indicate the lessened impact of acute exercise on conflict resolution or conflict response selection. Interestingly, prior research has suggested that acute exercise resulted in an increase in conflict detection indexed by the shorter N450 latency [86], suggesting the differential effects of acute exercise on the stages of conflict processing in young adults. In contrast to young adults, preadolescent children exhibit evidence of reduced conflict SP amplitude following acute exercise, which might be interpreted as a reduction in the interference effect and increased conflict-processing ability. This finding is accordance with a recent meta-analytic study [87] in which the authors suggested the greater benefits of acute exercise for preadolescent children who are undergoing executive function development changes, such as changes in the middle frontal gyrus and left extrastriate region [50].

4.3. Age and Stroop Congruency. The "Stroop effect" was observed in preadolescent children and young adults, with no differences between these two age groups. Our findings illustrated a robust interference effect that replicated the previous studies [5, 13, 73, 74] and indicated that the effect was similar in the groups with ages between 12 and 20 years. Inhibitory control dramatically increases in children between the ages of 3.5 and 5 years, and further improvements are only modest until 11 years of age [88]. Ikeda et al. [89] observed less Stroop interference in young adults than in 5- to 6-year-old, 7- to 8-year-old, and 9- to 10-year-old children. However, this difference was not observed when young adults were compared to 11- to 12-year-old children. Our findings are consistent with the reports showing that children aged approximately 12 years may have a similar inhibitory ability as young adults, but the behavioral measures may also have limited sensitivity to reflect age-specific differences. Our neuroelectrical indices may support this assertion.

Smaller P3 amplitudes were elicited in the incongruent condition than in the congruent condition in young adults in this study. The congruency-dependent P3 amplitude observed in young adults is consistent with the previous research [90–92]. Specifically, the smaller P3 amplitude is likely caused by the greater difficulty experienced in the evaluation and classification processes during incongruent trials [92]. Notably, the P3 amplitude did not reflect the Stroop congruency difference in preadolescent children. The P3 amplitude induced by visual stimuli likely decreases from childhood into early adulthood, as previously reported [93]. A few studies examined the conflict SP and Stroop congruency, and our finding of a main effect of Stroop congruency is consistent with the previous studies that observed larger conflict SP amplitudes in the incongruent condition. However, our study extended the idea of a greater conflict SP in both brain hemispheres in young adults than in preadolescent children. Based on these findings, young adults exhibit better interference suppression and conflict resolution abilities compared to those in preadolescent children. Moreover, young adults exhibited a larger conflict SP in the right central-parietal regions than that in the left regions; this finding replicates the results of a study of an applied conflict task that presented a Chinese stimulus [94]. Collectively, P3 neuroelectrical measures provide sensitive indices of the

modulatory role of Stroop congruency and age during various developmental stages. More research is required to explore which specific ERP components are relevant during different stages of neurocognitive development.

4.4. Limitations and Future Directions. Certain limitations of the current study should be acknowledged and considered in future research. Despite the evidence that acute exercise improves interference suppression, as assessed by the Stroop test, a response recorded by key pressing cannot distinguish whether the acute exercise-induced facilitation results from the stimulus or response processing benefits [49, 95]. Specifically, the "Stroop effect" is produced by both stimulus-stimulus incompatible (e.g., the word "red" printed in blue with a verbal response, which results in semantic competition) and response-response incompatible relations (e.g., the word "red" printed in blue, with the pressing "blue" of the assigned buttons, which results in a response competition). Future research may use the Stroop test paradigm with two colors that are assigned to the same manual response [49] or a paradigm in which the incongruent trials are either incongruent-eligible or incongruent-ineligible [96] to further characterize the beneficial effect of acute exercise. Additionally, the interaction of acute exercise and cognition may be moderated by individual differences, such as cardiovascular fitness. For example, individuals with higher cardiovascular fitness exhibited superior cognitive performance following acute exercise compared to their counterparts with lower fitness [97]. Other factors that differ among individuals are education level and inhibitory control capacity. We did not observe differences in either the congruent or incongruent conditions between preadolescents and young adults in the control session, suggesting that all participants presented a similar reading ability for the easy words that were tested (i.e., red, green, and blue in Chinese characters). However, this finding also implies that the task may be insufficient at revealing the developmental differences in cognitive control mechanisms. A future study that considers education level and manipulates the degree of task difficulty is recommended. A third limitation may be related to the use of reading in the control session. The use of videogames may serve as a better "active control" protocol since it may be able to maintain the arousal levels of the participants and prevent them from becoming bored [98]. Additionally, although differences in gender were not observed across the two age groups (chi square = 2.11, $p > 0.05$), our unbalanced gender proportion, particularly more males than females, limits the interpretation and generalization of these findings. The current study did not examine the correlation between the acute exercise and behavioral and neurological indices; therefore, we cannot establish the mediating role of the neurological indices on the variation in behavioral performance. Future studies are encouraged to use larger numbers of participants and conduct mediation analysis to further establish the potential mediator function of P3 and conflict SP on behavioral improvement. Finally, the present study compared the periods of preadolescence and young adulthood, but the recruited preadolescent children were limited to ages between 10 and 12 years. According to a previous developmental research, changes in the inhibitory capacity differ dramatically across childhood [19], and interference suppression develops in a nonlinear pattern in children [89]. A better understanding of the effect of acute exercise on inhibitory control may be achieved by the inclusion of children across a wider age range and a longitudinal examination of executive function in children.

5. Conclusions

This study is the first to reveal that the beneficial effect of acute exercise on interference suppression in the Stroop test is moderated by age, with young adults experiencing more benefit than preadolescent children, who showed limited benefit from acute exercise. Young adults had a larger P3 amplitude and an unaffected conflict SP amplitude following acute exercise, but preadolescent children exhibited a larger P3 amplitude and reduced conflict SP amplitude, indicating divergent mechanisms from a neuroelectrical perspective. Although the beneficial effects of acute exercise on cognitive function may be attributed to more general effects on perception and response processes, improved cognitive performance may be associated with enhanced attentional allocation in both age populations, but the positive effects associated with interference suppression and conflict resolution were only observed in young adults. These findings extend the current knowledge base by revealing a modulatory role of age in the relationship between acute exercise and interference suppression and provide preliminary evidence for the potential underlying mechanism by which acute exercise positively affects interference suppression throughout early adulthood.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Clinical Study

Exercise Promotes Neuroplasticity in Both Healthy and Depressed Brains: An fMRI Pilot Study

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Memory impairments are a frequently reported cognitive symptom in people suffering from major depressive disorder (MDD) and often persist despite antidepressant therapy. Neuroimaging studies have identified abnormal hippocampal activity during memory processes in MDD. Exercise as an ad-on treatment for MDD is a promising therapeutic strategy shown to improve mood, cognitive function, and neural structure and function. To advance our understanding of how exercise impacts neural function in MDD, we must also understand how exercise impacts healthy individuals without MDD. This pilot study used a subsequent memory paradigm to investigate the effects of an eight-week exercise intervention on hippocampal function in low-active healthy ($n = 8$) and low-active MDD ($n = 8$) individuals. Results showed a marked improvement in depression scores for the MDD group ($p < 0.0001$) and no change in memory performance for either group ($p > 0.05$). Functional imaging results showed a marginally significant decrease in hippocampal activity in both groups following the exercise intervention. Our whole brain analysis collapsed across groups revealed a similar deactivation pattern across several memory-associated regions. These results suggest that exercise may enhance neural efficiency in low-fit individuals while still resulting in a substantially greater mood effect for those suffering from MDD. This trial is registered with clinical trials.gov NCT03191994.

1. Introduction

Memory impairment is the most frequently reported cognitive symptom in people suffering from major depressive disorder (MDD) and often persists as a residual symptom following antidepressant therapy [1, 2]. Although the neural underpinnings of impaired memory in MDD remain unclear, research suggests that the hippocampus, which plays a critical role in the formation of new memories, also plays a role in the pathogenesis of MDD. To date, cognitive literature has presented mixed findings in terms of the type, severity, and specificity of memory deficits in people with MDD, although the plurality of data has suggested an impairment in episodic (autobiographical) memory with a sparing of semantic (general knowledge) memory and short-term memory [3–8]. The hippocampus has been shown to play an essential role in the encoding of episodic memories [5, 9–13], and pathologies associated with this neural structure may underlie the episodic memory impairments observed in MDD populations. The relationship between MDD, memory impairments, and hippocampal structure and function is based on converging lines of research from animal studies, neuroimaging, neuropsychology, and post-mortem investigations which have all shown hippocampal abnormalities at the structural, functional, and cellular level. Structural brain imaging studies have shown robust hippocampal volume reductions particularly in persistent and early onset MDD [14–16]. Functional neuroimaging studies have found that both the memory encoding and retrieval processes within the hippocampus are to be impaired in MDD [4, 6, 17–19]. Neuropathological evidence from animal models of depression and postmortem studies in depressed humans have revealed cellular abnormalities in the hippocampus such as dendritic atrophy and reduced neuron and glial densities [20–24].

Despite many efforts to develop effective antidepressant therapies, MDD remains a severely undertreated disorder in the primary care setting leaving more than half of

individuals plagued with symptoms [25–28]. Exercise as an add-on to conventional antidepressant therapies is a promising treatment strategy for MDD. It is well established that exercise is efficacious in treating mild to moderate depression with response rates comparable to mainstream therapies such as antidepressant medication and cognitive behavioral therapy [29–34]. However, there is a lack of understanding of the neurobiological mechanisms that underlie or mediate the antidepressant effects of exercise. It is well established that exercise facilitates neuroplasticity [35–37]. To date, much of our understanding of how exercise facilitates neural and cognitive plasticity has come from the extensive animal literature. For instance, rodent studies have shown that exercise increases new cells in the dentate gyrus of the hippocampus, and this is associated with improved learning and spatial memory [36, 38–40]. Further evidence has shown that exercise increases synaptogenesis [41] and angiogenesis [42] and improves dendritic morphology in the hippocampus [43, 44]. However, the effects of exercise on brain structure and function in humans have been more equivocal. In elderly populations, aerobics exercise training has been shown to improve spatial memory [45], executive function [46, 47], and short-term memory [48]; however, others observed no benefits [49–52]. Neuroimaging studies have found that aerobics exercise reverses age-associated brain volume loss in the prefrontal and temporal cortices [53, 54], improves functional connectivity in the default mode and frontal executive networks [47], and increases hippocampal volume in schizophrenics [55]. To date, the literature examining the effects of chronic exercise on neural function in both healthy and MDD populations remains scant. To capitalize on the full treatment potential of exercise in MDD populations, we must also understand the relationship between cardiovascular fitness, neural function, and cognitive performance in healthy individuals in order to identify neural mechanisms specific to MDD.

To our knowledge, this is the first study using a subsequent memory paradigm to determine the effects of an eight-week exercise prescription on the functional integrity of the hippocampus in low-active patients with MDD and low-active healthy individuals. The aim of this pilot study was twofold: (1) using fMRI to examine changes in hippocampal function following an exercise intervention, and (2) to conduct an exploratory whole brain analysis to determine how exercise affects overall brain activity.

2. Materials and Methods

2.1. Participants. Eight patients (mean age = 37.25, SD = 8.00; 7 females) with comorbid MDD and anxiety were recruited from an outpatient Mental Health Day Treatment Program at a local hospital in Oshawa, Ontario Canada. Eight healthy participants (mean age = 20.63, SD = 1.19; 4 females) with no history of mental health illness or neurological disease were recruited from a local university in Oshawa, Ontario Canada. Depressed patients had a diagnosis of MDD according to an unstructured clinical interview by hospital psychiatrists based on Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV-TR) [56] criteria, no coexisting DSM-V Axis I disorders apart from anxiety, and a score ≥20 on the Beck Depression Inventory—Second Edition (BDI-II) [57], and their pharmacological treatment was stabilized a minimum of six weeks prior to study enrolment. In order to be considered eligible for the study, participants needed to indicate that they exercised less than 20 minutes, three times per week. Both groups were also safety screened for MRI and screened with the Physical Activity Readiness Questionnaire (PAR-Q) to ensure they had no medical contraindications to exercise. All participants provided written consent.

2.2. Psychometric Evaluation. Participants completed the Montreal Cognitive Assessment (MoCA) which is a brief neurocognitive tool with high sensitivity for screening patients with mild cognitive impairment. This cognitive assessment was performed to identify participants who may have difficulty performing the associative memory task. The internal consistency of the MoCA is good, with a coefficient alpha of 0.83 [58]. Depression was measured using the Beck Depression Inventory (BDI-II) [57] which is one of the most widely used self-reported instrument capable of measuring depression severity ranging from not depressed to severely depressed. The BDI–II demonstrated excellent internal consistency, with a coefficient alpha of 0.91 [59]. All measures were performed before and after the eight-week exercise intervention.

2.3. Fitness Assessment. Cardiorespiratory fitness was measured before and after the exercise intervention using the YMCA cycle ergometer protocol recommended by the American College of Sports Medicine [60–62]. The YMCA cycle ergometer protocol is an indirect submaximal exercise test used to estimate maximal oxygen consumption (VO_2max) from heart rate (HR) measurements. The protocol consists of two or more consecutive 3-minute stages at a given workload. The objective was to elevate the participant's HR to a target zone to approximately 85% of the age-predicted maximum HR for two consecutive stages. The initial workload consisted of a 25-watt workload at a cadence of 50 revolutions per minute. HR was measured and recorded using the radial pulse method during the final 15 seconds of each minute, which determined the workload of subsequent stages indicated by the YMCA protocol. Once a steady state HR (two successive measures that differ from <5 bpm) was within 10 bpm of the 85% age-predicted maximum HR, the test was complete. VO_2max was estimated using an equation that includes workload, body mass, and derived constants.

2.4. Exercise Intervention. Participants performed an individualized eight-week exercise program consisting of three weekly sessions (described below). Exercise sessions were performed alone, on nonconsecutive days, and each session was supervised by a qualified exercise professional to increase compliance [34]. Attendance was recorded and all participants completed >80% of the exercise sessions.

The exercise prescription was based on international recommendation to obtain at least 150 minutes per week of moderate to vigorous intensity aerobics exercise and to

perform strengthening activities twice per week, for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in healthy adults [63, 64]. This minimum-effective dose of exercise was prescribed to encourage better compliance since people with depression, and are low active, tend to be less motivated [65]. Research has also shown that combining aerobics with strength training improves depression and cognitive function such as attention, processing speed, executive function, and memory performance more than aerobics exercise alone [51, 66].

2.4.1. Resistance Sessions. Resistance sessions were completed twice per week and incorporated a whole-body exercise prescription using larger muscle groups. Each session included eight resistance exercises using both resistance training machines and free weights. Initial workloads were approximately 95% of the 10 repetition maximum to ensure proper form. Exercises were performed in two or three supersets (one set of each exercise with no rest between sets) with an 8–12 repetition range in order to decrease rest times and to maintain target HR. Workload was increased approximately 5% once participants were able to complete three sets of 12 repetitions with proper form. Specific exercises were changed every four weeks; however, they targeted the same muscle groups. Resistance exercises included variations of the chest press, pull downs, triceps extension, biceps curl, shoulder press, leg press, leg extensions, leg curls, squats, split squats, calf raises, and abdominal exercises. During each session, HR was monitored to ensure that the participant maintained a HR of between 60–80% of their age-predicted maximum HR. Each session began with a 5-minute aerobics warmup and ended with 15 minutes of aerobics activity that was performed on either the treadmill, stationary bike, or elliptical trainer.

2.4.2. Aerobics Session. Participants completed an aerobics-only session once per week. They were given the choice to perform their aerobics activity on either the treadmill, stationary bike, or elliptical trainer. The aerobics session workloads were determined by HR response and increased by five-minute increments over the eight weeks reaching a maximum of 60 minutes per session. HR was monitored throughout the session to ensure the participant was in the target HR range.

2.5. Statistical Analysis. Statistical analyses were performed using GraphPad Prism software, version 6.0 data. Data are presented as mean (standard deviation (SD)). P values less than 0.05 were considered significant. Differences in baseline variables between groups were tested using a two-tailed Student's t-test and chi-square test for gender distribution. Within group differences for pre-post-BDI, MoCA, BMI, and VO_2max were tested using a paired t-test. A two-way repeated measures analysis of variance (ANOVA) was used to determine any group × time of interactions and to compare the changes between the two treatment groups. Cohen's d was used to represent the effect size within each group. For between group effect sizes, we used d_{ppc2} [67] which uses the difference between Hedge's g of two different treatment groups in pre-post research designs.

2.6. Associative Memory Task. To evaluate the encoding and retrieval processes of memory, fMRI studies frequently use a recognition memory paradigm that consists of an "encoding" and "recall" phase [5, 68]. Associative memory refers to memory for the relationships between memoranda rather than memory for objects themselves [69–71]. The role of the hippocampus in memory formation has also been specifically linked to associative memory [72]. A specific version of an associative paradigm [17] using face-name pairing known to reliably activate the hippocampus during the successful encoding event and sensitive enough to detect hippocampal dysregulation in a MDD sample [16] was used to investigate activation patterns of the hippocampus during the encoding process inside the MRI scanner (see Figure 1). During the encoding phase inside the MRI, participants were presented with face-name pairs and used a response box provided to indicate if the name suited the face. The retrieval phase was performed after the MRI scan. Participants were presented with a face and two names and instructed to indicate which name was paired with that face during the encoding phase. Participants also rated the confidence of their responses. Trials during the encoding phase were then reclassified based on the responses during the retrieval phase into correct (the participant selected the correct name for the face and indicated a high confidence in their response, suggesting that the face-name association was successfully encoded), guesses (a correct selection with low confidence), or incorrect (the wrong name was selected).

2.7. fMRI Scanning Parameters. Participants were scanned on a 3-Tesla Tim trio MRI scanner equipped with a 32-channel phased array head coil. E-prime software version 2.0 (Psychology Software Tools) was used to present stimuli on a rear-projection system (Avotec, Inc., Stuart, FL) in two separate nine-minute functional runs. To obtain optimal hippocampal resolution, all scans were acquired in the oblique coronal plane perpendicular to the long axis of the hippocampus to maximize the anatomic delineation. A total of 416 functional scans were acquired with a $T_2{}^*$-weighted gradient echo planar imaging sequence (TR =2500 ms, TE = 27 ms, FOV = 192 mm, 3 mm × 3 mm × 3 mm, and flip angle = 70°; in-plane resolution = 3 mm × 3 mm; and 50 slices with 3.5 mm slice thickness). The first 4 volumes of each run were discarded to allow for T1 equilibration. The anatomical scan lasted six minutes and was acquired with a T1 MPRAGE imaging sequence (TR = 2000 ms, TE = 2.63 ms, FOV 256 mm, 1 mm × 1 mm × 1 mm voxels, and flip angle = 9°).

2.8. fMRI Analysis. Image preprocessing was performed using SPM12 methods (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK: http://www.fil.ion.ucl.ac.uk/spm) within MatLab 8.3 (The MathWorks Inc., MA). Individual functional images were slice time corrected and realigned to the first image in the series to correct for motion. The EPI images were coregistered to the T1, and segmentation was applied to the T1

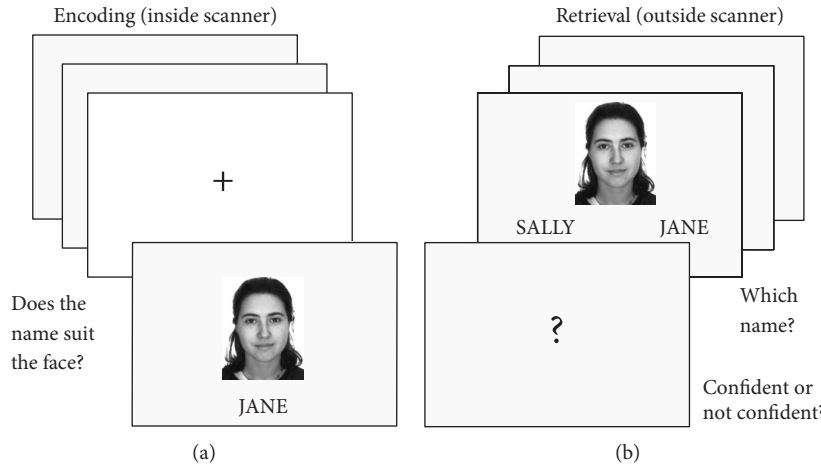

Figure 1: (a) During the encoding task, participants viewed 240 face-name pairs over two nine-minute fMRI runs. Participants were asked if they thought the name suited the face and responded using a response box. Each run included 120 face-name pairs presented for a duration of 3000 ms, jittered with 34 fixation crosses ranging from 3000–9000 ms in increments of 3000 ms. (b) The retrieval task was then performed on a laptop computer outside the MR scanner. Participants were instructed to choose which of the two names was originally paired with the face shown and then asked if they were confident with their choice. This was used to identify the correct successful encoding trials as remembered (correct) versus lucky guesses.

anatomical images to extract grey matter, white matter, and CSF masks and calculate a deformation field to transform the data into MNI space. All EPI images were then spatially normalized to the ICBM template using the deformation field, resampled to $3 \times 3 \times 3$, and smoothed using a 6 mm full-width-half maximum isotropic Gaussian filter. General linear model (GLM) was performed at the single-subject level and statistical contrasts were created modeling the hemodynamic response function (HRF) of remembered items with high confidence (correct), remembered items with low confidence (lucky guess), and incorrect trials (incorrect). Six head motion parameters (three rigid body translations and three rotations) were included in the model to reduce the potential effects of motion. Second-level random effects analysis was performed using the contrast of t-test of correct > incorrect. Correct retrieval requires well encoding of the items. As such, this contrast which differentiates between poorly and well-encoded trials, known as the subsequent memory effects, is a powerful tool for examining successful memory encoding in the brain [73, 74]. As our primary hypothesis was related to activity in the hippocampus, a hippocampal mask was defined using the automated anatomical labeling (AAL) atlas. Significant clusters from an independent sample t-test within the hippocampus ($p < 0.01$ uncorrected, 10 voxels, for this a priori ROI-defining analysis only) for correct > incorrect at baseline were used as an ROI to extract contrast beta values for correct > incorrect in pre- and postscans for each participant. The average beta values from each ROI were imported into SPSS version 20, and a 2×2 repeated measures ANOVA (group × time) was run. We then conducted an exploratory whole brain analysis to determine if other brain regions showed task-related effects. For our whole brain analysis, significant clusters were defined as 20 contiguous voxels (180 mm^3) with $p < 0.005$ uncorrected. A 2×2 repeated measures ANOVA (group × time) was run on β values for the correct > incorrect contrast in order to identify regions in which there was a difference in pre-post changes across groups. Additionally, an exploratory analysis was run examining a group × time interaction across the whole brain.

3. Results

3.1. Baseline Characteristics. At baseline, there were no significant differences between groups for BMI, VO_2max, and MoCA scores (all $p > 0.05$). BDI scores for the MDD group scores indicated severe depression while the healthy group BDI scores indicated no depression ($p < 0.0001$). The depressed group was also older than the healthy group ($p < 0.0001$). See Table 1.

3.2. Psychometric, Memory, and Fitness Results. A 2×2 repeated measures ANOVA revealed a group × time interaction for BDI scores (f (1,15) = 30.42, $p < 0.0001$) indicating that the MDD group had a greater decrease in depression scores pre-post. There were no significant changes in BMI, MoCA scores, or performance on the associative memory task ($p > 0.05$) for either group pre-post. Although baseline memory scores between groups were not significantly different ($p = 0.477$), our results showed that the MDD group performed more poorly on the associative memory task compared to the healthy group (71.48% versus 75.32%) indicating likely memory impairments in the MDD group. One MDD ($n = 1$) participant discontinued baseline VO_2max testing due to exhaustion and was excluded from VO_2max analysis. Baseline VO_2max scores revealed that one MDD participant ($n = 1$) was in the good health benefit rating zone, and the remaining participants ($n = 14$) were in the poor health benefit rating zone based on the Canadian Society for Exercise Physiology guidelines [63]. The healthy group showed a 47% increase in VO_2max that was significant ($p = 0.014$) while the MDD group showed a marginally significant increase of 31% ($p = 0.073$). There

Table 1: Baseline characteristics of participants.

Variables	MDD	*n*	Healthy	*n*	*df*	*p*
Sex (male/female)	1/7	8	4/4	8	1	0.106[a]
Age (years)	37.25 (8.00)	8	20.63 (1.19)	8	14	**<0.0001**[b]
Body mass index (kg/m^2)	28.33 (5.12)	8	28.29 (7.91)	8	14	0.993[b]
VO_2max (ml.kg^{-1}.min^{-1})	24.82 (8.00)	7	20.81 (6.48)	8	12	0.326[b]
BDI	41.75 (3.50)	8	5.88 (5.03)	8	14	**<0.0001**[b]
MoCA	24.63 (1.41)	8	26.13 (3.23)	8	14	0.248[b]

Data are expressed as the mean with the standard deviation in parentheses. [a]Pearson's chi-square. [b]Student's *t*-test. VO_2max: maximum oxygen consumption; BDI: Beck Depression Inventory; MoCA: Montreal Cognitive Assessment.

was no significant difference in VO_2max between groups ($p = 0.661$). These improvements in VO_2max suggest that the exercise intervention was successful at improving cardiorespiratory fitness (see Table 2).

3.3. fMRI Results. Using a main effect contrast of correct > incorrect, collapsing across groups, at baseline, we identified active voxels in the hippocampus and created ROIs for the right and left hippocampus (see Figure 2(a)). A repeated measures ANOVA examining group × time using β values for the correct > incorrect contrasts for pre and post revealed a marginal main effect of time (f (1,15) = 3.3, $p = 0.09$), no main effect of the group (f (1,15) = 0.005, $p = 0.957$) or group × time interaction (f (1,15) = 0.165, $p = 0.69$). This marginal main effect of time is driven by a decrease in the correct > incorrect contrast in the hippocampus indicating that there was a decrease in hippocampal activity during successful encoding in both groups following the exercise intervention (see Figure 2(b)).

The exploratory whole brain analysis did not reveal any clusters in which there were group differences in the pre-post changes following exercise or a main effect of group differences. Given the lack of interaction of the main effects of the group or group × time interaction, a post hoc whole brain analysis was run in which both groups were collapsed. Given the relatively small sample size, this analysis maximizes the power to detect changes in brain activity following the exercise intervention that are common to both healthy and MDD, using the more powerful paired sample *t*-test. Changes in neural activity in the correct > incorrect contrast were compared from the pretreatment to posttreatment MRI scans. Decreases in activity following exercise were noted in several regions (see Figure 3 and Table 3). Regions included a larger cluster in the left posterior insula and smaller clusters in the medial superior frontal/mid cingulate and postcentral superior parietal gyrus.

In order to examine regions in which changes in neural activity were related to changes in BDI score, an additional contrast was run, regressing change in BDI against the paired *t*-test described above. Again, in order to maximize power, the healthy and MDD cases were both included in this analysis. The justifications for including both groups are as follows: firstly, although the healthy group was not clinically depressed, there was some pre-post reduction in BDI scores for the healthy group, and secondly, since cases with depression tended to have a larger decrease in BDI, this analysis may be more sensitive to group × time effects, reflected as BDI changes, while also better reflecting areas in which the pre-post differences were behaviorally meaningful. The regression against BDI for pre-post changes found a negative relationship between changes in depression scores and activation in the right occipital, left occipital/fusiform, and left precentral gyrus (see Figure 4 and Table 4).

4. Discussion

This small fMRI pilot study used a subsequent memory paradigm to investigate the effects of an eight-week structured, supervised exercise intervention on hippocampal function and overall brain activity in low-active patients with MDD and low-active healthy individuals. The current study yielded two main findings. First, our ROI analysis of the hippocampus showed a marginal decrease in activation for both groups pre-post exercise. Although this decrease in hippocampal activation was only marginally significant, a deactivation pattern was present in both groups and was consistent across other memory-related brain regions noted in the whole brain analysis. These data provide the first evidence that improved cardiovascular fitness, following eight weeks of the minimum recommended dose of exercise, affects neural function alike in healthy and MDD brains. The overall deactivation pattern that we observed in the hippocampus and several other brain regions despite similar memory performance pre-post suggests increased cortical inhibition that attenuated neural activity in a subset of brain regions known to inhibit memory encoding and/or an increase in neural network efficiency during the memory encoding process. Second, our study showed that exercise had a robust antidepressant effect on the MDD group who went from the severe to mild depression range, providing additional support to the growing body of literature that exercise is an effective adjunctive therapy for MDD [75].

A common theme in the neurocognitive literature is that brain activity for remembered items is greater than brain activity for forgotten items, as this suggests successful memory encoding [17, 76–79]. However, neuroimaging studies employing a subsequent memory design have identified a negative relationship between remembered items and neural activity in brain regions such as the insula and the supramarginal gyrus, and hyperactivity in these regions may be detrimental to new memory formation [76, 80–82]. A candidate mechanism for the decrease in neural activity

Table 2: Results of pre-post changes for depression scores, cognitive assessment, memory performance, body mass index, and fitness.

Measure	MDD					Healthy					Between-group analysis		
	n	Premean (SD)	Postmean (SD)	p	d	n	Premean (SD)	Postmean (SD)	p	d	F	p	d_{ppc2}
BDI	8	41.75 (3.50)	15.50 (10.43)	**0.0004**	2.89	8	5.88 (5.03)	3.25 (4.53)	0.072	0.545	30.42	**<0.0001**	5.34
MOCA	8	24.63 (1.41)	25.75 (2.38)	0.229	0.564	8	26.13 (3.23)	27.13 (1.81)	0.286	0.338	0.011	0.920	0.047
Memory task (high confidence (correct) %)	8	71.48 (9.50)	69.08 (12.03)	0.359	0.210	8	75.32 (9.29)	75.13 (9.07)	0.942	0.020	0.418	0.529	0.230
BMI (kg/m^2)	8	28.33 (5.12)	28.29 (4.48)	0.934	0.007	8	28.29 (7.91)	27.95 (6.61)	0.530	0.023	0.205	0.657	0.044
VO_2max ($ml.kg^{-1}.min^{-1}$)	7	24.82 (8.00)	32.52 (10.12)	0.073	0.834	8	20.81 (6.48)	30.57 (8.66)	**0.014**	1.26	7.96	0.661	0.279

Data are expressed as mean with SD in parentheses. BDI: Beck Depression Inventory; MoCA: Montreal Cognitive Assessment; BMI: body mass index; VO_2max: maximum oxygen consumption; d: Cohen's d.

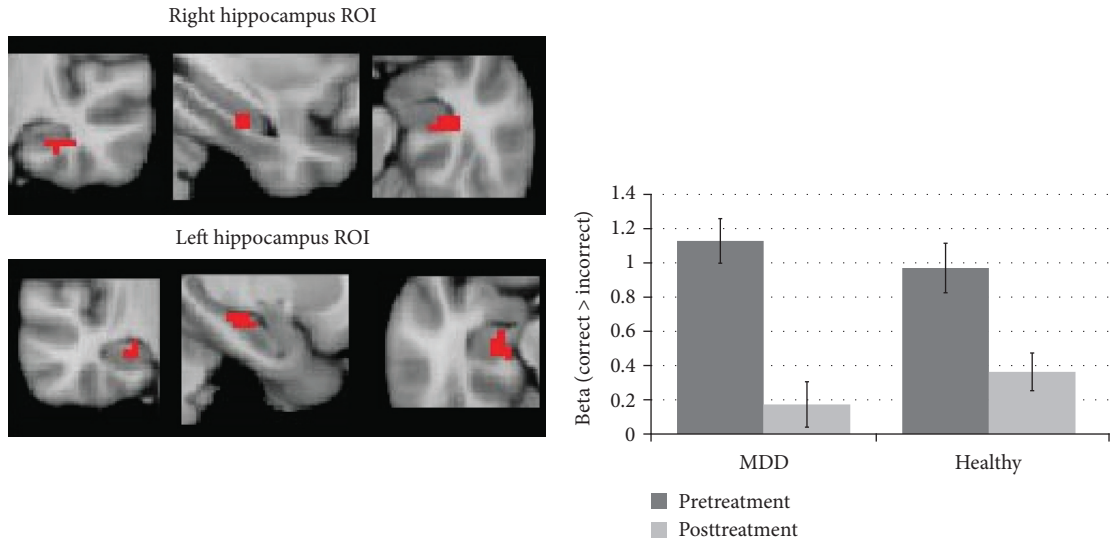

Figure 2: (a) Regions within the hippocampus found to be active in the correct > incorrect contrast for both healthy and MDD at baseline, used as an ROI to extract beta values for an analysis of activity in the hippocampus. (b) Beta values for correct > incorrect from both groups at pretreatment and posttreatment. Both groups showed a reduction in hippocampal activity within the bilateral ROI following exercise. Error bars represent standard error.

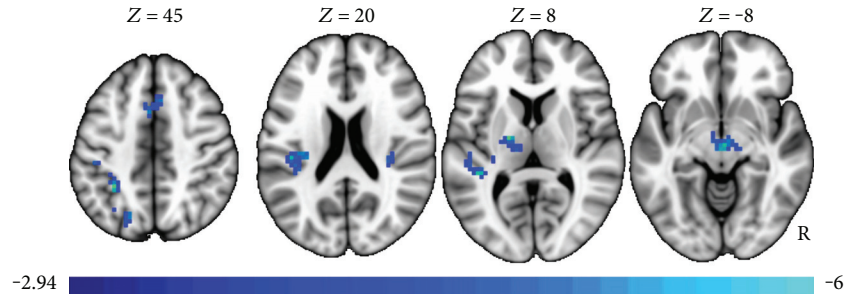

Figure 3: Pre to post changes in neural activity in the correct > incorrect contrast (paired sample t-test). Decreases in activity following exercise were noted in several regions, irrespective of group.

that we observed following the exercise intervention may be a modulation in the main inhibitory neurotransmitter γ-aminobutyric acid (GABA). Cortical inhibition, mediated by GABA via cortical interneurons, is an essential mechanism that eliminates task-irrelevant distractors that increase neural noise, which negatively affects attention for task demands. Inhibitory pathways consisting of GABAergic projections between the thalamus and cortex provide a mechanism that may eliminate task-irrelevant distractors by suppressing irrelevant sensory inputs early in sensory processing [83, 84]. A plethora of evidence has identified GABA deficits in MDD, and it has been postulated that GABAergic dysregulation may play a significant role in the pathogenesis of the disorder [85–88]. For example, neuroimaging studies have identified GABA deficits in the dorsolateral prefrontal and occipital cortex in depressed individuals [89–91]. Histopathological studies of postmortem tissue from MDD brains have revealed a reduction in both the density and size of GABAergic neurons in the prefrontal and occipital cortex that conceivably underlie the low levels of GABA seen in neuroimaging studies [92, 93]. Research has shown that exercise may facilitate cortical inhibition by regulating the interplay between glutamatergic excitatory neurons and GABAergic inhibitory interneurons. In mice, running engaged inhibitory mechanisms in the hippocampus through an increased expression of vesicular GABA transporter and extracellular GABA release that was also associated with improved anxiety regulation [94]. In humans with early Parkinson's disease, a neurophysiological study used transcranial magnetic stimulation (TMS) to examine cortical inhibition of the primary motor cortex (M1) following an eight-week, high-intensity aerobics exercise intervention. In addition to improving clinical symptoms, the exercise intervention normalized corticomotor excitability through an increase in GABA-mediated cortical inhibition [95]. Nonetheless, literature supporting the role of exercise in normalizing cortical inhibition via the GABAergic system remains sparse.

Table 3: Brain regions showing pre-post changes in activity for the correct > incorrect, irrespective of group.

Voxels	Peak T	MNI coordinates			BA	Location
		X	Y	Z		
37	−6.27	−6	17	41	32	Medial superior frontal/mid cingulate
35	−5.85	−18	−10	8		Left putamen
35	−5.79	−30	−46	44	40	Left supramarginal/intraparietal sulcus
45	−5.61	−42	−28	35	3	Postcentral, superior parietal gyrus
50	−5.34	3	−16	−7		Thalamus/midbrain
139	−5.3	−42	−37	8	41	Left posterior insula
30	−5.22	−18	−70	47	7	Left superior parietal
36	−5.17	30	−28	14		Right posterior insula
20	−4.75	54	−43	−4	21	Right posterior mid temporal
25	−3.82	12	−82	−7	18	Right occipital gyrus

MNI: Montreal Neurological Institute; BA: Broadmann area.

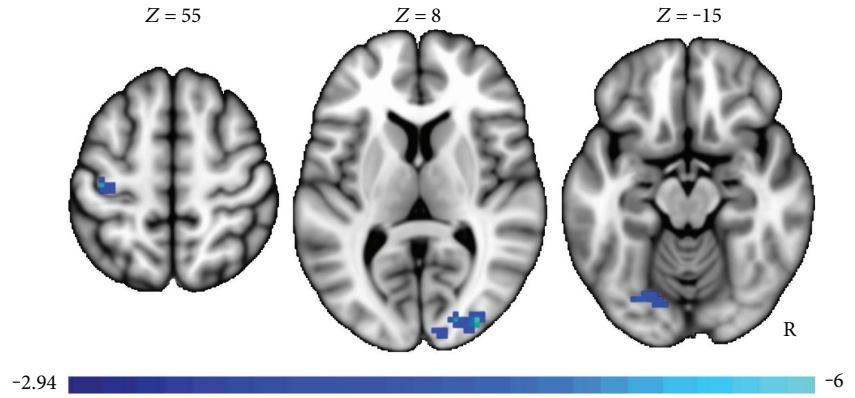

Figure 4: Pre-post changes found a negative relationship between changes in depression scores and activation in the right occipital, left occipital/fusiform, and left precentral gyrus, irrespective of group.

Our observed decrease in brain activity during successful memory encoding pre-post the exercise intervention also suggests lowered demands on neural networks and increased neural processing efficiency. Our results provide additional support to a recent body of literature, which postulates that exercise increases neural efficiency. In children, an eight-month aerobics exercise program was associated with decreased activity in several brain regions during an antisaccade task alongside improvements in performance [96]. In elderly adults, a 12-week aerobics exercise program was associated with decreased prefrontal activation despite improvements in visual short-term memory [97]. A similar study conducted in elderly adults with mild cognitive impairment found that 12 weeks of aerobics exercise decreased brain activity in 11 brain regions during memory retrieval despite improvements in memory performance [98]. In adolescence, high-fit individuals showed a pattern of decreased activation in the hippocampus and right superior frontal gyrus combined with a deactivation in the default mode network (DMN) during the encoding of subsequently remembered items, that was absent in low-fit individuals [99]. To determine if aerobics exercise influences learning and memory-associated neural circuitry, a group of researchers examined the brain activity in high-fit and low-fit adolescents during an SME paradigm. Despite comparable memory performance between the two groups, there were notable differences in memory-related and default mode (DMN) brain regions during encoding of successfully remembered word pairs versus forgotten word pairs. Results showed that high-fit individuals displayed a robust deactivation pattern in the DMN areas, such as the ventral medial prefrontal cortex and posterior cingulate cortex, which was absent in the low-fit group. The low-fit group also showed a greater bilateral hippocampal and right superior frontal gyrus activation during encoding of later remembered versus forgotten word pairs. Our results taken together with previous research suggest that improvements in aerobics fitness from the exercise intervention can promote neural processing efficiency during memory encoding processes.

Finally, the neurocognitive benefits associated with exercise may be attributed to increases in cerebral blood flow and neural growth factors, particularly brain-derived neurotrophic factor (BDNF), a key mediator of neuroplasticity in the brain [36, 37]. BDNF, a member of the neurotrophin family, upregulates neurogenesis, promotes neural survival, improves neural structure, and increases synaptic efficacy

Table 4: Regions showing decreased activation associated with depression, irrespective of group.

Voxels	Peak T	MNI coordinates			BA	Location
		X	Y	Z		
58	−6.41	36	−88	11	19	Right occipital
27	−4.92	−39	−22	56	4	Left precentral gyrus
29	−4.1	−24	−73	−13	18	Left occipital/fusiform

MNI: Montreal Neurological Institute; BA: Broadmann area.

[100–103]. BDNF also modulates the formation and plasticity of GABAergic synapses and promotes maturation of GABAergic inhibitory networks [104–106]. Reduced BDNF levels are a consistent finding in animal models of depression [107], and administration of exogenous BDNF into the hippocampus is able to produce antidepressant behavioral responses comparable to antidepressant medications [108]. Exercise is known to elevate BDNF production in the hippocampus [35, 109] and has been postulated as a leading candidate mechanism underlying the antidepressant effects of exercise [110, 111].

5. Limitations

This pilot study has some limitations. First, the sample size used is rather small and therefore statistically underpowered. We did not age match our groups, which resulted in the MDD group being significantly older than the healthy group. Intrinsically, we wanted to compare MDD brains to young healthy brains with no history of mental health illness or other confounding comorbidities that increase with age and determine if exercise affects neural function in healthy populations who are low active. Also, we did not measure sedentary behavior time which has been shown to have deleterious health consequences independent of daily physical activity levels [112]; as a result, future work must consider sedentary behavior independent of physical activity levels and cardiorespiratory fitness. Another limitation is that our MDD samples were all medicated which may have also affected results. However, this is the typical patient seen in clinical practice, and in any real-world clinical intervention using exercise, the participants would likewise be similarly medicated. Next, even though our analysis collapsing across groups mediates some of the power issues for a transdiagnostic analysis of the effects of exercise on neural activity, the analysis was still underpowered to detect group × time interaction effects.

While we did not closely replicate the results of Fairhall et al., it should be noted that they used a contrast comparing correct trials to fixation, while we made use of a more standard subsequent memory contrast (correct > incorrect). Nevertheless, we did observe a decrease in the correct > incorrect contrast in the hippocampus indicating that there was a decrease in hippocampal activity during successful encoding in both groups following the exercise intervention. We did not however observe any group effects. Given the small sample size, we were likely underpowered to detect any subtle group effects, though it remains possible that the decreases in activity observed following the intervention are common across low-active individuals regardless of diagnostic status. In fact, it should also be noted there was even a small decrease in BDI scores amongst the healthy group. The physiological effects of exercise on the brain may be common amongst both healthy and MDD while still resulting in a substantially greater mood effect for those suffering from depression.

6. Future Research

This small pilot study demonstrates that eight weeks of the minimum recommended dose of exercise improved cardiorespiratory and significantly reduced depression severity in the MDD group. Importantly, we were able to demonstrate that combining the minimum recommended dose of exercise with conventional treatments was effective in treating the typical patient seen in the primary care setting who continues to experience severe depressive symptoms despite being treated with antidepressant medication. On the other hand, prescribing exercise to MDD patients presents many challenges to the practitioner since many patients lack motivation to initiate and maintain an exercise routine. Introducing patients to the minimum recommended dose of exercise as an add-on therapy may offer a practical approach for practitioners to help patients initiate and maintain a routine of daily exercise [113, 114].

An interesting finding from this pilot study was that eight weeks of exercise affected healthy and MDD brains similarly. The deactivation pattern we observed in several brain regions warrants further investigation with a larger sample size to allow a more robust statistical analysis. Future work must also include an MDD control group, as this will help us understand the magnitude of the effect of exercise, in combination with other therapies, on depressive symptomology and neural function. Moreover, there is a shortage of reporting sedentary behavior, physical activity levels, and cardiovascular fitness parameters in the MDD literature. As such, some of the differences observed in studies comparing MDD to controls might be confounded by a low-active lifestyle, which may be more prevalent in MDD. To address this gap, future research should compare "fit" and "low-fit" MDD groups to identify markers independent of cardiorespiratory fitness and unique to MDD. Furthermore, the exercise and cognitive literature have not established whether the psychological effects from engaging in exercise, independent of changes in fitness, are still beneficial to mental health and brain function. Future research must indicate whether the effects seen following an exercise intervention are associated with improved cardiovascular fitness or from the psychological benefits from engaging in exercise.

Lastly, MDD is a heterogeneous disorder, and it is likely to be a multifaceted interaction of psychological and neurobiological mechanisms that underlie or mediate the effects of exercise. Future research must consider using a combination approach of multimodal imaging techniques, behavioral assessments, and biochemical analysis to delineate the biological and clinical signatures of fit and unfit MDD populations. Once we are able to elucidate these key biomarkers

unique to MDD, novel intervention strategies can then be designed to prevent or reverse neuropsychological pathologies such as MDD.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Review Article

Enkephalins: Endogenous Analgesics with an Emerging Role in Stress Resilience

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Psychological stress is a state of mental or emotional strain or tension that results from adverse or demanding circumstances. Chronic stress is well known to induce anxiety disorders and major depression; it is also considered a risk factor for Alzheimer's disease. Stress resilience is a positive outcome that is associated with preserved cognition and healthy aging. Resilience presents psychological and biological characteristics intrinsic to an individual conferring protection against the development of psychopathologies in the face of adversity. How can we promote or improve resilience to chronic stress? Numerous studies have proposed mechanisms that could trigger this desirable process. The roles of enkephalin transmission in the control of pain, physiological functions, like respiration, and affective disorders have been studied for more than 30 years. However, their role in the resilience to chronic stress has received much less attention. This review presents the evidence for an emerging involvement of enkephalin signaling through its two associated opioid receptors, μ opioid peptide receptor and δ opioid peptide receptor, in the natural adaptation to stressful lifestyles.

1. Introduction

Psychological stress is a state of mental or emotional strain or tension that results from adverse or demanding circumstances. It has multifaceted causes and occurs frequently over a lifetime with varying dimensions and intensity, affecting all walks of life, irrespective of a person's occupation or position within a society [1]. While depression is often the devastating outcome of chronic stress [2] and also a risk factor and common comorbidity in Alzheimer's disease [3, 4], stress resilience, on the other hand, is a positive outcome that is associated with preserved cognition, reduced oxidative damage, and healthy aging [5, 6]. The American Psychological Association defines resilience as "the process of adapting well in the face of adversity, trauma, tragedy, threats or even significant sources of threat." Heterogeneity in the response to chronic stress suggests that resilience is a complex neurobiological process that emerges from a multitude of gene-environment interactions. Several mechanisms are proposed to underlie the interindividual differences in resilience or vulnerability to chronic stress.

Within the neuropeptidergic system, the endogenous opioids enkephalins (ENK) which signal through the opioid peptide receptors (OPr), μ opioid peptide receptor (MOPr) and δ opioid peptide receptor (DOPr), could be interesting candidates to naturally promote the adaptation to chronic stress. ENK are members of the endorphin family and the first ones to be isolated in the brain [7]. Considering the binding of morphine and ENK to the same receptors, their role as a natural analgesic was rapidly proposed. Pioneered studies have provided the first experimental evidence supporting a role of ENK in analgesia and stress-induced analgesia (i.e., pain suppression after an exposure to stressful stimuli). More specifically, it was shown in the rat that 1)

the cerebroventricular injection of ENK produces analgesia [8, 9]; 2) stress increases blood concentrations of ENK [10]; and 3) stress-induced analgesia, such as immobilization stress on a hot plate or cold water stress, could be reversed by an opioid antagonist [11, 12]. Subsequently, it was hypothesized that ENK were playing a major role in stress processes independently of their analgesic functions. Madden et al. reported that inescapable stress induced by footshocks (mimicking a posttraumatic stress disorder; PTSD) increases brain levels of ENK [10]. Another study showed a decrease of ENK immunoreactivity in the rat hypothalamus (HPT) after stress induced by footshocks [13]. More recently, ENK in the rat amygdala (AMG) were implicated in Pavlovian conditioned fear [14, 15] as well as in various behavioral and neuroendocrine aspects of the stress response [16–18]. The ENK are known to be involved in a large set of physiological and emotional processes, but their role in the individual capacity for stress adaptation has received less interest. In this review, the biochemistry of ENK and their anatomical distribution within the central nervous system (CNS) will be described first, followed by coverage of the well-known functions of ENK in emotional behaviors, including their key involvement in Pavlovian conditioned fear, anxiety, and stress response. Subsequently, the emerging role of ENK in the development of stress resilience will be discussed, with an emphasis on the recruitment of ENK projections coming from the AMG. The AMG is considered a key brain structure mediating the regulation of emotions and affective behavior, and the role of ENK in the stress response is notably suggested by their extended distribution in the AMG.

2. Enkephalins and Their Opioid Receptors

2.1. Biochemistry and Anatomical Distribution of Enkephalins and Their Receptors, DOPr and MOPr, in the CNS. ENK are produced from a propeptide precursor, proenkephalin (proENK), which is translated from preproenkephalin mRNA that is encoded by a gene distinct from the other endogenous opioid peptides [19, 20]. The maturation of propeptides into functional peptides is performed during the vesicular transport within large dense-core vesicles (LDCVs) and requires the joint action of several endopeptidases (cathepsin L, aminopeptidase B and E, and prohormone convertase 2) [21–23]. In the rat, the proENK is cleaved proteolitycally to produce four copies of methionine-ENK (Met-ENK), one leucine-ENK (Leu-ENK), and two C-terminal extended Met-ENK. Subsequently, LDCVs are stored near release sites (i.e., presynaptic, extrasynaptic, and dendritic) and released following an increase in intracellular calcium [24]. Once released by neurons, ENK are degraded in order to control the diffusion and synchrony of the signal. Some studies demonstrated that radioactively labeled ENK are completely degraded in less than a minute upon injection (intracerebroventricular) in the rat brain [25]. ENK degradation is performed by two neuropeptidases called metallopeptidases: aminopeptidase N and neutral endopeptidase (or neprilysin) [26, 27]. In vitro, ENK have a slightly higher affinity for DOPr, even though they can also bind and activate MOPr and κ opioid peptide receptor (KOPr) in transfected cells transiently expressing MOPr, DOPr, or KOPr [28]. Studies describing the distribution of ENK in the rat brain have demonstrated their preferential binding to DOPr and MOPr by autoradiographic labelling [29].

Given the vast extent of biological processes and physiological systems in which ENK are involved (cardiovascular system, thirst and feeding, pain and analgesia, gastrointestinal functions, respiration, etc. [30]), the expression of ENK, DOPr, and MOPr is ubiquitous. Indeed, ENK are distributed among the central, peripheral, and autonomous nervous systems, as well as in endocrine tissues (adrenal medulla, endocrine pancreas) and their target organs (liver, skin, bones, and lungs) [31, 32]. For the purpose of this review, we will focus mainly on the neuroanatomical distribution of ENK and their receptors within the "emotional brain" known as the limbic system that includes the cingulate and entorhinal cortex, hippocampus (HPC), septum, HPT, and the extended AMG [33]. Most of neuroanatomic studies have been conducted in rats, although several studies have also been conducted in humans, showing a similar distribution across species, especially in the limbic system [34]. Fallon and Leslie extensively reported in 1986 the distribution of ENK neurons as well as ENK fibers in the rat brain using an indirect immunofluorescence technique [35]. ENK neurons are found among the entorhinal, piriform, and medial prefrontal cortex (mPFC, infralimbic and prelimbic). Most nuclei of the HPT were shown to contain ENK neurons (paraventricular, posterior, ventromedial, dorsal, dorsomedial, and lateral nuclei). They are widely distributed in the central (CEA), medial (MEA), and basolateral (BLA) AMG and its intercalated (IC) nuclei. ENK neurons are also located in the lateral septum, preoptic area, bed nuclei of the stria terminalis (BST), nucleus accumbens (NAc), and ventral tegmental area (VTA). In the HPC, ENK are present in mossy fibers and granular cells. ENK fibers mainly project from the dentate gyrus to the CA3 region of Ammon's horn, but also target some neurons of the CA1 and CA2, and dentate gyrus. Additionally, ENK fibers are found in the dorsal and ventral pallidum [35, 36].

Similar to ENK, OPr are extensively expressed throughout the CNS [37]. The anatomical distribution of MOPr and DOPr is relatively similar to that of ENK projections [38]. To study the relative distributions of MOPr and DOPr throughout the CNS, Scherrer and colleagues have generated a very useful mouse model. They first developed DOPr-eGFP *knock in* (KI) mice, presenting a complete functional receptor fused to an enhanced green fluorescent protein (eGFP) [39]. These mutant mice were subsequently crossed to another model containing a similar construct, MOPr-mcherry KI mice [40]. This breeding generated a double KI mouse useful for in situ visualization of DOPr and MOPr simultaneously [40, 41]. The study of DOPr and MOPr distribution in the CNS showed that coexpression of DOPr and MOPr is observed in HPT, HPC, the lateral parabrachial nucleus and vestibular nuclei, circuitries which are involved in survival including water and food consumption, sexual behavior, and response to aversive stimuli [40]. The large distribution of ENK and their associated receptors in the limbic system

of rodents and humans further suggests that ENK transmission plays a major role in emotional behaviors.

2.2. Roles in Emotional Behaviors. ENK are indeed involved in several emotional behaviors, including fear conditioning [14, 15, 42–45], anxiety, and stress response [46–65]. This section will describe the experimental evidence for such a role, mainly derived from studies conducted in rodents, using different approaches, neuroanatomical, silencing, pharmacological, and genetic, as well as stress paradigms varying in chronicity and intensity.

2.2.1. Fear Conditioning. The fear conditioning paradigm allows assessment of learning and memory in association with fear (see Table 1). The first evidence that ENK participate in fear conditioning comes from an in situ hybridization study showing an increase in ENK mRNA levels in the CEA neurons of rats undergoing this paradigm [14]. Thereafter, it was shown that ENK *knockout* (KO) mice exhibit an exaggerated immobility compared to wild-type controls during the auditory-conditioned fear acquisition [42]. A population of GABAergic neurons expressing protein kinase C-δ (PKC-δ) was identified in the lateral part of CEA (CEAl), using a molecular genetic approach in mice. Interestingly, this population appears to overlap with ENK neurons [45]. In another study, it was shown that this neuronal population expressing PKC-δ in the CEAl is implicated in the inhibition of fear acquisition [66]. However, the exact role of ENK expressed by these PKC-δ GABAergic neurons is still undetermined.

Asok et al. also showed that exposure to a component of fox odor, 2,5-dihydro-2,4,5-trimethylthiazoline (TMT), which triggers innate fear in rats, increases ENK mRNA levels in the paraventricular nucleus (PVN) of the HPT [43]. An increased expression of ENK mRNA levels is similarly observed after repeated footshocks, in the AMG of SWR/J mice, an inbred strain showing a reduced fear response, while this expression was unchanged in C57Bl/6J mice, an inbred strain showing a high fear response [44]. In the same study, administration of MOPr antagonist (naltrexone) or DOPr antagonist (naltrindole) increased fear response in SWR/J mice, which could be restored with a DOPr agonist. These results suggest that resistance in the face of traumatic experiences inducing fear involves ENK from the AMG and that vulnerability can be modulated by administration of OPr agonists [44]. Finally, it has been shown by Poulin et al. that the downregulation of ENK in the rat CEA decreases unconditioned fear [15]. In this study, rats were submitted to a contextual conditioning paradigm consisting of footshocks administered in a novel environment. ENK *knockdown* (KD) rats showed a reduced fear response during conditioning, while the context alone, presented 48 h later, did not produce change in freezing behavior. These results indicate that ENK release from CEA neurons is involved in the freezing behavior to an unconditioned stimulus, but not in the formation of an associative memory [15]. Results of ENK distribution studies—in addition to pharmacological, silencing, and genetic studies—demonstrate the prominent role of ENK, especially amygdalar ENK, in mediating fear behavior. This connection may further suggest a role for ENK in anxiety and stress responses, which are closely related to fear behavior.

2.2.2. Stress and Anxiety. Several studies performed in humans showed the importance of ENK in anxiety, depression, and PTSD, a mental illness that appears after experiencing a traumatic event. Indeed, a polymorphism in the gene encoding neutral endopeptidase, involved in ENK metabolism, was identified in patients with anxiety disorder, tested with the SCL-90-R inventory of psychological symptoms [48]. Positron emission tomography (PET) studies have shown that MOPr expression is decreased in the anterior cingulate cortex of patients with PTSD [47]. In patients with depression, PET further revealed that the expression of MOPr is decreased in the HPT and AMG [49]. These studies suggest that a reduced tone of ENK neurotransmission is a key component in the expression of anxiety.

In rodents, several behavioral paradigms are commonly used to assess the level of anxiety, including the elevated plus maze (EPM), open field (OF), and light-dark box (LDB) tests. These tests are based on the natural aversion of rodents for open, elevated, or illuminated areas and their natural exploratory behavior in novel environments. In addition, the social interaction test (SI) allows evaluating the propensity to socialize. The startle response (SR) corresponds to an unconscious defensive response to unexpected or threatening stimuli. All behavioral tests discussed in our review are detailed in Table 1.

The ENK KO mice show an increased anxiety with the EPM, OF, and LDB tests, have an exaggerated SR, and a reduced duration of SI [42, 50, 51]. ENK KO mice exposed to a stress induced by footshocks, mimicking PTSD, similarly present anxiety- and depressive-like behaviors, contrary to wild-type controls, using the OF, EPM, and LDB tests (see Table 1) [52]. However, the downregulation of ENK in CEA was shown to reduce anxiety as characterized by an increase of exploratory behavior [15]. ENK KO mice are resistant to anxiety- and depression-like behaviors after a chronic mild unpredictable stress—consisting of daily exposure to different stressors, such as food deprivation and restraint stress for five weeks—suggesting that ENK enhance the reactivity to chronic stress [67]. ENK appear to have varying and even opposing effects on anxiety, depending on the considered CNS region and the type and intensity of stress.

The high levels of anxiety generally observed in ENK KO mice are also seen upon gene inactivation of DOPr [53]. Pharmacological studies conducted in rodents support these results obtained through gene inactivation of DOPr, since subcutaneous administration of naltrindole, a DOPr antagonist, induces anxiety [54]. Conversely, intraperitoneal injection of DOPr agonists (SNC80, UFP-512, (+)BW373U86) was shown to be anxiolytic [55–57]. Moreover, infusion of [D-Pen 2,5]-ENK (DPDPE), a DOPr agonist, in CEA exerted similar effects, which could be reversed by the administration of naltrindole, a DOPr antagonist. Recently, a new DOPr agonist, KNT-127, has received an increasing interest as a potential therapeutic treatment for anxiety and depression, although the efficacy of this molecule has not yet been

Table 1: Evidence for ENK signaling involvement using different behavioral tests.

Behavior	Paradigm	Principles and procedures	Evidence for involvement of ENK signaling
Fear	Contextual fear conditioning	In this paradigm, an animal learns to predict aversive events based on their environmental context. It is a form of learning and memory in which an aversive stimulus is associated to a neutral context and/or stimulus, resulting in fear responses upon presentation of the originally neutral context and/or stimulus. The animal is placed into a chamber to administer an aversive stimulus (e.g., electric footshocks). This procedure can be paired with another conditioning stimulus, a sound for example. After a delay, the animal is reexposed to the environment and/or conditioning stimulus, without the aversive one. Freezing which is characterized by the total absence of movement except those required for respiration is then measured to assess fear responses.	(i) In rats, ENK mRNA levels are increased in CEA upon contextual fear conditioning [14] (ii) ENK *knockout* (KO) mice show an exaggerated immobility during auditory fear conditioning [42] (iii) ENK neurons in CEAl overlap with PKC-δ GABAergic neurons, which are involved in fear behavior [45, 66] (iv) In SWR/J mice (showing a reduced fear response induced by footshocks), ENK mRNA levels are increased in AMG [44] (v) In SWR/J mice (showing a reduced fear response induced by footshocks), administration of MOPr and DOPr antagonists increase fear response [44] (vi) In rats, ENK *knockdown* (KD) of CEA decreased unconditioned fear [15].
	Startle response	The startle reflex is considered as an innate and involuntary reaction that appears upon exposure to an unexpected or threatening stimuli. The response corresponds to a quick involuntary contraction of the animal's skeletal muscles. The test is conducted in an automated startle chamber that allows measurement of the reflex.	(i) ENK KO mice show an exaggerated startle response [50].
Anxiety	Open-field	This task is based on a rodent's preference for dark areas. The animal is placed in an open-field chamber, an arena with surrounding walls to prevent escape, and the exploratory behavior of the center (lit) versus periphery (dark) is assessed over time with a video-recording.	(i) ENK KO mice show a decreased exploratory behavior and avoid the central part of the open-field (OF) arena [42, 50, 51] (ii) ENK KO mice, exposed to stress induced by footshocks, present an anxiety-like behavior [52].
	Elevated plus maze	This task is based on a rodent's natural preference for dark and enclosed areas, compared to lit and uncovered areas, as well as on their natural exploratory behavior of a novel environment. The animal is placed in the maze, and its exploratory behavior is assessed over time with a video-recording. The maze has a cross shape with two opposite arms surrounded by walls (dark and enclosed area) whereas the two other arms do not present walls (lit and uncovered).	(i) ENK KO mice present anxiety-like behavior in the elevated plus maze (EPM) [50] (ii) ENK KO mice, exposed to stress induced by footshocks, present anxiety-like behavior in EPM [52] (iii) In rats, ENK KD in CEA increases the exploratory behavior in EPM [15] (iv) Infusion of a DOPr agonist in CEA increases the number of entries and the time spent in open arms of the EPM [82] (v) Administration of a DOPr antagonist diminishes the exploratory behavior in EPM [54] (vi) Administration of a DOPr agonist increases this behavior [55–57, 59, 60] (vii) DOPr KO mice spent less time in the open arms of EPM [53] (viii) MOPr KO mice increase the exploratory behavior in EPM [53] (ix) Administration of MOPr agonist increases the exploratory behavior in EPM [58].
	Light-dark box	This task is based on a rodent's natural preference for dark areas, compared to lit ones. The box contains two chambers, one light and one dark. The animal is placed into the box and its exploratory behavior is assessed over time with a video-recording.	(i) ENK KO mice show a decreased exploratory behavior in the light-dark box (LDB) [42, 50] (ii) ENK KO mice, exposed to stress induced by footshocks, present an anxiety-like behavior in LDB [52] (iii) DOPr KO mice spent less time in the illuminated portions of the LDB [53].
	Social interaction test	This test allows evaluating the propensity of an individual to socialize. The rodent is placed in an open-field arena alone in the first place and then with another individual. The time spent interacting with the intruder is measured.	(i) ENK KO mice present a reduced duration of social interaction [50].

Table 1: Continued.

Behavior	Paradigm	Principles and procedures	Evidence for involvement of ENK signaling
	Forced swim test	This test is used to evaluate the antidepressant efficacy of new compounds. A rodent is placed in a pool containing approximately 15 cm^3 of water, and its mobility is measured on a video-recording.	(i) Administration of a DOPr agonist increases mobility in the forced swim test [59].
Anhedonia	Sucrose preference test	This task is used as an indicator of anhedonia, characterized by a lack of interest for a reward. Two bottles, one containing a sucrose solution (between 1% and 5%) and another plain water, are presented to the animal. Its preference for the sweetened versus plain water reveals anhedonia state.	(i) After restraint stress, rats showing increased anhedonia (assessed with the sucrose preference test) present a reduced expression of ENK mRNA in the NAc [70].

investigated in clinical trials. In rodents, KNT-127 produces anxiolytic and antidepressant-like effects in a dose-dependent manner (see Table 1) [59, 60]. These results are consistent between models and suggest that signaling onto DOPr mainly exerts anxiolytic effects.

In contrast to these findings, a conditional KO mouse for DOPr (Dlx-DOR) in forebrain GABAergic neurons showed a reduced level of anxiety compared to wild-type littermates, demonstrating that stimulation of DOPr in GABAergic neurons of the forebrain is anxiogenic (see Table 1) [62]. In the same way, the gene inactivation of MOPr has anxiolytic effects, with MOPr KO mice presenting an increased time spent in the open arms of an EPM [53]. Nevertheless, several pharmacological studies instead demonstrated that MOPr activation is anxiolytic. For example, intraperitoneal administration of morphine, a MOPr agonist, decreases vocalizations in rats exposed to a predator and anxiety assessed with the EPM test [58]. Overall, MOPr appear to have varying effects on anxiety, depending on the methodological approaches used.

A few recent studies explored the neuroanatomical specificity of ENK projections that are recruited in steady-state conditions or upon stress in rats. Single housing (see Table 2) in early life was shown to decrease immunoreactivity of Met-ENK-Arg^6Phe^7 (MEAP) in the brain areas that include the AMG, substantia nigra (SN), HPT, and periaqueductal grey (PAG) [63]. Hernández et al. also measured ENK neuropeptidase activities in the three main regions of the stress response circuitry (AMG, HPC, and mPFC) after acute restraint in rats (see Table 2; [46]). Neuropeptidases regulate the expression of neuropeptides at the release sites. Peptidase activity can thus be used to indicate the functional status of neuropeptides. This neuropeptidase activity was found to be more intense in AMG than in HPC or mPFC both in control and stressful conditions, suggesting that ENK metabolism is preponderant in the AMG. After acute restraint stress, ENK-degrading activity was reduced in AMG and increased in HPC, while it remained unchanged in the mPFC. In stressed rats, a positive correlation was described between the AMG and HPC, while in control rats, a negative correlation was observed between the mPFC and HPC. These results suggest a neuropeptidergic functional connection between the mPFC, HPC, and AMG, which could be triggered by stress and involved in some of the adaptive functions performed by this circuit.

Overall, these contradictory results found in the literature regarding the influence of ENK signaling on anxiety could be attributed first, to the technical approaches (pharmacological, genetic), then to the considered nucleus (CEA for example) or associated neurotransmitters (GABA), and finally to the type (acute, chronic stress) and intensity of stress. It still remains unknown whether the many effects of ENK circuitry acting in such a diverse array of brain circuits might all be recruited together in response to a variety of different stressors and different modalities. Different brain circuits could synergistically contribute to the stress response, highlighting the huge challenge we face in understanding the functions of ENK signaling. Taken together, the combined findings from these silencing, pharmacological, genetic, and neuroanatomical studies suggest that the stimulation of ENK transmission onto DOPr and/or MOPr might enhance the natural strategies to cope with stress.

3. Enkephalin Signaling through DOPr and MOPr, a Major Component of the Stress Resilience Circuitry

An extreme amount of stress can lead to maladaptive behavioral changes such as anhedonia and social avoidance, in rodents and humans, as well as serious health consequences by impacting on the nervous, endocrine, and immune systems. However, chronic exposure to stress can also engender compensatory physiological responses in order to reduce these deleterious effects of stress. This mechanism of defense allows maintaining homeostasis in the face of adversity. This phenomenon of "resilience" corresponds to the ability of an individual to maintain normal psychological and physical functioning in the front of stress or trauma, in order to avoid mental and physical illnesses [68].

Recent findings regarding the functions of ENK transmission in stress resilience revealed the involvement of different brain areas such as the NAc [69, 70] or septum, PVN and PAG [17, 18, 71], or locus coeruleus (LC) and paragigantocellularis nucleus (PGi) [72], in addition to the BLA as we will discuss below, thus suggesting a high level complexity of ENK circuitry in stress resilience.

Sweis et al. associated the resilience to chronic stress—measured by a lack of memory impairment post-stress—to an increased expression of ENK mRNA in the

Table 2: Evidence for ENK signaling involvement under different stress paradigms.

Paradigm	Principles and procedures	Evidence for involvement of ENK signaling
Single housing	Given the social behavior of rodents, chronic or acute single housing is used to mimic the stress due to social isolation. The animal is placed alone in its home cage.	(i) Prolonged single housing in early life decreases ENK immunoreactivity in AMG, SN, HPT, and PAG [63].
Restraint stress	The animal is placed in a tube in such a way that all movements are prevented. The psychological and physiological effects due to restraint stress result from the distress and aversive nature of the forced immobility.	(i) After acute restraint stress, ENK-degrading activity is reduced in AMG and increased in HPC [46] (ii) After chronic restraint stress, ENK *knockout* (KO) mice do not exhibit anxiety nor depression-like behavior [67] (iii) After chronic restraint stress, rats showing increased anhedonia present a reduced expression of ENK mRNA in the NAc [70].
Social defeat stress (or resident-intruder paradigm)	This task exploits the social conflict between two individuals to initiate psychological stress. This experiment can be related to the intimidation or victimization in humans. An intruder is placed in the home cage of a resident each day for a given period of time.	(i) After a chronic social defeat, *Oprm1* A112G mice show a strong resilience [71] (ii) After a chronic social defeat, resilient rats demonstrate a high recruitment of ENK afferents from PGi to LC [72] (iii) After a chronic social defeat in rats and mice, ENK mRNA levels decrease in BLA of vulnerable individuals [17, 81].
Chronic unpredictable stress	This test allows to mimic the unpredictable disruptions of daily life. An animal is subjected to different stressors each day for a given period of time. Stressors can include restraint stress, electric footschocks, wet bedding, group housing, mild shaking of the home cage, cold water swim, etc.	(i) ENK *knockdown* (KD) in BLA increases anxiety reproducing behavioral responses encountered in individuals vulnerable to chronic unpredictable stress [18].

rat NAc, proposing that an ENK-mediated increase of dopaminergic tone could improve motivation-based cognitive performance [69]. This predominant role of ENK projections from the NAc is supported by the results of another study. Indeed, it was shown that after 14 days of restraint stress, rats showing increased anhedonia (as measured by their preference for sucrose—see Table 1) also presented in the NAc a reduced expression of ENK mRNA and ΔFosB, a transcription factor that is expressed by ENK neurons. These results suggest that the individual vulnerability to chronic stress, determined here by measuring anhedonia, is associated with a ΔFosB-mediated downregulation of ENK [70]. The relationship between ΔFosB and the resilience to chronic stress was already known [73].

Downstream of ENK, Akil et al. also studied in rats the effects of dominance status and housing conditions on the response to a DOPr agonist, SNC80 [74]. This study revealed that single housing for 50 days leads to a stronger DOPr activation in the mPFC, CEA, and NAc. Triad housing for the same period of time also increases DOPr activation in the mPFC, CEA, and NAc, in addition to the median eminence and thalamus, of β rats that we can assimilate to stress resilient individuals considering their defensive behaviors and frequent aggressive interactions with α dominant rats, which instead display an offensive behavior [74]. This mechanism could be involved in the regulation of ENK transmission upon stress.

Two types of behavioral paradigms are commonly conducted in rodents for studying stress resilience (see Table 2). The social defeat paradigm, also named resident-intruder paradigm, in which intruder animals are repeatedly submitted to daily interactions with a home-cage unfamiliar resident over a given period of time, induces stress resilience by mimicking the unpredictable social disruptions of daily life. This paradigm has been shown to present excellent etiological, predictive, discriminative, and face validity [75]. Moreover, unlike other stress paradigm, social defeat stress leads to long-lasting changes in hypothalamic-pituitary-adrenal axis function, making it a stress paradigm of choice [76]. The majority of rodents exposed to this paradigm exhibits reduced motivation, anhedonia, and avoids social interactions [77]. Conversely, despite the deleterious effects of social stress, around 30% of the population presents a phenotype of stress resilience, being resistant to the emergence of depressive-like behavior. In rats, the daily interaction between individuals results in subordination of the intruder, indicated by adoption of a supine position. The latency to assume a defeated posture is recorded, and the averaged latency over stress exposition is used as a predictive value to define resilience or vulnerability to stress. In mice, the resilience or vulnerability to stress is instead assessed at the end of this experiment by using a SI test (see Table 1). The second chronic stress paradigm that is commonly used to study stress resilience is chronic unpredictable stress. In this experiment, individuals are daily submitted to different stressors that include restraint stress, wet bedding, food deprivation, and footshocks. The phenotype of resilience or vulnerability to stress is assessed at the end of the experiment in mice and rats using behavioral tests previously described such as SI, EPM, and OF (also see Table 1).

For example, Briand et al. used the repeated social defeat paradigm in a mouse model of OPRM1 A118G polymorphism (single nucleotide polymorphism, SNP) corresponding to a genetic mutation of MOPr observed in humans

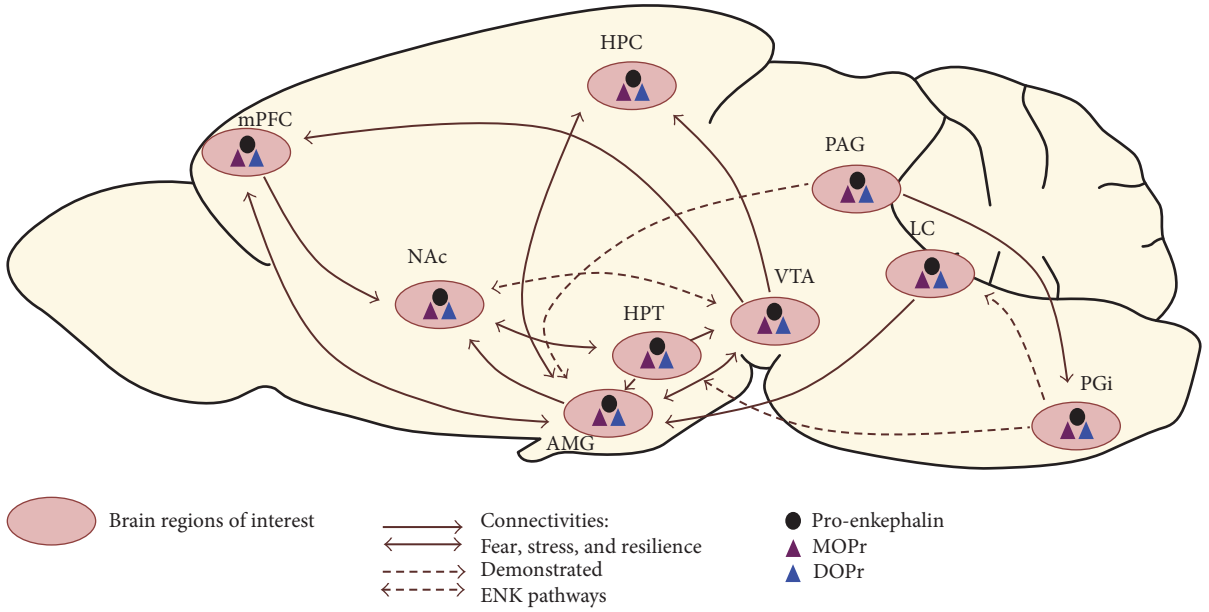

Figure 1: Cartography of main connectivities involved in fear, stress, and resilience, as well as demonstrated ENK pathways between areas and expression of ENK, MOPr, and DOPr. Pink circles represent brain regions of interest. Full arrows correspond to circuitries of stress, fear, and resilience. Dotted arrows represent demonstrated ENK circuitries. The black dot corresponds to expression of pro-enkephalin, and purple and blue triangles correspond to MOPr and DOPr expression, respectively. AMG: amygdala; HPC: hippocampus; HPT: hypothalamus; LC: locus ceruleus; mPFC: medial prefrontal cortex; NAc: nucleus accumbens; PAG: periaqueducal grey; PGi: paragigantocellularis nucleus; VTA: ventral tegmental area.

that is associated with an overall reduction of baseline MOPr availability in regions implicated in pain and affective regulation [78], thus allowing to unravel a potential role of MOPr in the resilience to chronic stress [71]. This model presents increased home-cage dominance and nonaggressive social interactions, similar to the human carriers of this mutation. In the presence of an aggressor during social defeat stress, it also showed a strong resilience to chronic stress, determined by a blunted anhedonia and social avoidance following the social defeat. Neuronal activation measured by c-fos staining was additionally increased in the NAc, septum, BLA, PVN, and PAG, thus suggesting an increased release of endogenous opioids upon stress [71]. In humans, Troisi et al. demonstrated that the carriers of this mutation have a greater capacity to experience social reward and are more prone to fearful attachment, a personality trait that is related to rejection sensitivity, regardless of the quality of maternal care [79, 80].

Reyes et al. also revealed involvement of the ENK circuitry between the LC and PGi in stress resilience in rats. In this study, fluorogold, a retrograde tracer, was injected into the LC to determine involvement of different afferents (corticotropin-releasing factor, CRF neurons from CEA and ENK neurons from PGi) in resilience under the resident-intruder paradigm [72]. Individuals presenting a reduced latency to present a defeated posture (defined as vulnerable rats) showed an increased activation of LC neurons and afferents of CRF neurons from CEA. Conversely, resilient rats (longer latency to present a defeated posture) demonstrated a higher recruitment of ENK afferents from PGi. Thus, two different afferent pathways to the LC, from CRF neurons in the CEA and ENK neurons from the PGi, would partly define the interindividual variation with regard to the capacity to resist chronic stress.

Two studies conducted in our laboratory demonstrated that resilience to social defeat and chronic unpredictable stress share common variations of expression among the ENK systems within specific brain regions in rats [17, 18]. ENK mRNA (transcripts) were quantified in 23 nuclei of the mPFC, NAc, dorsal striatum, and AMG. Only one significant difference between control, resilient, and vulnerable individuals was found in the BLA of vulnerable individuals; ENK mRNA levels were decreased in vulnerable rats compared to control and resilient rats. In contrast, no difference was found in ENK expression in the BLA between controls and resilient animals [17]. In addition to revealing these associations, the functional role of ENK in the AMG was evaluated. The downregulation of ENK in the BLA was shown to increase anxiety both in the SI test and EPM thus reproducing certain behavioral responses encountered in individuals that are vulnerable to chronic stress [18]. Finally, the chronic social defeat stress was conducted in mice in order to assess ENK signature in the BLA. The expression of ENK mRNA was found to be decreased by 33% in vulnerable mice, only in the BLA. No difference was found between the control and resilient individuals [81]. These combined results suggest that specific neuroadaptations mediated by ENK neurotransmission in the BLA could represent a key mediator of stress resilience. Based on these results, we can hypothesize that

the decrease in ENK transmission from the BLA is a maladaptive mechanism, which mediates the behavioral dichotomy observed between vulnerable and resilient animals experiencing chronic stress.

4. Conclusion

Overall, most of animal studies covered in this review suggest that ENK signaling could be targeted for promoting resilience to chronic stress. Resilience to chronic stress is a very complex process involving several brain structures and neurotransmitters. When considering only one neuropeptidergic system, the ENK acting through DOPr and MOPr, numerous implicated brain structures and circuits emerge (see Figure 1 for a schematic representation that we overlapped with the cartography of main connectivities known to be involved in stress response, fear, and resilience). While the roles of ENK signaling within certain brain structures such as AMG, HPT, and NAc were largely described, its involvement in other brain regions remains unknown with regard to stress resilience. For example, the preoptic area, BST, and piriform cortex express ENK without evidence for a potential role in resilience to chronic stress, to our knowledge. All of these circuits must be individually dissected. Complete ENK KO models may thus be inadequate for characterizing the involvement of ENK signaling in stress resilience. Hence, modulating ENK or DOPr/MOPr expression within circumscribed regions or modulating selected neuronal circuits appear to be more appropriate. In this regard, optogenetic tools could provide a unique opportunity to modulate ENK transmission among selected neuronal circuits, over the course of chronic stress and associated pathologies, as required to unravel the mechanisms through which distinct ENK pathways exert their functional role in stress resilience. Understanding the synergistic involvement of different circuits in stress resilience could additionally provide accurate, powerful, and effective therapeutic strategies to prevent or treat long-term anxiety and depression, in addition to a variety of stress- and anxiety-related disorders.

Abbreviations

DPDPE: [D-Pen 2,5]-enkephalin
TMT: 2,5-Dihydro-2,4,5-trimethylthiazoline
AMG: Amygdala
BLA: Basolateral nucleus of amygdala
BST: Bed nuclei of the stria terminalis
CNS: Central nervous system
CEA: Central part of amygdala
CRF: Corticotropin-releasing factor
EPM: Elevated plus maze
ENK: Enkephalin
FST: Forced swim test
HPC: Hippocampus
HPT: Hypothalamus
IC: Intercalated nuclei of amygdala
KD: *Knock down*
KI: *Knock in*
KO: *Knockout*
LDCVs: Large dense-core vesicles
CEAl: Lateral part of central amygdala
Leu-ENK: Leucine-enkephalin
LC: Locus ceruleus
MEA: Medial part of amygdala
mPFC: Medial prefrontal cortex
MEAP: Met-ENK-Arg^6Phe^7
Met-ENK: Methionine-enkephalin
NAc: Nucleus accumbens
OF: Open-field
LDB: Light-dark box
OPr: Opioid peptide receptor
PGi: Paragigantocellularis nucleus
PVN: Paraventricular nucleus of HPT
PAG: Periaqueducal grey
PET: Positron emission tomography
PTSD: Posttraumatic stress disorder
Pro-ENK: Proenkephalin
PKC-δ: Protein kinase C-δ
SI: Social interaction
SN: Substantia nigra
SR: Startle response
VTA: Ventral tegmental area
DOPr: δ opioid peptide receptor
KOPr: κ opioid peptide receptor
MOPr: μ opioid peptide receptor.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Marie-Eve Tremblay and Guy Drolet contributed equally to this work.

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Review Article

Environmental Factors Promoting Neural Plasticity: Insights from Animal and Human Studies

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We do not all grow older in the same way. Some individuals have a cognitive decline earlier and faster than others who are older in years but cerebrally younger. This is particularly easy to verify in people who have maintained regular physical activity and healthy and cognitively stimulating lifestyle and even in the clinical field. There are patients with advanced neurodegeneration, such as Alzheimer's disease (AD), that, despite this, have mild cognitive impairment. What determines this interindividual difference? Certainly, it cannot be the result of only genetic factors. We are made in a certain manner and what we do acts on our brain. In fact, our genetic basis can be modulated, modified, and changed by our experiences such as education and life events; daily, by sleep schedules and habits; or also by dietary elements. And this can be seen as true even if our experiences are indirectly driven by our genetic basis. In this paper, we will review some current scientific research on how our experiences are able to modulate the structural organization of the brain and how a healthy lifestyle (regular physical activity, correct sleep hygiene, and healthy diet) appears to positively affect cognitive reserve.

1. Introduction

Numerous clinical and experimental studies demonstrated that many environmental factors may affect both the physiological functions of the central nervous system (CNS) and its ability to counteract pathological changes. It has been demonstrated that experience shapes our neural circuits, making them more functional, keeping them "young." Experience is then the factor which induces our brain to be more plastic. In other words, experience may increase neuroplasticity. The complex of molecular and cellular processes known as neuroplasticity represents the biological basis of the so called "cerebral reserves." The first to introduce the concept of "reserve" was Yaakov Stern who noticed a higher prevalence of Alzheimer's disease (AD) in people with lower education. For Stern, the reserve is a mechanism, which may explain how, in the face of neurodegenerative changes that are similar in nature and extent, individuals vary considerably in the severity of cognitive aging and clinical dementia [1]. Clinical studies provide evidence that people with a high level of education have a slower cognitive decline [2, 3].

According to Stern, two types of cerebral reserves are recognized: brain reserve (BR) and cognitive reserve (CR). BR is based on the protective potential of anatomical features such

as brain size, neuronal density, and synaptic connectivity. This reserve is passive and is also defined as the amount of brain damage that can be sustained before reaching a threshold for clinical expression [1]. It also explains differential susceptibility to functional impairment in the presence of pathology or neurological insult [4]. This concept arose by the observation that the prevalence of dementia is lower in individuals with larger brains [5–7]. In contrast, CR posits the differences in cognitive processes as a function of lifetime intellectual activities and other environmental factors that explain the nonlinear relationship between the severity of patients' brain damage and the correspondent clinical symptoms. The CR suggests that the brain actively copes with brain damage by using the preexisting cognitive processes or by enlisting compensatory mechanisms [1, 3]. Thus, CR represents a functional reserve because it is based on the efficiency of neural circuits [8]. CR is considered an "active reserve" because the brain dynamically attempts to cope with brain damage by using preexisting cognitive processing networks or by enlisting compensatory networks [1, 3]. It is important to emphasize that BR and CR are not mutually exclusive but are involved together, at different levels, in providing protection against brain damage [9]. For this reason, it is possible to refer to the accumulated structural reserve (BR) and capacity for functional compensation (CR) using the new construct of "brain and cognitive reserve" (BCR) [10]. In fact, any morphological change results in a modification of the functional properties of a circuit and vice versa, and any change in neuronal efficiency and functionality is based on morphological modifications. For example, factors associated with an increased CR, such as cognitively stimulating experiences or a great deal of physical activity, are associated with neurogenesis, increased levels of neurotrophic factors, and diminution of neuronal apoptosis [11]. Therefore, functional and anatomical factors interact in the construction of the cerebral reserves [12].

In clinical research, we can study the relation between structural (BR) and functional (CR) changes by analyzing the gray matter damage in AD patients (structural measure) and then correlating it with a cognitive evaluation (functional measure) [13].

More direct measures of experience-due structural and functional changes are provided by experimental research on animal models. For example, BR measures are the changes at cellular and molecular levels [14], while direct CR measures are the performances in behavioral tasks, such as spatial tasks [8, 15]. The studies carried out by using enriched environment animal models enabled us to understand what kinds of experiences are necessary to trigger the phenomenon of brain plasticity and thus to increase cerebral reserves.

The purpose of the present work is to provide an up-to-date overview on the effects of the environmental factors on promoting neural plasticity in physiological and pathological conditions taking into account both human and animal studies.

2. Animal Studies

There is evidence showing that individuals with more CR are those who have a high level of education, who maintain regular physical activity, and who eat in a healthy way [16–19]. Despite such evidence, human studies do not allow us to determine whether one kind of experience determines the increase in cognitive reserve more than the other ones. Human research cannot separate the different variables that make up experience because we cannot analyze them separately. The experimental research on animals may compensate for these shortcomings by forcing the stimulation of a specific experience or a combination of experiences, as occurs in enriched environment animal models. The animal models of environmental enrichment (EE) allow us to obtain a direct, real, and tangible measure of which environmental factors are able to model neuronal circuits [8].

EE represents an experimental model in which the animal is exposed for a certain time period to a combination of experiences, such as an intense motor activity and sustained cognitive stimulation. This condition is usually compared to the standard condition of regular laboratory housing [20].

The majority of EE animal models concern rodents, but studies have also been carried out on nonhuman primates, birds, and fish [21].

At the first glance, it may seem strange that the EE in animals may be really compared to cognitive, motor, social, and emotional experiences in humans. Although this correlation may seem impossible, exposure of animals to an enriched environment is actually similar to that which occurs in human lifestyle [8]. In fact, in humans, the development of reserves can be influenced by several factors, such as educational level, physical activity, social integration, and emotional involvement. In animal models, all these factors are provided by the environmental complexity and novelty the animals are exposed to. The repeated replacing of objects in the home cages creates a wide range of opportunities for enhanced cognitive stimulation, formation of efficient spatial maps, and heightened ability to detect novelty. Physical training is represented by foraging in large cages, exploration of new objects that are constantly introduced into the cages, and general motor activity related to the use of wheels. The social aspect that characterizes human relationships may be mimicked by rearing the animals in a group of conspecifics. In fact, if the animals are stimulated to live together in the same cage, a social hierarchy emerges and a dominant figure arranges and controls the spaces of the cage and when to eat. Figure 1 shows an example of the rearing in an enriched environment.

The first to introduce the experimental concept of enriched environment was Donald Hebb, although it was the famous American psychologist Mark Richard Rosenzweig who clarified the enriched environment as "a combination of complex inanimate and social stimulations" [22].

Thus, the implementation of a setting of EE is a quite complex procedure, in which motor activity, cognitive abilities, and social interaction should be taken into account. Although recently it has been shown that also physical activity alone is able to increase CR, most studies show that all these factors should be stimulated to increase brain plasticity [8].

An EE paradigm is used with healthy animals to analyze neuroplastic functional and structural changes [23], with animals that present neurodegenerative lesions or transgenic mutations to analyze neuroprotective and therapeutic effects

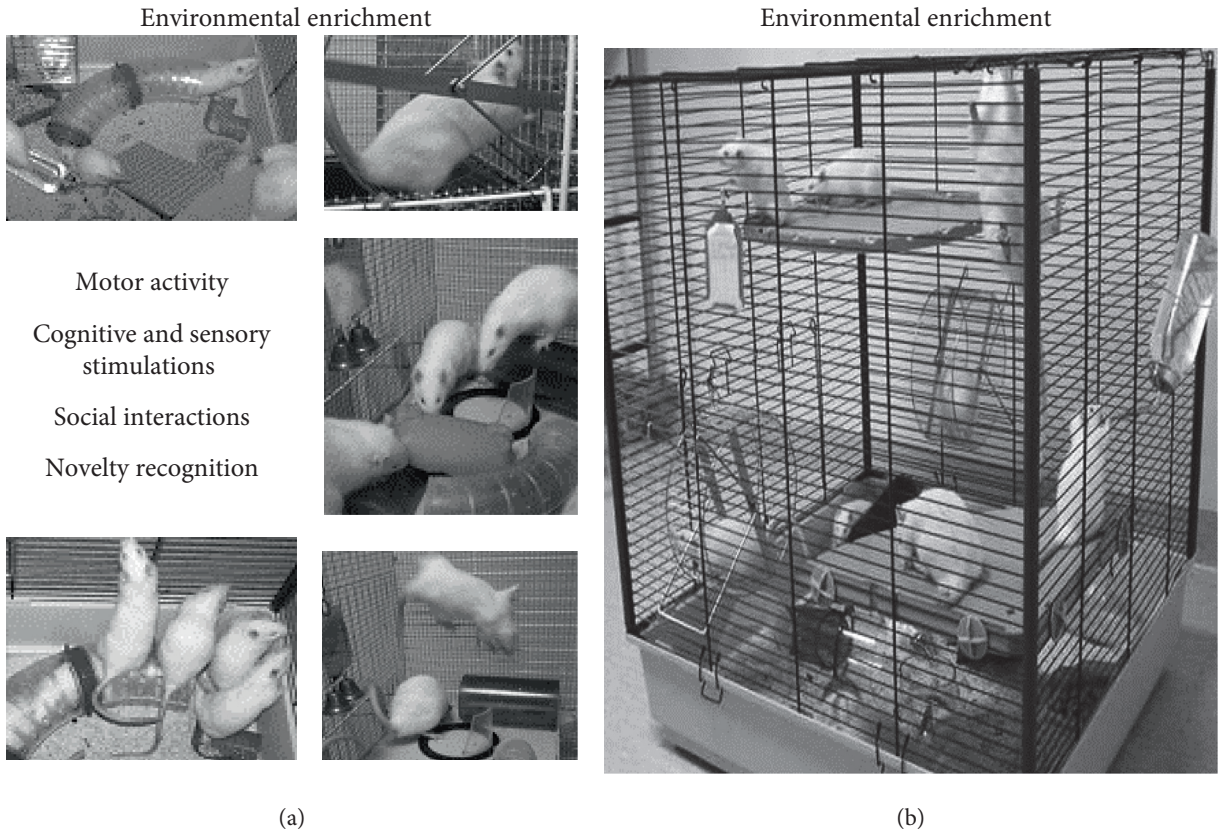

Figure 1: A typical enriched setting that enhances motor, sensory, cognitive, and social stimulations in rodents is illustrated in (b). In (a), the different components acting in the environmental enrichment are shown. Modified from [8].

[10, 15, 24–27], and recently even with an animal model of psychiatric disorders, such as schizophrenia, to evaluate the ameliorative effects on behavioral symptoms [28–30].

In general, cognitive abilities in animals are evaluated by means of specific behavioral tasks such as Morris water maze (MWM) and radial arm maze (RAM) that analyze the different facets of spatial memory. In fact, the memory can be divided into at least two types, such as declarative and procedural. Declarative knowledge refers to things that we know that are accessible to conscious recollection ("knowing that"), while procedural material regards memories on how to do something ("knowing how") and those that are seen as implicit and unconsciously learned [31]. The two types of memory have different and specific neural correlates. Declarative memory mainly involves the hippocampal structures, while procedural learning and memory rely more on the cerebellum and basal ganglia [32–34]. Majority results discussed in the next sessions come from MWM and RAM behavioral tasks.

2.1. Functional and Structural Effects of EE. Many studies conducted on healthy animals show that rearing in an enriched environment has significant functional and structural effects (Table 1, Figure 2).

To evaluate the functional effects of EE on the performances in behavioral tasks, spatial tasks are analyzed. In particular, these tasks permit us to analyze the different facets of spatial cognitive function and then to evaluate the functioning of underlying neural circuits. For example, Leggio and coworkers compared the spatial performances in radial arm maze and in Morris water maze of healthy animals reared in an enriched environment for three months after the weaning with those of animals reared in standard conditions [23]. In both spatial tasks, the animals reared in an enriched environment made fewer errors than the conspecifics reared in standard laboratory conditions and showed a precocious development of spatial cognitive mapping of the environment.

In EE structural effects, the changes at cellular level (such as neurogenesis, gliogenesis, angiogenesis, and synaptogenesis) and the alterations at molecular level (such as changes in neurotransmitter and neurotrophin expression) are considered [15]. By studying synaptogenesis, Gelfo and coworkers evidenced as indices of improved neuronal circuitry the increased dendritic length and spine density shown by the frontal and parietal pyramidal neuron apical and basal arborizations of rats reared in EE [35]. Molecular effects that follow EE have been demonstrated by analyzing the neurotrophin levels in brain structures where neurotrophins are produced or transported. In particular, multiple studies in rodent models showed that EE increases the expression of a brain-derived neurotrophic factor (BDNF) in the hippocampus that heavily supports the EE-induced improvement in learning and memory [36, 37]. Moreover, neurotrophin

Table 1: Structural and functional effects of environmental enrichment (EE).

Sample		EE condition	Functional Effects (behavioral effects)	Structural Effects (molecular and cellular effects)	Refs.
Effects of EE on healthy rodents					
Wistar rats		EE from weaning for 2.5/3 months	Precocious development of spatial cognitive map; enhanced spatial memory and cognitive flexibility	Increases dendritic length and spine density in frontal and parietal pyramidal neuron apical and basal arborizations; synaptogenesis; increases of BDNF levels in the hippocampus and cerebellum	[14, 23, 35–37, 40]
Wistar rats C57BL/6J mice		Maternal and paternal EE: a transgenerational model	In pups: accelerated acquisition of complex motor behaviors; decreased anxiety-related behaviors	In pups: high expression of neurotrophin in cerebellar and striatal areas; low ACTH levels	[38–41]
Neuroprotective effects of EE on neurodegeneration					
Neurodegenerative disorders	HD mouse models	Running exercise about from 4 weeks of age	Partially delayed onset of motor symptoms and cognitive deficits (memory/executive functions)	Altered BDNF mRNA levels	[10, 15, 42–45]
		EE about from 4 weeks of age	Delayed onset of motor symptoms and cognitive deficits (memory/executive functions)	Decreased cortical and striatal volume loss; ameliorated deficit in neurogenesis; increased neurotrophin expression; enhanced CB1 receptor levels	
	PD mouse models	Running exercise from 6 weeks	Attenuated motor impairment, reduced anxiety behavior	Decreased loss of striatal DA	[10, 15, 46–49]
	AD mouse/rat models	Intensive locomotor training	Increases performances in spatial memory tasks	Decreased beta-amyloid plaques	[10, 15, 24–27, 50–57, 62]
		EE from weaning for 2.5/3 months; EE for 2 months at different age	Enhanced spatial memory and executive functions (cognitive flexibility)	Decreased beta-amyloid plaques; increased levels of neurotrophic substances; increased spine number and density in pyramidal neurons	
Aging		EE and locomotor training in middle age	Preservation of spatial abilities in old age	Changes in hippocampal astrocytes; hippocampal neurogenesis	[58–61]

EE refers to a complex stimulation of experiences. BDNF: brain-derived neurotrophic factor; NGF: nerve growth factor; ACTH: adrenocorticotropic hormone; HD: huntington's disease; PD: parkinson's disease; AD: alzheimer's disease; DA: dopamine.

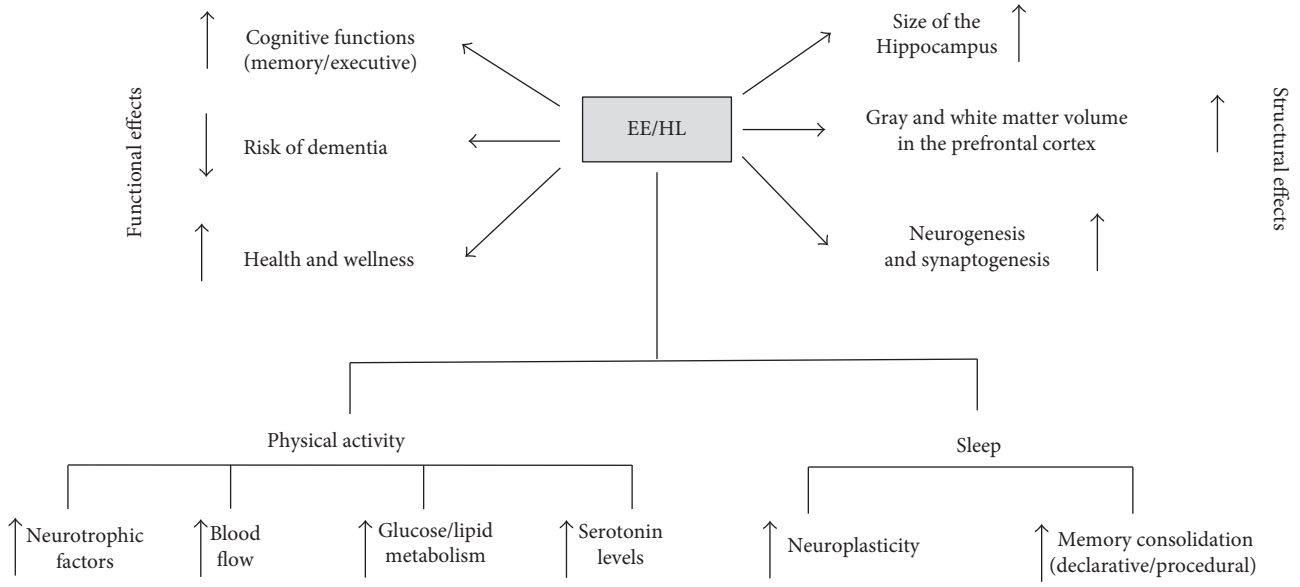

Figure 2: Schematic representation of the structural and functional effects of environmental enrichment (EE) on animal models and healthy lifestyle (HL) on humans.

levels were found to be also increased in the cerebellum and other cerebral areas following EE [14].

Functional and structural effects of EE are analyzed even from a transgenerational point of view. In particular, Caporali and coworkers [38] reared female rats in enriched conditions and then studied the motor behavior and the neurotrophin levels of their pups reared in standard conditions. This study demonstrates that positive maternal experiences were transgenerationally transmitted and influenced offspring phenotype at both behavioral and biochemical levels. In fact, the pups from enriched mothers acquired complex motor behaviors earlier than the pups from mothers reared in standard conditions. Moreover, in the pups from enriched mothers, the cerebellar and striatal neurotrophin expression was significantly higher. Evidence presents that also paternal EE is able to transgenerationally alter affective behavioral and neuroendocrine phenotypes of the offspring [39–41]. These studies suggest that the cerebral reserves could be even inherited.

2.2. Neuroprotective Effects of EE. As we mentioned, many studies showed that EE or even just motor exercise induces neuroprotection against neurodegenerative diseases [15, 24–26]. In a brilliant review on the EE models, Nithianantharajah and Hannan showed that motor exercise alone produces a positive effect at behavioral, cellular, and molecular levels on some diseases that affect the cognitive-motor sphere, such as Huntington's disease (HD), Parkinson's disease (PD), and AD [15]. To give some examples, in HD mouse models, it was demonstrated that wheel-running exercise delays the onset of specific motor deficits [42–44] and diminished the impairment in spatial memory and cognitive flexibility, also attenuating neuropathology [45]. Behavioral performance has been demonstrated to be improved by physical training also in PD rodent models [46, 47], with neuroprotective effects on the regulation of neurochemical factors [48, 49]. Finally, in AD, an intensive locomotor training increases the quality of performance in behavioral tasks concerning spatial learning and memory [50]. At cellular level, a decrease in beta-amyloid plaques occurs and, only in the case of more complex stimulation, an increase in the levels of neurotrophic substances as synaptophysin was also observed [51–53].

Examples coming from transgenic murine models, which provide the precious advantage to determine exactly when a structural alteration occurs, allow to evaluate when it is best to enrich the animals. For example, by means of transgenic AD mice (Tg2576), Verret and coworkers showed that the EE effects are more powerful if the animals are reared in an enriched environment before the formation of beta-amyloid plaques [54], that is, before their deleterious effects on brain function and memory processing become permanent.

Decreased levels of beta-amyloid plaque in response to EE have been highlighted also by Beauquis and coworkers who analyzed the astroglial changes in the hippocampus of transgenic animals [55]. In fact, growing evidence shows that glial changes may precede neuronal alterations and behavioral impairment in the progression of AD and that the modulation of these changes could be addressed as a potential therapeutic strategy [56–58]. In particular, Beauquis and coworkers evidenced that in enriched transgenic animals (APP mice), a decrement in levels of astrocytes was present, suggesting that glial alterations have an early onset in AD pathogenesis and the exposure to an enriched environment is an appropriate strategy to reverse them.

Moreover, the confirmation that glial alterations play an important role in cerebral reserves comes from a recent study that investigated the functional and structural effects of intermittent EE (3 hours/day for two months) on aged rats [58]. In fact, even at advanced ages, behavioral results showed that EE improved performances in a radial water maze task and structural data evidenced plastic changes in the

hippocampal astrocytes suggesting that these neuroplastic alterations are involved in a coping mechanism with age-related cognitive impairment.

Several authors wondered until which point in life the enrichment has positive effects on cognitive function. Fuchs and coworkers assessed the impact of late housing condition (e.g., from the age of 18 months) on spatial learning and memory of aged rats (24 months) previously exposed or unexposed to EE during young adulthood (until 18 months) [59]. The results showed that late EE was not required for spatial memory maintenance in aged rats previously housed in EE. In contrast, late EE mitigates spatial memory deficit in aged rats previously unexposed to EE. These outcomes suggest that EE exposure up to middle age provides a reserve-like advantage that supports an enduring preservation of spatial capabilities in old age [60, 61].

In addition to the transgenic animal models of EE, also the studies on lesioned animals contributed to highlighting the neuroprotective role of environmental stimulation. For example, it was found that rats exposed to EE at weaning about three months before a cholinergic basal forebrain depletion (which mimics AD) recover some cognitive abilities such as spatial memory and cognitive flexibility [62]. These improvements in the cognitive-motor domain were also accompanied by changes at the morphological level [26], demonstrating once again the close link between structure and function and, in this case, between CR and BR.

The main neuroprotective effects of EE are shown in Table 1.

3. Environmental Factors and Lifestyle in Human

Research on animal models provides an important insight into understanding the key role of environmental factors in promoting cognitive reserve. On the other hand, human studies showed that not only high-demand cognitive activities are able to improve cognitive skills and counteract a physiological and pathological cognitive decline but even other environmental factors such as regular physical activity and correct sleep hygiene can substantially contribute to brain well-being.

3.1. Physical Activity (PA) and Neuroplasticity. In EE animal models, it has been shown that motor exercise has significant effects on neuroplasticity and counteracts a pathological cognitive decline [10, 15]. In humans, it seems necessary to distinguish between physical activity (PA) and physical exercise (PE). In fact, PA is any movement of the body produced by skeletal muscles that results in energy expenditure over the baseline levels, including all structured daily activities, such as housework and leisure activities. Conversely, PE is a structured and repetitive physical activity, aimed at maintaining or improving one or more components of physical fitness.

PA and PE are often related to health benefits in the prevention and in the treatment of many pathological conditions, such as metabolic diseases [63–65] as well as diseases associated with compromised cognition and brain function [66]. Several studies do exist showing that the practice of regular and constant PA reduces the risk of developing dementia [67].

PA increases blood flow, improves cerebrovascular health, and determines benefits of glucose and lipid metabolism carrying "food" to the brain. It has been showed that PA causes neural plasticity phenomena. For example, PA facilitates the release of neurotrophic factors like BDNF, stimulates neurogenesis phenomena, and determines structural changes such as the improvement of white matter integrity [68]. The brain changes are inevitably reflected in functional modifications. In this context, children with higher levels of aerobic fitness showed greater brain volumes in gray matter brain regions (structural changes) and the best performances in learning and memory tasks (functional changes) in comparison to sedentary children [69]. It is important to underlie that all the structural and functional changes are derived by an aerobic type of PA. Recently, it has been showed that only regular aerobic exercise is associated with larger size of the hippocampal regions [70]. Moreover, aerobic exercise increases gray and white matter volume in the prefrontal cortex [71] and increases the functioning of key nodes in the executive control network [72, 73] (Figure 2).

3.2. Sleep and Neuroplasticity. In the last decades, it has been shown that sleep is an essential feature of animal and human brain plasticity, which involves both basic (e.g., [74]) and higher-order functions (e.g., [75]).

Sleep is an active, repetitive, and reversible behavior that is in the service of several different functions that occur all over the brain and the body [76, 77]: from repair and growth to learning or memory consolidation and up to restorative processes. This basic role of sleep is also indirectly substantiated by the fact that almost all the animal species, from fruit flies to the biggest mammals [78], share a behavioral state that can be defined as "sleeplike." Thus, if sleep subserves all these aspects of animal life, it would be seen as a crucial survival-directed drive, so that chronic or repeated sleep deprivation in rodents brings cellular and molecular changes in the brain [79] while in humans, it can dramatically disrupt several high-order cognitive functions [75, 80–83].

Different hypotheses have been suggested to deeply explain the functions of sleep, and one of the well-accepted ideas is that sleep is linked to memory, learning, and neuroplasticity mechanisms [74] (Figure 2).

Several studies showed that sleep plays an important role in learning processes and memory consolidation [84, 85] although no direct relationships have been found between different kinds of memory and different sleep stages [86]. These studies clearly indicated that sleep deprivation can impair learning and different kinds of memory that can be divided into at least two types, such as declarative and procedural (as discussed above). Thanks to this distinction, a dual-process hypothesis has been proposed [87]: the effect of a sleep state on memory processes would be task-dependent, with the procedural memory gaining from REM (rapid eye movement) sleep and declarative memory from NREM (nonrapid eye movement) sleep [88].

But other data [89] have been interpreted as in line with the alternative point of view, that is, the hypothesis of a

sequential processing of memories during sleep stages [90, 91] suggesting that memory formation would be prompted by NREM sleep (and particularly by its slow-wave content, namely, stages 3 and 4) and then consolidated by REM sleep, indicating that for an efficient consolidation of both knowledge (declarative) and skills (procedural), the worst enemy is sleep loss or, at least, sleep fragmentation.

The nature of the link between sleep and synaptic plasticity is not fully understood: several different processes of synaptic reorganization would occur during sleep period, but their functional role needs to be clarified. In a very recent review [74], it has been discussed that induction of plastic changes during wake can produce coherent and topographically specific local changes in EEG slow activity in the subsequent sleep and that during sleep, synaptic plasticity would be restored.

Independently by the actual nature of the link between sleep and neuroplasticity, now, it is well known and accepted that a good quality of sleep allows an efficient and successful aging [92]. In fact, several recent studies have clearly indicated the relevance of sleep quantity and quality as a marker of general health, well-being, and adaptability in later life [93–95]. This literature can help in developing health programs devoted to the oldest aim of improving sleep hygiene in order to guarantee avoidance of disease, maintenance of high cognitive and physical function, and continued engagement with life.

4. Conclusions

Experimental research strongly suggests that in order to increase our cerebral reserves, we have to follow a lifestyle that takes into account many factors. Clinical studies provided evidence that individuals with more cerebral reserves are those who have a high level of education, who maintain regular physical activity, who eat in a healthy way, and so on. The EE animal models confirmed that the experience plays a key role in increasing brain plasticity phenomena. Although we are still far from identifying the basic ingredient responsible for increasing our brain plasticity and for counteracting neurodegenerative damage, we can say with confidence that to deal with physiological and pathological situations, it is not only important to be "genetically lucky" but also to maintain a lifestyle rich in experiences also including high levels of physical activity and good sleep hygiene.

Ethical Approval

This article is based on the review of previous papers, and thus, it does not contain any studies with human participants or animals performed by any of the authors.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Review Article

Lifestyle Modulators of Neuroplasticity: How Physical Activity, Mental Engagement, and Diet Promote Cognitive Health during Aging

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The number of the elderly across the globe will approximate 2.1 billion by 2050. Juxtaposed against this burgeoning segment of the population is evidence that nonpathological aging is associated with an increased risk for cognitive decline in a variety of domains, changes that can cause mild disability even before the onset of dementia. Given that pharmacological treatments that mitigate dementia are still outstanding, alternative therapeutic options are being investigated increasingly. The results from translational studies have shown that modifiable lifestyle factors—including physical activity, cognitive engagement, and diet—are a key strategy for maintaining brain health during aging. Indeed, a multiplicity of studies has demonstrated relationships between lifestyle factors, brain structure and function, and cognitive function in aging adults. For example, physical activity and diet modulate common neuroplasticity substrates (neurotrophic signaling, neurogenesis, inflammation, stress response, and antioxidant defense) in the brain whereas cognitive engagement enhances brain and cognitive reserve. The aims of this review are to evaluate the relationship between modifiable lifestyle factors, neuroplasticity, and optimal brain health during aging; to identify putative mechanisms that contribute positive brain aging; and to highlight future directions for scientists and clinicians. Undoubtedly, the translation of cutting-edge knowledge derived from the field of cognitive neuroscience will advance our understanding and enhance clinical treatment interventions as we endeavor to promote brain health during aging.

1. Introduction

The number of elderly across the globe will approximate 2.1 billion by the year 2050 [1, 2]. Accompanying this increase will be the personal, social, and economic burden of care for individuals with age-related disorders. These challenges are even more worrisome given that nonpathological aging is associated with decrements in key regions of the brain vital for cognitive function and, thereby, decline in several cognitive domains (including memory, attention, speed of processing, and executive function) [3, 4], changes that may result in mild disability even prior to the onset of dementia. Notwithstanding, pharmacological treatments that mitigate dementia are still outstanding, creating an imperative to diversify efforts to find efficacious alternatives. Modifiable lifestyle factors are among the candidate therapeutics particularly well-poised to mitigate age-related disorders [5–11]. Evidence strongly suggests that the maintenance of adequate levels of physical activity (PA), engagement in cognitive stimulation, and optimization of nutritional intake can increase neural plasticity and resilience of the brain [12–15].

The ability of neurons in the brain to change and reorganize continuously to meet the dynamic demands of the internal and external environment is termed neuronal plasticity. This process is dependent on membrane depolarization of the neuron, stimulus-induced synaptic activity, and subsequent changes in dendritic morphology, central hallmarks of learning and memory. Importantly, long-term PA moderates processes that are cornerstone for neuroplasticity [16]. Van Praag et al. demonstrated that mice that were given voluntary access to running wheels exhibited selective enhancement of long-term potentiation (LTP) in the dentate gyrus [17], a phenomenon linked with concomitant increases

in brain-derived neurotrophic factor (BDNF) [18]. Eadie et al. demonstrated that long-term PA significantly increased dendritic length, dendritic complexity, and spine density in the dentate gyrus of mice [19]. Stranahan et al. demonstrated that long-term voluntary wheel running in rats induced changes in spine density along with changes in arborization and spine morphology [20]. Altogether, these findings suggest that PA induces neuroplastic changes in brain structure and function and, therefore, may be an effective component of therapeutic regimes that aim to improve cognition. Interestingly, other work suggests that mental engagement and dietary factors also effectuate changes in plasticity by altering neurotrophic signaling, neurogenesis, inflammation, stress response, and antioxidant defense mechanisms, which are outcomes similar to those implicated in the cognitive response to PA [16].

Knowledge of the dynamic relationship between brain plasticity and lifestyle factors creates an imperative to better understand and harness these links to promote healthy aging and forestall the onset of disease. Several national bodies have affirmed this notion, including the National Institutes of Health [21], the Centers for Disease Control, the Alzheimer's Association, and the American Association of Retired Persons (AARP). Accordingly, the purpose of this review is to (1) explicate key lifestyle factors (in particular PA, cognitive engagement, and diet) that can be harnessed to enhance neuroplasticity and optimal brain health; (2) explore the putative mechanisms by which these factors affect age-related biology; and (3) highlight implications for clinicians and researchers.

2. Physical Activity

Numerous studies have reported a robust relationship between higher levels of PA and improved learning and memory [22, 23]. Epidemiological studies show that regular PA reduces the risk of cognitive decline in aging adults [15, 24–26], with some evidence intimating that midlife PA may be especially beneficial. A population-based study of PA at midlife, followed up 26 years later with an assessment of late-life cognitive function, found that groups who participated in PA during midlife exhibited a faster speed of processing along with better memory and executive function. Additionally, those in the moderate PA group were significantly less likely to have dementia in late life [15]. A meta-analysis of 29 randomized controlled trials ($n = 2049$) showed that aerobic exercisers exhibited improvements in attention, processing speed, memory, and executive function [27]. Another meta-analysis of 15 prospective studies ($n = 33,816$ persons without dementia) reported that PA consistently resulted in a protective effect at all levels of activity [28]. Findings from a study of school children clearly demonstrates a positive correlation between PA and academic performance [29]. Indeed, higher cardiorespiratory fitness levels have been associated with better performance on a relational memory task and greater hippocampal volumes in children [30], findings that have been recapitulated in adolescents [31, 32]. Together, these results suggest that the pervasive central benefits of PA on cognition span age groups.

Clinical studies demonstrate a positive relationship between PA and brain structure and function. A neuroanatomical study of persons aged 55 to 79 years demonstrated that age-related declines in cortical tissue density in the frontal, temporal, and parietal cortices were significantly reduced as a function of cardiovascular fitness [33], an interesting fact given that these areas underlie executive function and yet exhibit the greatest rate of age-related decline in humans [34]. Another study of elderly persons showed a direct correlation between increased levels of PA and improved cognition, with increased hippocampal volume seen after chronic exercise [35], supporting the idea that PA may prevent age-related anatomical and physiological deterioration in the brain [36, 37].

Bolstering the notion of PA's positive central effects are preclinical and clinical studies demonstrating neuroprotective and neuroplastic effects across a variety of neurodegenerative and neuropsychiatric diseases [36, 38–44]. A recent systematic analysis of 38 animal and human studies reported that PA attenuates Alzheimer-related neuropathology and positively affects hippocampal-mediated cognitive function, particularly when deployed early in the disease process [36]. Findings from another systematic review and meta-analysis demonstrate that PA is beneficial for people with Parkinson's disorder, specifically in areas of physical functioning, health-related quality of life, strength, balance, and gait speed [45]. Moreover, a recent review of clinical trials demonstrated that acute and chronic exercise generally increased levels of trophic factors in plasma and serum in persons with neurodegenerative conditions, including those with multiple sclerosis [46]. Also, PA has shown clear and consistent promise in promoting neuroplasticity in persons with mood disorders and, thereby, improving behavioral and neurobiological outcomes [38, 47], effects that extend to persons with posttraumatic stress disorder [48]. In persons with schizophrenia, evidence suggests that PA improves global cognition, working memory, social cognition, and attention [49]. A randomized controlled trial in persons with schizophrenia demonstrated that PA induced a 12% increase in hippocampal volume relative to nonexercisers [50]. While the dynamic cellular and molecular cascades that underlie the association between PA, cognition, and brain structure and function have yet to be elucidated fully, several modifiable mechanisms that alter neural plasticity have garnered increased attention recently, especially neurotrophic signaling, neurogenesis, inflammation, stress response, and antioxidant defense mechanisms [16]. Admittedly, an exhaustive review of all factors related to cognitive aging is beyond the scope of this article. Therefore, the reader is referred to the following excellent reviews for other factors that have been implicated in cognitive aging [51–59].

2.1. Neurotrophic Signaling. Neurotrophins are essential modulators of PA-induced neural plasticity. As one of the most widely distributed neurotrophins in the brain, BDNF plays a critical role in the maintenance, growth, and synaptic plasticity of neurons that underlie emotion and cognition

[18, 60–62] and also modifies neuronal excitability [62, 63]. BDNF is centrally and peripherally upregulated [64–67] following acute and long-term PA [68, 69], changes that endure for days [70] and are prominent in the hippocampus [22]. While higher levels of training intensity are requisite for maximal effects [66, 71], both resistance [72] and aerobic [71] exercise can effectuate the increases in BDNF levels once sufficient intensity of PA is achieved.

Extending these studies to humans, it has been shown that moderate levels of PA mitigate cognitive decline in aging persons through putative mechanisms that involve BDNF. Laurin and colleagues demonstrated that PA levels were inversely correlated with the risk for cognitive impairment and all-cause dementia [73]. Lautenschlager and colleagues reported that persons with subjective memory impairments who were randomized to 6 months of aerobic exercise exhibited lower clinical dementia rating scores, increased delayed recall, and better outcomes on the cognitive subscale scores of the Alzheimer's Disease Assessment Scale relative to controls during an 18-month follow-up period [74]. Coelho and colleagues investigated the effects of acute aerobic exercise on BDNF levels in older persons with AD and found a significant correlation between BDNF levels and levels of PA [75], suggesting that long-term PA may persistently elevate BDNF levels and modulate cognitive function in older adults. The latter notion is important given that BDNF gene expression levels naturally decrease in age-related disorders such as AD [76]. Decrements in BDNF are problematic because retrograde transport of BDNF from the hippocampus to forebrain cholinergic neurons protects against neuronal damage and degeneration [66]. Moreover, the maintenance of basal BDNF levels is requisite for hippocampal neurogenesis [77]. Interestingly, while both PA and cognitive training improve cognitive function, only PA increases plasma BDNF levels in rodents, suggesting that an adequate level of PA is essential for BDNF-mediated plasticity [78]. Furthering this notion is work demonstrating that the blockade of BDNF on TrkB receptors reduced the positive effects of PA on synaptic plasticity [79].

Altogether, these results suggest that PA effectuates central neuroplastic adaptations via the optimization of BDNF levels. The ability of PA to enhance BDNF release and function in the synapse, to promote dendritic spine integrity, and to activate other cellular pathways that contribute to plasticity [80–83] is a cornerstone for homeostatic processes that maintain, repair, and reorganize circuits damaged during aging and disease.

2.2. Neurogenesis. The addition of new neurons to existing circuits through adult neurogenesis represents a unique form of synaptic plasticity. The majority of the neurons in the brain are formed in the womb. However, the brain maintains the ability to generate new neurons throughout life in certain regions (e.g., dentate gyrus and olfactory bulb) [84, 85]. Importantly, preclinical work suggests that PA increases adult neurogenesis, synaptic plasticity, and learning in the dentate gyrus of the hippocampus. Van Praag and colleagues demonstrated that voluntary wheel running simultaneously increased bromodeoxyuridine-positive cell numbers (precursor cell proliferation) and improved water maze performance (learning) [17]. Schmidt-Hieber and colleagues showed that newly born neurons in the hippocampus exhibit a lower excitability threshold and enhanced capabilities for synaptic plasticity [86], altering the rate by which new dentate granule cells are functionally integrated into hippocampal circuitry [87]. Eadie et al. demonstrated that long-term PA significantly increased total length and complexity of dendrites. Fascinatingly, they also demonstrated that long-term PA induced a more immature state of dentate granule cells [19], suggesting that PA reopens windows of plasticity. Stranahan et al. demonstrated that long-term voluntary wheel running in rats induced changes in spine density along with changes in arborization and spine morphology [20]. Others demonstrated that PA and cognitive stimulation exert differential effects on neurogenesis in rodents [88–91]. Whereas PA increases proliferation of neural precursor cells, cognitive stimulation promotes survival of the newly born cells. Thus, the absence of complex stimulation can block differentiation into mature neurons [92].

Translating the preclinical work to humans, clinical investigations using functional magnetic imaging have demonstrated that long-term aerobic exercise (3 months) increased blood volume in the dentate gyrus of the hippocampus and improved performance on the modified Rey Auditory Verbal Learning Test [93]. A randomized controlled study of healthy community-dwelling older adults demonstrated that those who participated in moderate aerobic exercise 3 times per week for 12 months showed a significant increase in size in the right and left hippocampus with concomitant improvements in spatial memory, a reversal that mitigated 1-2 years of age-related loss in hippocampal volume [94]. Encouragingly, increases in hippocampal size have been correlated with increases in spatial memory performance in both healthy adults [94] and persons with mild cognitive impairment [95]. The fact that PA upregulates neuronal proliferation and increases plasticity offers much hope for exploiting newly born neurons to maintain hippocampal volume in healthy and high-risk populations during aging [36, 96].

2.3. Inflammation. Long-term PA upregulates anti-inflammatory processes, an important finding given that chronic inflammation is mechanistically linked to cognitive impairment, mood disorders, cardiovascular diseases, and neurodegenerative disorders [22, 97]. Several studies have demonstrated that persons who regularly participate in PA have fewer viral and bacterial infections and a reduced incidence of systemic low-grade inflammation [98–102]. For instance, Kohut and colleagues studied the effects of PA on immune function and found that elderly individuals who participated in aerobic exercise (45 minutes per day, 3 days/week for 10 months) exhibited a reduction in plasma interleukin 6 (IL-6), interleukin 8 (IL-8), C-reactive protein (CRP), and tumor necrosis factor (TNF) levels [101]. A randomized control trial in sedentary elderly adults demonstrated that those who participated in a supervised exercise program (3 days/week for 6 months) showed improvement

in their inflammatory profile [103]. Other studies suggest that the beneficial effects of long-term exercise on cognition may stem in part from anti-inflammatory factors, specifically IL-6 [104–107], IL-8 [108–110], CRP [111–113], and TNF [114–116]. These findings are in line with several recent reviews that found that long-term moderate intensity PA can exert anti-inflammatory and neuroprotective effects [117–122]. Moreover, a recent review explicated mechanisms that contribute to neuroinflammation-induced impairments in neurogenesis in several conditions (aging, Alzheimer's, traumatic brain injury, and stroke), underscoring the importance of therapeutics such as PA that target the interplay between multiple neuroplasticity substrates, not isolated factors per se [123]. Together, these studies offer hope that PA can be used to mitigate age-related changes in immune senescence and preserve cognitive function with aging.

2.4. Stress Response. The hypothalamic-pituitary-adrenal axis (HPA) is a neuroendocrine circuit that coordinates emotional, cognitive, autonomic, and neuroendocrine responses to acute and chronic stress. Acute deactivation and activation of the HPA effectuates various changes in brain activation patterns: significant deactivation occurs in the hippocampus, hypothalamus, medio-orbitofrontal cortex, and anterior cingulate cortex following stress [124], whereas significant activation occurs in the amygdala [125, 126]. These activation patterns likely reflect adaptations to help a person recognize and counteract similar stressors in the future [127]. Conversely, persistent activation of the HPA as a result of chronic stress can mediate long-term changes in the stress response including damage to keys areas of the brain (e.g., prefrontal cortex, paraventricular neurons, and hippocampus) [127]. It has been shown that persistently elevated levels of glucocorticoids are neurotoxic [128, 129]. Specifically, HPA dysregulation induces neuronal atrophy secondary to changes in neurochemistry, resilience, and plasticity in the hippocampus [130].

Activation of the HPA is induced by corticotropin-releasing hormone (CRH) in the paraventricular nucleus in response to a stressor challenge, which induces adrenocorticotropic hormone (ACTH) from the pituitary and, in turn, effectuates the release of glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal glands [131]. Glucocorticoids then modulate the stress response along with metabolic, immunologic, and genetic functioning [132–134]. Notably, the release of cortisol following an HPA stress response occurs within the context of ongoing basal cortisol release. That is, cortisol is naturally secreted over a 24-hour period daily in the absence of stressors according to a diurnal cycle [135]. Notwithstanding, cortisol levels naturally vary in response to endogenous and exogenous factors (e.g., sleep wake cycle, exposure to light and dark, hormones, food consumption, and psychosocial variables) [136]. Thus, HPA function reflects an individual's basal diurnal secretion along with their response to ongoing endogenous and exogenous stress.

Negative feedback mechanisms tightly regulate the HPA response via mechanisms that involve high-affinity binding to mineralocorticoid receptors and low affinity glucocorticoid receptors [137]. Glucocorticoids "turn off" their own secretion by downregulating the release of hormones (CRH and ACTH), a response that then decreases mineralocorticoid and glucocorticoid receptor signaling and, in turn, downregulates the activity of the HPA to prestress baselines. Appropriate modulation of the HPA response appears paramount to brain health given several lines of evidence implicating stress-related hyperactivity and dysregulation of the HPA with age-related, neuropsychiatric, and neurodegenerative disorders [128, 133, 138–142].

Unfortunately, some evidence suggests that HPA changes may occur during the aging process. It has been shown that cortisol levels increase with age [143, 144] and diurnal slopes flatten [144–147]. Aging also engenders decreased glucocorticoid sensitivity and impaired negative feedback, changes that could prolong the stress response [148]. Finally, the HPA axis may become dysregulated in aging persons following exposure to chronic stress (e.g., health impairments, loss of function, and bereavement) [149]. With time, these changes may effectuate systemic changes that are deleterious to physical and cognitive health. Indeed, increased basal cortisol levels are associated with hippocampal-related memory impairments [150] and frailty [151], whereas lower levels of basal cortisol are associated with longevity [152].

Fortunately, a bevy of research suggests that long-term, voluntary PA mitigates an overactive stress response [153, 154]. Supporting this notion is evidence that exercise reduces the response to stressor challenge [155], an effect that may stem from exercise-induced fluctuations of glucocorticoid and mineralocorticoid receptor expression in the brain [155, 156]. The ability of PA to attenuate rises in cortisol levels may be especially important for preventing hippocampal atrophy [157–159] and for reversing cognitive deficits in the aging population [94, 160] given that hippocampal neurons exposed to persistently elevated glucocorticoids retract their dendrites and exhibit fewer dendritic spines [161]. Also, preclinical evidence suggests that the degree of dendritic branching in hippocampal neurons and overall number of dendritic spines increase with voluntary wheel running [19, 20, 162], potentially mitigating the effects of stress exposure. Together, this evidence suggests that PA may bolster physiological resilience by optimizing the stress response during aging.

2.5. Antioxidant Protection. Humans have a highly evolved antioxidant system designed to protect neurons from oxidative stress. By definition, oxidative stress is an imbalance between antioxidants and reactive oxygen species (ROS) (e.g., superoxide, hydrogen peroxide, and hydroxyl radical) [163]. Oxidative stress is widely deleterious in the central nervous system given that reactive oxygen species damage proteins, DNA, and lipids [164] and the fact that the brain has high metabolic demands and low antioxidant capacity [165, 166]. Notwithstanding, aerobic exercise decreases overall levels of ROS and increases adaptations to ROS-induced lipid peroxidation [167, 168]. These mechanisms stem in part from the ability of PA to increase antioxidant gene expression (e.g., superoxide dismutases and glutathione peroxidase) and, thereby, antioxidant enzymatic activities in

the brain [167, 169]. Together, these studies suggest that long-term exercise optimizes redox homeostasis. Such is important for aging persons given that the kinase proteins that induce structural and functional changes in synapses require specific redox environments and that synaptic activity can be modulated via ROS levels.

3. Cognitive Engagement as a Component of Healthy Lifestyle

Convergent evidence suggests that engagement in mental activity also conveys neuroprotective and neuroplastic benefits during aging. Higher levels of education, a proxy for cognitive reserve, are associated with a reduced risk for cognitive impairment [170, 171], even in those with high-risk genetic backgrounds (e.g., apolipoprotein E4 carriers) [172, 173], possibly by increasing the threshold at which impairments become clinically manifest [174]. Another study demonstrates that higher education is protective against cognitive deficits in elderly individuals with white matter lesions [175]. Moreover, persons engaged in cognitively demanding occupational [176–179], leisure [180, 181], and social activities exhibit a reduced risk for cognitive decline with aging [13, 14, 176–180, 182–188]. Leisure activities that have demonstrated procognitive effects include reading, discussion groups, computer usage, participation in card and board games, solving puzzles, playing musical instruments, and learning a second language [180, 189–194]. Social activities that have demonstrated procognitive effects include traveling; attending theater, concerts, or art events; participating in social groups or pension organizations; socializing with family; and dancing [180, 191, 192, 194].

Underlying the effects of mental, leisure, and social engagement on cognition is a concept called "reserve." According to the reserve hypothesis, impairments in cognition become manifest after a pool of brain and cognitive resources is depleted. Brain reserve refers to structural differences that increase tolerance to pathology, whereas cognitive reserve refers to variability in approach to task performance. The idea of brain reserve derives from studies showing that the occurrence of dementia is lower in persons with larger brain weights [195, 196] and that persons who engage in intellectually stimulating activities experience less hippocampal atrophy with aging [197]. Cognitive reserve suggests that a person can mitigate the effects of brain pathology by deploying pre-existing processing approaches or by deriving alternative strategies [198, 199]. By corollary, persons with decreased brain or cognitive reserve are more likely to exhibit clinical impairments with age- or disease-related insult given their fewer brain resources, whereas those with a higher reserve have more resources to rely upon following age- or disease-related insult, raising their threshold for clinical impairments.

Contemporary views of brain and cognitive reserve espouse more nuanced conceptualizations. Enriched environments infused with challenging activities are thought to effectuate the formation of new dendritic branches and synapses. These morphological changes then deepen the brain's capacity to resist insult while increasing augmentation of glial support cells, enhancement of the brain's capillary network, and the induction and incorporation of new neurons [200]. Indeed, preclinical work shows that stimulating environments increase neurogenesis [17, 201, 202] and upregulate BDNF [203–205], benefits that contribute to neural plasticity and extend to aging animals [206]. Enriched physical and social environments may provide short-lived mild to moderate stressors that induce locus coeruleus neurons to release noradrenaline and facilitate the formation and maintenance of adaptive memories [47], a process that could enhance adaptive structural changes in the brain (brain reserve) and cognitive and socioemotional learning (cognitive reserve). Supporting the latter notion is a multiplicity of studies showing that mental and socioemotional factors—including positive coping, optimism, sense of purpose, self-efficacy, and social support—are correlated with the stress response [207], are essential for the maintenance of high resilience [208–215], and are vital for mitigating age-related cognitive decline [216–218].

Another strategy that is garnering increased attention for enhancing brain and cognitive reserve is mindfulness meditation. A meta-analytic review (of 21 studies with approximately 300 participants) by Fox and colleagues examined the structural brain changes associated with mindfulness meditation and found that several brain regions consistently exhibited morphological differences in practitioners: the frontopolar cortex, sensory cortex, insula, anterior and mid-cingulate, hippocampus, and orbitofrontal cortex [219]. These areas are known to participate in awareness, attention, and emotional regulation, but are adversely affected in age-related disease and mood disorders [220, 221]. Tang and colleagues [222] reviewed a myriad of studies to determine the effects of mindfulness meditation on structural brain changes, functional activation, and neural connectivity. These authors reported that mindfulness meditation was associated with structural (in the prefrontal cortex, anterior and posterior cingulate, insula, hippocampus, and amygdala), functional activation (prefrontal cortex, anterior cingulate, amygdala, insula, and orbitofrontal cortex), and neuroplastic changes (anterior cingulate cortex and prefrontal cortex) in the brain of meditators versus controls [222]. While the underlying mechanisms that contribute to the structural, functional, and neuroplastic changes associated with mindfulness have yet to be elucidated fully, it seems plausible that neurogenesis, dendritic branching, and synaptogenesis may be involved in emotional and cognitive regions of the brain, particularly given that meditation reduces cortisol release following stress [223–225].

Correspondingly, it is also held that cognitive rehabilitative protocols may serve as a form of enriched environment and effectuate cognitive gains in the aging population. Approaches to cognitive rehabilitation involve exercises carefully designed to harness neuroplasticity. Investigating the effects of cognitive rehabilitation in healthy older adults and persons with mild cognitive impairment, a Cochrane review demonstrated that immediate and delayed verbal recall improved significantly following training as compared to a no-treatment control condition [226]. Extending these

studies further, another review assessed the effect of cognitive interventions on activities of daily living, mood, quality of life, and metacognition in persons with mild cognitive impairment. The authors found that computerized cognitive interventions conferred benefits to mood compared to controls, whereas therapist-based and multimodal interventions had a greater impact on activities of daily living and metacognitive outcomes than control conditions [227]. The notion that computerized cognitive rehabilitation may convey positive cognitive effects during aging is intriguing given that (1) these techniques can be deployed in a relatively quick and cost-effective manner; (2) the training can be personalized; (3) the rehabilitation can be used to target vulnerable and underserved populations, that is, persons who are homebound, residents of nursing homes, and those without access to transportation; and (4) preliminary evidence suggests residual effects are retained long-term (5 years) [228].

4. Diet and Healthy Lifestyle

Food consumption is an intrinsically motivated behavior with the potential to modulate brain structure and function. Driving this behavior is energy demand: whereas the brain comprises 2% of total body weight, it consumes 20% of the total energy derived from nutrients [229]. The exorbitant demand for energy derives from the requisite needs of neurons to maintain ionic gradients across their membranes to facilitate neurotransmission via oxidative metabolism. Accordingly, neurons are extremely sensitive to mitochondrial dysfunction and oxidative stress [166, 230, 231].

The centrality of feeding behavior for survivability makes it seem plausible that optimized food consumption represents a means to impact brain function positively. This putative effect stems in part from the ability of dietary factors to modulate synaptic plasticity by altering neurogenesis, inflammation, antioxidant defense mechanisms, neurotrophin levels, and energy metabolism [232], mechanisms similar to those induced by long-term PA [16]. For example, preclinical studies suggest that increased consumption of dietary fructose in the presence of an omega-3 fatty acid deficiency adversely affects learning and memory [233] by altering the function of molecules that are important in mitochondrial bioenergetics [234] in key brain regions such as the hippocampus [235]. Parallel evidence demonstrates that nutritional content, along with the level and frequency of food intake, effectuates changes in energy metabolism and neuroplasticity [229]. Population-based studies suggest that diets rich in polyphenols promote better performance in several cognitive abilities in a dose-dependent manner [9] and lower the risk of cognitive decline [10, 11] in older persons. Accordingly, it is increasingly held that bioactive substances in food represent a novel target for lifestyle interventions that may promote healthy brain aging and preserve cognitive function, especially in aging adults at risk for nutritional deficits [236]. Given that dietary modifications are considered by many to be safer and more easily integrated into lifestyle changes than conventional pharmacotherapeutics, several bioactive substances that have received intense investigation are reviewed below in brief.

Polyphenols (e.g., phenolic acids, stilbenes, lignans, flavonols, and anthocyanidins) comprise a class of approximately 8000 compounds with antioxidant properties. These compounds are found in fruits, vegetables, tea, wine, juices, plants, and some herbs. Whereas polyphenols are not considered "essential nutrients," convergent evidence does suggest that these factors can mitigate risk for neurodegenerative diseases, age-related cognitive decline, and oxidative stress [12, 237–245] via mechanisms involving the maintenance of metabolic homeostasis [241, 246] and the promotion of synaptic plasticity [241, 247]. Several dietary choices of polyphenols with putative neuroprotective [232], neuroplastic [248], neurogenic [249–251], and anti-inflammatory effects [252] have been explored, with a particular emphasis on curcumin, catechins, resveratrol, and omega-3 fatty acids.

4.1. Curcumin. As a plant-based diarylheptanoid produced by the plant turmeric, curcumin is a component of yellow curry spice. This bright-yellow pigment was first isolated more than a century ago and has been used extensively in Indian medicine. Historically, it has been deployed to mitigation inflammation [253, 254], oxidative damage [255], and amyloid build-up [256, 257]. The antioxidant capabilities of curcumin appear to stem from its unique structure that can donate H-atoms or transfer electrons from two phenolic sites, allowing it to scavenge free radicals easily. More recently, curcumin has garnered attention for its effects on neuroplasticity and its ability to ameliorate processes involved in brain aging and neurodegeneration.

Preclinical investigations show that dietary supplementation of curcumin 3 weeks prior to [258] and after [259] experimentally induced traumatic brain injury partially ameliorate the consequence of injury on markers of synaptic plasticity (e.g., BDNF and cAMP response element-binding protein), mechanisms that may partly involve the restoration of energy homeostasis [258–260] and facilitation of neurogenesis in the dentate gyrus of the hippocampus [261]. Also, curcumin may prevent secondary sequelae following brain injury by inhibiting the formation of oligomers and fibrils and the aggregation of amyloid proteins [262–264]. Interestingly, curcumin appears to cross the blood-brain barrier. Curcumin injected into the tail vein of rodents altered plaque formation in a model of AD [265]. A recent meta-analysis and systematic review of eight preclinical studies demonstrated that curcumin significantly improved neurological function in the central nervous system, an effect that was proportional to dosage [266].

Recently, preclinical studies have focused on the effects of curcumin administration on aging. One recent study has demonstrated that curcumin rescued age-related loss of hippocampal synapse input specificity of LTP by favoring N-methyl-D-aspartic acid receptor activity [267]. Also, curcumin and its metabolite, tetrahydrocurcumin, increased the mean lifespan of at least three model organisms [268] and modulated the expression of aging genes in some models [269].

Extending these studies to humans, a large population-based study of elderly nondemented Asians investigated the association between curry consumption and cognitive function, finding that persons who frequently consumed curry scored significantly better on the Mini-Mental State Examination relative to those who infrequently consumed curry [270]. Another 6-month randomized, placebo-controlled, double-blind, clinical study of curcumin in persons with progressive cognitive decline and memory found increased serum amyloid beta-40, but not improvements on the Mini-Mental State Examination [271]. Cox and colleagues investigated the acute, chronic, and acute-on-chronic effects of a curcumin formulation (400 mg) on cognitive function, mood, and blood biomarkers in healthy older adults. They found that curcumin significantly improved (1) performance in attention and working memory 1 hour following administration as compared with placebo, (2) working memory and mood following 4 weeks of treatment, (3) alertness and contentedness 1 hour and 3 hours after a single dose following chronic treatment, and (4) LDL cholesterol via reduced total concentration [272]. Daily and colleagues examined the efficacy of curcumin for alleviating the symptoms of arthritis and found supportive treatment evidence for turmeric extract (about 1000 mg/day of curcumin) [273], suggesting a translational avenue for its anti-inflammatory effects. Derosa and colleagues evaluated the efficacy of curcuminoid supplementation on circulating concentrations of IL-6 in randomized controlled trials and reported a significant effect of curcumin in lowering circulating IL-6 concentrations, an effect that was more evident in patients with greater systemic inflammation [274]. A systematic review and meta-analysis of randomized controlled trials evaluated the efficacy of curcumin supplementation on circulating levels of TNF-α and reported a significant effect of curcumin in lowering circulating TNF-α concentration [275]. The ability of curcumin to mitigate chronic inflammatory processes is important because chronic inflammation dysregulates neurotransmission and trophic factor signaling and disrupts the processes of neurogenesis and neuroplasticity [276–279]. Moreover, chronic inflammatory processes can contribute to glutamate-mediated excitotoxicity [279] and loss and dysfunction of glial cells [280–282].

To date, the results from preclinical research suggest that curcumin may benefit the brain and cognitive function during aging, but the level of evidence is still weak. One of the main limitations with curcumin studies and interventions is related to its limited bioavailability, a factor that could be addressed by chemical modification, conjugation with lipophilic compounds or coadministration with other compounds. No clinical trials to date provide conclusive evidence of the efficacy of long-term curcumin consumption for preventing or treating cognitive decline with aging. More studies are needed to explore the effects of this factor in persons with different genetic backgrounds and at different states of health and wellness.

4.2. Catechin Polyphenols. Found naturally in teas, catechin polyphenols are potent bioactive compounds with antioxidant [283, 284] and anti-inflammatory properties [285, 286]. Their ability to donate hydrogens and scavenge reactive oxygen and nitrogen species underlies their antioxidant capabilities [283, 284]. Among the catechins found in tea, (−)epigallocatechin-3-gallate (EGCG) is a major constituent and therapeutic agent. EGCG has been shown to have neuroprotective functions that include antioxidant, iron chelating, and anti-inflammatory properties [287, 288]. Also, EGCG promotes amyloid precursor protein processing via the nontoxic amyloid precursor pathway [289] to reduce amyloid-beta pathology [290]. EGCG also appears to modulate cell survival genes [291].

Emerging preclinical and clinical evidence has suggested that EGCG modulates mechanisms involved in learning and cognitive decline. EGCG facilitated glutamate release by enhancing Ca^{2+} entry through voltage-dependent Ca^{2+} channels in isolated nerve terminals from rat cerebral cortex, a process linked to protein kinase C (PKC) activation [289, 291, 292]. This ability is important because increased release of glutamate in the brain has been shown to be a proxy for learning and memory [293, 294]. EGCG also affected synaptic plasticity as high-frequency stimulation-evoked LTP was enhanced following preincubation of hippocampal slices with EGCG [295]. Another study has demonstrated that the application of EGCG modulated synaptic transmission and produced a dose-dependent improvement in the induction of LTP in the rat in vivo [296]. Moreover, long-term administration of green tea catechins to rats improved their reference and working memory-related learning ability and decreased reactive oxygen species concentrations in the hippocampus [297]. These results are not surprising given the relationship of EGCG to neurogenesis and BDNF: oral administration of EGCG enhances cell proliferation and increases the number of progenitor cells in the hippocampus of rodents [250, 251]. Submicromolar concentrations of EGCG (<0.1 μg/ml) of unfractionated green tea and low concentrations (<0.5 μM) of EGCG potentiated the neuritogenic ability of low-concentration BDNF [298].

Parallel study has investigated the effects of catechins in humans. A large-scale study of middle-aged adults investigated the long-term association between polyphenol intake and cognitive performance, finding that catechins were positively associated with language and verbal memory [299]. A study of community-living Chinese adults aged 55 years or older demonstrated that consumption of black and oolong tea was associated with lower risks of cognitive impairment and decline after a 1- to 2-year follow-up [300]. A cross-sectional study of community-dwelling Japanese adults aged 70 years or older examined the association between green tea consumption and cognitive function, finding that higher consumption of green tea was associated with a lower prevalence of cognitive impairment as assessed by the Mini-Mental State Examination [301]. In a small interventional study in healthy volunteers, increased brain activity on functional magnetic resonance imaging in the dorsolateral prefrontal cortex, a proxy for memory processing, was reported in a dose-dependent manner following administration of green tea [302]. The effects of green tea

consumption on the brain activity of healthy volunteers were measured using simplified EEG during passive activity in another study, with findings demonstrating significantly increased theta waves between 30 minutes and 1-hour post-consumption, suggesting a role for enhancing cognitive function [303].

4.3. Resveratrol. As a plant-based stilbene found in grapes, wine, and peanuts, resveratrol possesses significant free radical scavenging capabilities [304] given its three OH groups in positions 3, 4, and 5; aromatic rings; and a double bond in the molecule. Recently, it has garnered increased attention amidst reports of its neuroprotective and antiamyloid properties [305, 306] in rodents through mechanisms that likely involve oxidative stress [306], energy homeostasis [307], and neural plasticity [308, 309]. Bolstering this notion are cell culture studies that demonstrated that resveratrol reduced amyloid beta accumulation, ROS, and apoptosis [310] via modulation of nuclear factor-kB and Sirtuin 1 pathways [310–312]. Some preclinical studies suggest that resveratrol extends the lifespan [310, 313, 314]. For example, resveratrol increased cell survival by stimulating Sirtuin 2, a change that increased DNA stability, slowed aging, and extended the lifespan by 70% in yeast models [315]. Resveratrol added to the food of seasonal fish in early adulthood induced a dose-dependent increase of median and maximum lifespan [313]. Dietary consumption of resveratrol enhanced proliferative states in neuronal stem cells in the rat hippocampus [316]. Several parallel preclinical studies have demonstrated that resveratrol attenuated stress-induced learning deficits, depressive symptoms, and hippocampal degeneration by mechanisms that involved the restoration of BDNF [308, 309, 317–320]. Altogether, this preclinical data provides evidence that resveratrol treatment may be efficacious for improving mood and cognitive function.

Extending this line of investigation to humans, one small-scale, randomized, placebo-controlled, double-blind trial with Concord grape juice supplementation for 12 weeks demonstrated that older adults with memory decline but not dementia significantly improved in a measure of verbal learning [321]. Also, a double-blind, placebo-controlled study tested whether supplementation with resveratrol enhanced memory performance in older adults, finding that administration of 200 mg of resveratrol daily with 320 mg quercetin for six months duration in healthy older adults (50–80 years) effectuated greater hippocampal activity at rest (as assessed by functional magnetic resonance imaging) and improved memory performance [322]. Notwithstanding, low bioavailability of resveratrol is a major drawback [323]. Therefore, methods to enhance bioavailability (nanosized particles and oral lozenges) are being investigated [324–326].

4.4. Omega-3 Fatty Acids. Whereas transfats have deleterious effects in the brain, omega-3 fatty acids (found in oily fish such as salmon, mackerel, herring, anchovies, menhaden, and sardines) have neuroprotective effects. Omega-3 fatty acids [e.g., α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid (DHA)] are polyunsaturated fatty acids that are vitally involved in neuronal physiology. Among the omega-3 fatty acid family members is DHA, one of the most important because of its role in maintaining the structural balance of cell membranes, its ability to mediate phospholipid signal transduction at the synapse, and its ability to modulate enzymatic activity [327, 328]. Also, DHA stabilizes molecular mechanisms important for mitochondrial function [329], brain glucose utilization [330], and oxidative stress [331]. Dietary DHA also contributes to epigenetic changes that confer resilience to metabolic perturbations [332]. Notably, humans are reliant on consumption of dietary DHA from oily fish since the body is inefficient at synthesizing it. Clinical evidence suggests that dietary deficiencies can have adverse cognitive effects [333], yet one study demonstrated that less than half of women consume the recommended dietary allowance [334, 335], a trend that can be reversed with supplementation. Preclinical studies show that dietary restrictions in omega-3 fatty acids are associated with reductions in neuronal size and neurotrophin levels [336], whereas dietary supplementation reverses age-related impairments in LTP and depolarization-induced glutamate transmitter release [337], effectuates increased levels of hippocampal neurotrophin levels [331], and upregulates genes that are important for maintaining synaptic function and plasticity [338].

A number of studies on omega-3 fatty acids have been extended to humans. Epidemiological studies demonstrate that high intake of fish rich in polyunsaturated fatty acids is associated with positive cognitive function. Results from the Rotterdam study demonstrate that high fish intake is inversely associated with incident dementia at baseline and at 2-year follow-up [339]. Elderly persons in the PAQUID cognitive and functional aging study who ate fish or seafood at least once a week exhibited a significantly lower risk of developing dementia in the 7-year follow-up period [340]. Similarly, community-dwelling elders in the Chicago Health and Aging Project who were in the upper quintile for consumption of saturated fat had a twofold increased risk for AD as compared to persons in the lowest quintile [341], suggesting that high intake of unsaturated, unhydrogenated fats may be protective against AD. Another study investigated whether omega-3 fatty acid intake is correlated with gray matter volume in brain structures associated with emotional circuitry, finding positive associations between reported dietary omega-3 intake and gray matter volume in the subgenual anterior cingulate cortex, right hippocampus, and right amygdala, intimating a mechanism by which omega-3 fatty acid intake may mediate memory, mood, and affect regulation [342]. Other study demonstrated that weekly consumption of baked or broiled fish is positively associated with increases in gray matter volumes in the hippocampus, precuneus, posterior cingulate, and orbitofrontal cortex [343]. Moreover, adults with subjective memory impairment who were administered fish oil (eicosapentaenoic acid + DHA) for 24 weeks in a randomized, double-blind, placebo-controlled study exhibited increased cortical blood oxygen level-dependent activity in the right posterior cingulate and left superior frontal regions during a memory task as well as enhanced overall working memory performance [344], results that mirror earlier results of the

Framingham Heart Study wherein DHA levels in the top quartile were associated with a 47% lower risk of all-cause dementia [345]. Another study investigated the effects of DHA and arachidonic acid (240 mg/day of DHA and arachidonic acid) on cognition in amnesic patients and found that DHA supplementation improved cognitive dysfunction secondary to aging and organic brain pathology [346]. Finally, a recent study demonstrated that higher-fasting plasma levels of omega-3 polyunsaturated fatty acids correlated with larger gray matter volume within the left rostral anterior cingulate cortex, a characteristic that partially mediated the relationship between cognitive flexibility in at-risk (apolipoprotein E4 carriers) older adults [347].

Admittedly, a National Institute of Health State of the Science Conference panel previously concluded that there is insufficient evidence to recommend omega-3 fatty acids for age-related cognitive decline. Notwithstanding, there are ongoing clinical trials designed to elucidate efficacy, trials that may be chiefly beneficial for persons in the lower quartile of omega-3 consumption or in at-risk groups for cognitive decline [348].

4.5. Caloric Restriction and Intermittent Fasting. In the context of adequate consumption of nutrients, caloric restriction conveys lifespan and healthspan benefits, including preservation of cognitive function. Convergent evidence suggests that a reduction of caloric intake by 20–40% extends the lifespan of organisms throughout phylogeny [349]. Population studies in Danish and Norwegian men and women revealed that involuntary caloric restriction without malnutrition for periods of 2–4 years reduced overall mortality rates [350]. Moreover, it has been shown that centenarians from Okinawa consumed 17% fewer calories than average Japanese adults, and they consumed 40% fewer calories than American adults [333]. A recent review by Most and colleagues detailed the positive health benefits demonstrated from several recent randomized trials, reporting that caloric restriction in humans effectuate some of the same metabolic and molecular adaptations seen in preclinical models of longevity [351]. Finally, a 30% reduction in calories for 3 months has been associated with a 20% improvement in verbal memory in healthy elderly adults [352].

The mechanisms underlying caloric restriction appear to be multifold. Caloric restriction has been shown to increase cellular repair of DNA [353], reduce oxidative stress [354], improve the metabolism of glucose [355], and optimize immune [356] and neuroendocrine function [357, 358]. Moreover, caloric restriction counteracts age-related alterations in the expression of genes related to synaptic transmission [359]. For example, caloric restriction increases the expression of BDNF, TrkB, and NR2B subunits of NMDA receptors [359, 360] to mitigate age-related decrements in the hippocampus [361, 362]. Similarly, intermittent fasting exerts neuroprotective effects. It has been shown that synaptic resilience and function [363], levels of stress protein chaperones [364, 365], and neurotrophic factors [364] are increased following intermittent fasting, effects that may be particularly beneficial during times of injury [366].

5. Conclusions and Future Directions

Finding an effective treatment for age-related cognitive decline represents an unmet goal. However, considerable progress has been made in better understanding how PA and diet modulate common neuroplasticity substrates (neurotrophic signaling, neurogenesis, inflammation, stress response, and antioxidant defense mechanisms) in the brain [16]. Accordingly, this study highlights the importance of lifestyle modification for protecting cognitive function and brain health during aging and advocates for higher levels of PA and consumption of healthy foods to optimize neural plasticity. Once plasticity has been primed, cognitive training and rehabilitation can be used to facilitate the reorganization and proper function of cognitive circuits (to enhance brain reserve) and practice processing strategies and skills that translate to daily living (cognitive reserve). The deployment of techniques to optimize lifestyle are critical given the expanding size of the aging population juxtaposed with evidence that 97% of adults nationwide fail to exhibit healthy lifestyle characteristics [367]. Undoubtedly, the success of healthy lifestyle campaigns will require more emphasis on midlife, long-term, preventive approaches—with the goal of promoting positive health habits that delay progression and overt cognitive decline. Necessarily, these approaches should be paralleled by research that aims to disentangle the effects of lifestyle habits at different points along the aging and disease continuum.

Admittedly, large-scale, well-conducted, randomized controlled trials with PA, mental engagement, and dietary intake are only beginning to emerge. Undoubtedly, there is a need for future research in human populations that are well standardized and stratified in relation to genetic backgrounds, age, sex, and disease severity and duration. This research is needed to better understand the optimum mode, intensity, and duration of PA according to biologically distinct subgroups. Moreover, future studies will need to disentangle the individual and common pathways that exist between PA, mental activity, diet, social factors, and cognitive aging, particularly given evidence that various components may exert additive protection against cognitive decline [188]. In the area of cognitive rehabilitation, there remains a need to derive protocols whose outcomes reify as generalized, functional improvement in real-world environments [368]. While doing so, methodological standards will necessarily have to be considered more fully. It is known that noradrenergic function is essential for learning and memory [47] and that optimization of noradrenergic function (via PA or pharmacotherapeutics) during aging and disease [16, 47] may likely optimize learning and memory in certain populations (e.g., Down syndrome, Alzheimer's, and persons with mild cognitive impairment). Future studies should take into account the effects of noradrenergic function on cognitive training and rehabilitation outcomes in aging populations. Similarly, the duration of cognitive training and rehabilitation should be considered more fully. It is known that the effects of PA takes several weeks to reify at the behavioral level, a reflection of mechanisms that likely involve BDNF, neurogenesis, and the optimization of neurotransmitter

levels [16]. Thus, it seems likely that the deployment of PA prior to cognitive training and rehabilitation could be used to normalize these factors to enhance outcomes, a notion that awaits further study. Finally, a greater understanding of antioxidant status in regard to plasma and brain bioavailability is needed, as are studies that disentangle dose-response effects, safety, tolerability, efficacy, and interactions with other dietary factors. The latter studies are imperative as it seems likely that the effects of nutrients in the brain are the product of a mélange of metabolites and interacting factors, not isolated factors per se. Together, these future efforts will help to ensure that research at the frontiers of cognitive neuroscience will provide a personalized approach to intervention during states of health, disease, and aging.

In the interim, the Alzheimer's Association and the AARP have launched public health initiatives that aim to foster a greater awareness of strategies that can be deployed to optimize cognitive function during aging. The initiative of the Alzheimer's Association is called Maintain Your Brain and promotes brain-centered healthy lifestyle choices (e.g., maintaining physical, mental, and social activity levels while concomitantly consuming a low-fat diet rich in antioxidants) [369]. Similarly, the AARP initiative, called Staying Sharp, encourages aging individuals to engage in a lifetime of learning and provides strategies to augment memory [370]. While neither program has been evaluated long-term, preliminary results from a two-year, multidomain, randomized, controlled study designed to prevent cognitive impairment are promising. The intervention consisted of PA, cognitive training, nutritional guidance, and social activities along with the management of vascular risk factors. The control group received regular health advice. After 2 years, a comprehensive neuropsychological test battery revealed a significant beneficial intervention effect on overall cognitive performance, including the domains of memory, executive function, and psychomotor speed. This novel study demonstrates the possibility of preventing cognitive decline using a multidomain intervention among older at-risk individuals [371]. It also highlights the importance in convincing patients of the value of a healthy lifestyle while concomitantly underscoring the importance of preventive public health policy.

Abbreviations

AARP: American Association of Retired Persons
ACTH: Adrenocorticotropic hormone
AD: Alzheimer's disease
BDNF: Brain-derived neurotrophic factor
CRH: Corticotropin-releasing hormone
CRP: C-reactive protein
DHA: Docosahexaenoic acid
EGCG: (−)epigallocatechin-3-gallate
HPA: Hypothalamic-pituitary-adrenal axis
IL: Interleukin
LTP: Long-term potentiation
PA: Physical activity
ROS: Reactive oxygen species
TNF: Tumor necrosis factor.

Conflicts of Interest

No conflict of interest is declared.

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Research Article

Exercise Modality Is Differentially Associated with Neurocognition in Older Adults

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This study explored the effects of exercise modality and type of fitness index on cognitive function in the older adults as assessed via behavioral and neuroelectrical approaches. Sixty older adults were assigned to an aerobic exercise, a coordination exercise, or a control group based on their previous exercise experience. The participants completed congruent and incongruent trials of a modified Stroop Test, during which, event-related potentials were recorded. The participants also completed multiple physical tests that assessed health- and skill-related fitness. Our findings suggest that, in general, both aerobic and coordination exercise, as well as higher scores on health- and skill-related fitness indices, are positively associated with better performance of various cognitive functions in the elderly population. The mechanisms underlying these relationships may be differentially related to specific neuroelectrical processes involved in neurocognitive control.

1. Introduction

Although aging is generally accompanied by the deterioration of multiple facets of cognition [1], extensive research has demonstrated that older adults who regularly engage in physical exercise or who possess a high level of fitness experience a reduced degree of cognitive decline or show improvements in cognitive function. The positive relationships between physical exercise, fitness, and cognitive function have been further demonstrated by a meta-analysis that showed a significant positive effect with the small to large in magnitude [2–4].

The benefits of physical exercise and fitness on cognitive function appear to be disproportionally distributed. Colcombe and Kramer [3] indicated that although exercise training leads to improvements in multiple aspects of cognitive function (i.e., executive function, controlled, spatial, and speed aspects), the executive function aspect of cognition displays the largest enhancement, suggesting that exercise training impacts different types of cognition not only generally but also specifically. Executive function refers to high-level hierarchical cognitive processing that involves inhibitory control, task switching, and working memory [5] to achieve purposeful or goal-directed behavior, particularly in novel situations [6]. The disproportionate improvement in executive function that results from exercise training or fitness in older populations is interesting because executive function is particularly vulnerable to age-related cognitive decline [1]. However, a subsequent meta-analysis indicated that exercise training is moderately associated with cognitive improvements, regardless of whether executive function, attention, processing speed, or memory is considered [7]. This finding demonstrates that the modulatory effects of exercise training on cognitive function remain unclear.

One possibility worth considering is whether exercise modality modulates the relationship between exercise and cognition. The majority of studies have investigated either

aerobic exercise (AE) or cardiovascular fitness. Pesce [8] argued the importance of shifting the emphasis from quantitative to qualitative exercise characteristics to advance our understanding of the exercise-cognition relationship. Nonetheless, the effects of other modalities, such as coordination exercise (CE), that involve a variety of exercise characteristics (e.g., muscular strength and endurance, motor coordination, agility, flexibility, and visual-spatial perception) on cognition have received only little or indirect attention until recently. For example, relative to their nonexercising counterparts, older adults in both closed-skill (e.g., jogging) and open-skill (e.g., table tennis) groups demonstrated superior cognitive performances in terms of inhibitory control [9] and task switching [10], which are both aspects of executive function. A similar facilitation of task switching was observed in older adults in both AE and mind-body CE (i.e., Tai Chi Chuan) groups compared with the control [11]. Notably, open-skill exercise and Tai Chi Chuan might be confounded by factors related to environment prediction and light intensity or to the exercise characteristics of meditation. Therefore, the current study replicates and extends existing knowledge by examining the effects of CE that is more closed-skill and more intense than Tai Chi Chuan and that involves less meditation (i.e., routine-based Chinese martial arts).

Cardiovascular fitness has been recognized as a primary behavioral mediator and moderator of AE and cognition. Although cardiovascular fitness is an essential fitness index, it is only one of many fitness indices. Fitness is a multifaceted concept that includes both health-related fitness, involving cardiovascular endurance, muscular strength, muscular endurance, flexibility, body composition, and flexibility, and skill-related fitness, involving agility, power, coordination, balance, reaction time, and speed [12]. Although the relationships between each of these other fitness types and cognition are not yet fully understood [13], a few recent neuroimaging studies showed that both physical fitness (i.e., cardiovascular and muscular strength) and motor fitness indices (i.e., flexibility, motor coordination, movement speed, and balance) not only were positively associated with cognitive performance but also elicited activity in different brain regions [14]. Utilizing cross-sectional and longitudinal approaches, recent neuroimaging studies revealed that both physical and motor fitness are associated with superior and more efficient information processing and enlarged volumes of cognition-related brain areas such as the hippocampus and the basal ganglia [15, 16]. These findings of positive alterations in brain function and structure suggest that types of fitness other than cardiovascular fitness may be positively associated with cognitive performance. However, these studies categorized two types of fitness indices within the category of physical fitness and categorized health- and skill-related fitness indices within the category of motor fitness. As such, the relationships between specific fitness indices and cognition have yet to be determined.

Neuroelectrical studies using event-related potentials (ERPs) have provided insight beyond overt behavioral responses into the potential mechanisms underlying the relationships among exercise, fitness, and cognition [17, 18]. ERPs are characterized by high temporal sensitivity between stimulus engagement and response execution and are believed to reflect implicit and distinct cognitive processes that are reflected by specific ERP components. For example, P3, a positively deflecting waveform that occurs between 300 and 600 ms following stimulus onset, represents the amount of attentional resources allocated to a given task [19]. Previous ERP studies have revealed positive relationships between exercise and neurocognitive performance in executive function-related tasks; older adults with a higher fitness status or who are more engaged in physical activity demonstrate greater P3 amplitudes than those with a lower fitness status or who are less engaged in physical activity, respectively [17, 18, 20, 21]. Similarly, larger P3 amplitudes were recently observed in older adults engaged in either AE or CE compared with controls, with no difference in P3 amplitude between these two modalities [10, 11]. These results suggest that exercise enhances neuroelectrical activation that is related to higher cognitive performance regardless of the exercise modality and fitness type. Although P3 has been extensively examined, the utilization of executive tasks and the study of exercise and other ERP components have been limited. The current study utilized the Stroop Test, a widely used and recommended neuropsychological assessment of executive function [6, 22]. In the Stroop Test, subjects in the incongruent condition, in which the name of the color is different from the meaning of the word, show increased reaction times and decreased accuracy compared with their performance under the congruent condition, in which the name of the color is the same as the meaning of the word. These behavioral differences are believed to be associated with the inhibition aspect of executive function [22, 23]. The combination of the ERP paradigm with the Stroop Test not only incorporates congruent and incongruent trials that reflect information processing and executive function, respectively, but also elicits late (i.e., P3 and N450) and early components (i.e., N1 and N2) [24], facilitating the simultaneous evaluation of the nature of cognitive function and multiple ERP components.

Accordingly, the purposes of the current study were to investigate (a) whether AE and CE are generally or specifically associated with multiple cognitive functions as assessed by the Stroop Test, (b) the correlations between cognitive functions and cardiovascular fitness versus other health-related (i.e., muscular strength and endurance, body composition, and flexibility) and skill-related fitness measures (i.e., agility and power), and (c) the mechanisms underlying the effects of AE and CE on executive-function task performance based on the time course of early and late neuroelectrical activation. It was predicted that individuals engaged in exercise of two modalities would demonstrate superior cognitive performance, both generally and specifically. It was also predicted that fitness, regardless of type, would correlate positively with cognitive performance. Finally, we predicted that exercise of both modalities would not only induce a larger P3 amplitude during a cognitive task but would also affect other ERP components that reflect different aspects of neuroelectrical processing.

Table 1: Participant demographic and fitness data for the three groups (mean ± SD).

Measures	Group		
	Control ($n = 20$)	Coordination ($n = 20$)	Aerobic ($n = 20$)
Female/male	5/15	7/13	10/10
Age (year)	57.51 ± 3.68	59.15 ± 4.62	58.80 ± 3.82
Height (cm)	159.13 ± 0.15	162.52 ± 0.31	161.55 ± 0.01
Weight (kg)	67.1 ± 9.52	63.62 ± 9.77	61.22 ± 6.84
Education	9.30 ± 3.62	10.01 ± 0.12	9.52 ± 2.12
MMSE	27.71 ± 2.31	27.82 ± 1.01	28.23 ± 2.60
Resting HR	66.30 ± 11.00	67.41 ± 12.14	65.25 ± 5.29
WAIS-III			
Digit forward span test	12.00 ± 2.43	12.45 ± 1.82	12.55 ± 2.35
Digit backward span test	6.30 ± 1.71	6.40 ± 1.86	6.30 ± 2.83
Digit span total	17.50 ± 3.50	18.85 ± 2.30	19.15 ± 4.68
Exercise characteristics			
Exercise years	0.10 ± 0.31	3.80 ± 1.47	3.20 ± 1.24
Exercise duration/session	0.11 ± 0.00	1.80 ± 0.41	1.85 ± 0.86
Session/week	0.01 ± 0.00	1.15 ± 0.81	1.85 ± 0.75
Fitness data			
VO_{2peak} (mL/kg min)	26.91 ± 6.14	33.67 ± 8.24	41.16 ± 9.73
Muscular strength	51.45 ± 17.72	71.40 ± 20.01	71.65 ± 20.49
Muscular endur./press-up	2.50 ± 3.71	11.40 ± 10.81	12.70 ± 9.80
Muscular endur./CCU 30	4.10 ± 4.18	11.25 ± 5.025	12.95 ± 6.35
Muscular endur./CCU 60	5.70 ± 5.76	19.60 ± 8.55	20.35 ± 11.63
Flexibility (cm)	24.90 ± 11.43	37.20 ± 7.58	35.60 ± 9.51
% body fat mass	30.17 ± 6.58	25.41 ± 5.47	24.97 ± 4.60
Agility (sec)	25.10 ± 6.05	18.12 ± 2.85	18.24 ± 2.67
Power (cm)	21.65 ± 7.85	31.95 ± 7.38	33.35 ± 12.56

MMSE: Mini-Mental State Exam; Muscular endur.: muscular endurance; WAIS-III: Wechsler adult intelligence scale-third edition.

2. Materials and Methods

2.1. Participants. Healthy older adults were recruited via flyers posted in universities, communities, hospitals, parks, jogging clubs, and Chinese Martial Art/Kung Fu establishments (clubs for routine-based Chinese martial arts that involve a series of complex and intense motor skills). Participant referrals were also received from the greater New Taipei and Taipei regions of Taiwan. Eligible participants met the following initial criteria: (a) age between 55 and 70 years, (b) score ≥ 26 on the Mini-Mental State Exam (MMSE), (c) no psychiatric or neurological disorders, (d) no history of stroke or head injury, (e) normal or corrected-to-normal vision without color blindness, (f) right hand dominance, and (g) score ≥ 7 on the Physical Activity Readiness Questionnaire (PAR-Q).

The participants in the AE and CE groups were required to meet additional criteria based on a self-reported exercise experience survey. The AE and CE groups included older adults who regularly participated in AE (i.e., jogging, walking, and/or swimming) and CE (i.e., Chinese Marital Art and/or Tai Chi Chuan), respectively, for at least 30 minutes per session and three times per week for the previous 6 months. The control group included older adults who irregularly participated in exercise (i.e., less than two times per week). Each group included 20 participants, with a total of 60 participants. The sample size was sufficiently sensitive to reveal differences in cognitive function according to the G*Power 3 method based on Colcombe and Kramer [3]. All of the participants read and signed an informed consent form that was approved by the Institutional Review Board of National Taiwan University. Table 1 presents the participant demographic, exercise experience, and fitness data.

2.2. Assessment of Health-Related Fitness

2.2.1. Cardiorespiratory Fitness. Cardiovascular fitness was evaluated based on estimated peak oxygen consumption (VO_{2peak}) using the submaximal exercise test of the YMCA cycle ergometry protocol [25]. This protocol, recommended for individuals of a Class A risk stratification [26], consisted of two to four three-minute stages with a progressively increasing workload. VO_{2peak} was estimated based on the slope of the heart rate, the workload, and the body weight. During testing, objective and subjective assessments of exercise intensity were conducted using a Polar heart rate monitor (Sport Tester PE 3000, Polar Electro Oy, Kempele,

Finland) and a 6- to 20-point version of the rating of perceived exertion (RPE) scale, respectively [27].

2.2.2. Muscular Fitness. Muscular strength was defined as the average hand force assessed with a handgrip dynamometer (three attempts each for the left and the right hand). Muscular endurance was defined as the number of push-ups (regular push-ups for males and knee push-ups for females) in one minute and the number of abdominal crunches/curl-ups in 30 seconds for males and 60 seconds for females.

2.2.3. Flexibility and Body Composition. Flexibility was assessed using the YMCA sit-and-reach test and was reported relative to the distance (cm) between the hamstring and the lower back. Body composition was presented as the body mass index and was measured by bioimpedance spectroscopy (InBody 3.0 DS12B887, Dallas, TX, USA) by determining the percentage of body fat mass.

2.3. Assessment of Skill-Related Fitness. The skill-related fitness measures agility and power were evaluated as the time to complete the T-test and the distance of the vertical jump test, respectively [28]. During the T-test, each participant was asked to jump to different corners arranged as T-figures. During the vertical jump test, participants were asked to jump from a static position as fast and as high as possible.

2.4. Stroop Test. This task was modified from the Stroop Color-Word task [29] and consisted of 6 blocks of 60 trials. The task involved two types of trials: congruent and incongruent. In the congruent trials, one of three Chinese color words (紅RED, 綠 GREEN, and 藍 BLUE) was presented, printed in the same color ink (e.g., RED printed in red ink). Incongruent trials consisted of one of the same three words printed in a different ink color (e.g., RED printed in green ink). One-third of the trials were incongruent, and the remaining trials were congruent; the trials were randomly presented. In each trial, a fixation cross (+) appeared in the center of the screen for 506 ms and followed by stimulus presentation for 500 ms. The participants were instructed to respond based on the color of the ink and to ignore the meaning of the word by pressing one of the three colored buttons on a response pad. The button colors corresponded to ink colors. The response was considered as incorrect if no response was recorded within 1000 ms following stimulus presentation. The stimuli were $2\,cm^2$ in size and were presented in the center of a 15-inch screen, with a visual angle of $28.14 \times 1.4^\circ$. All of the participants performed 20 practice trials prior to beginning the official task. The reaction times and the accuracy of each participant were recorded and analyzed as the behavioral outcome measures.

2.5. EEG Recording and ERP Measures. All participants were instructed to sit in a comfortable chair in an electrically shielded electroencephalography (EEG) recording chamber with attenuated sound levels. The participants focused on the center of the screen and made minimal body movements during the recording. The EEG data were recorded from 32 Ag/AgCl electrodes embedded in an elastic cap (Quick-Cap, NeuroScan Inc.) and positioned in accordance with the standard 10–20 system [30]. During recording, the impedance of all electrodes was maintained at or below 10 kΩ. Online EEG recording data were referenced to the left and right mastoids, and the AFz electrode site served as the ground. The EEG data were sampled at 1000 Hz, filtered using an online band-bass filter (0.05–70 Hz), and DC-amplified. A 60 Hz notch filter was applied using a SynAmps^2 amplifier system. Electrooculographic (EOG) activity was recorded using two additional sets of electrodes, which were located at the outer canthus of each orbit and above and below the left orbit. These sets of electrodes recorded the horizontal and vertical electrooculograms.

The offline EEG data were corrected for ocular artifacts using the eye movement correction algorithm of the NeuroScan software. The stimulus-locked epochs acquired for the Stroop trials were extracted offline from 200 ms prestimulus onset to 1000 ms poststimulus onset, and the period from 100 to 0 ms prestimulus onset was used as the baseline. The data were filtered using a zero phase shift, 30 Hz (12 dB/oct) low-pass filter. Trials were rejected if the response was incorrect or if the voltage exceeded $\pm 100\,\mu V$. Following the offline analysis processes, ERP data from six participants were excluded (two from the control group and four from the CE group). The grand average waveform across all accepted trials was calculated. The poststimulus onset time windows used for the calculation of the mean amplitude of each ERP component at Fz, Cz, and Pz were 80–150 ms for N1, 200–300 ms for N2, 350–550 ms for P3, and 400–500 ms for N450. The topographic distribution of the specific components across all of the electrode sites is presented.

2.6. Procedure. The participants were required to come to the laboratory of National Taiwan Sport University. Eligibility was assessed using a demographic questionnaire, a health-screening questionnaire, the MMSE, the PAR-Q, and a survey about exercise experience. The eligible participants were administered with the digit-span test of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) to assess the working memory component of intelligence [31] and were instructed to conduct the Stroop Test during EEG recording. Following the completion of cognition testing, the electrodes were removed, and body composition, muscular-related fitness, and flexibility were measured by trained experimenters, followed by measurements of agility, power, and cardiorespiratory fitness. The experimental procedure spanned approximately two hours. The participants were informed of the purpose of the study and received $30 in remuneration.

2.7. Statistical Analysis. The characteristics of the participants were compared among the three groups using a one-way analysis of variance (ANOVA). The behavioral measures of reaction time and accuracy were assessed separately via a 3 (Group: control, CE, AE) × 2 (Stroop congruency: congruent, incongruent) repeated-measures ANOVA. Pearson product-moment correlations were used to examine the associations between the fitness variables and the behavioral measures. The neuroelectrical measures for each ERP component

Table 2: Behavioral and neuroelectrical data for the two congruency conditions in the three groups (mean ± SEM).

Measures	Group		
	Control	Coordination	Aerobic
Reaction time (ms)			
Congruent trial	651.69 ± 14.24	570.89 ± 14.24	565.01 ± 14.24
Incongruent trial	738.89 ± 19.78	647.43 ± 19.78	636.31 ± 19.78
Accuracy (%)			
Congruent trial	0.96 ± 0.01	0.97 ± 0.01	0.96 ± 0.01
Incongruent trial	0.81 ± 0.02	0.93 ± 0.02	0.91 ± 0.02
N1 amplitude (μV)			
Congruent trial	−1.76 ± 059	−1.18 ± 0.63	0.03 ± 0.56
Incongruent trial	−2.18 ± 058	−1.31 ± 0.61	−0.73 ± 0.55
N2 amplitude (μV)			
Congruent trial	4.13 ± 1.4	4.23 ± 1.49	10.76 ± 1.33
Incongruent trial	3.77 ± 1.1	4.16 ± 1.16	9.74 ± 1.04
P3 amplitude (μV)			
Congruent trial	5.52 ± 1.23	11.45 ± 1.3	17.39 ± 1.16
Incongruent trial	4.42 ± 0.62	9.69 ± 0.66	14.03 ± 0.59
N450 amplitude (μV)			
Congruent trial	5.94 ± 1.2	11.92 ± 1.27	17.54 ± 1.14
Incongruent trial	4.82 ± 0.64	10.07 ± 0.68	14.35 ± 0.61

(i.e., N1, N2, P3, and N450) were analyzed separately using a 3 (Group) × 2 (Stroop congruency) × 3 (Site: Fz, Cz, and Pz) repeated-measures ANOVA. Multiple pairwise comparisons were Bonferroni-corrected and applied for post hoc comparison. Statistical values were presented following Greenhouse-Geisser corrections, in which a partial eta-square (η_p^2) value was provided for the significant effects. The family-wise alpha value of 0.05 was set prior to Bonferroni adjustment.

3. Results

3.1. Participant Characteristics. One-way ANOVA revealed significant differences among groups only for the fitness-related variables (Table 1, $p < 0.001$). Post hoc comparison indicated that the VO_{2peak} value of the AE group was significantly higher than the values of the CE and control groups and that the VO_{2peak} value of the CE group was significantly higher than that of the control group. Muscular strength, endurance, flexibility, and power were significantly higher in both the AE and CE groups than in the control group, whereas no differences were observed between the AE and CE groups. In addition, higher % body fat mass was observed in the control group than those in the AE and CE groups. Regarding agility, the AE and CE groups were significantly faster than the control group, with no difference observed between the AE and CE groups.

3.2. Behavioral Measures. Table 2 summarizes the behavioral and neuroelectrical values (mean and SE) for the two congruency conditions across the three groups.

3.2.1. Reaction Time. Two-way ANOVA revealed a main effect of Group ($F_{2,57} = 9.82$, $p < 0.001$, $\eta_p^2 = 0.26$), with a shorter reaction time for each of the AE and CE groups than that for the control group ($p < 0.002$ for both), and a main effect of Stroop congruency ($F_{1,57} = 258.42$, $p < 0.001$, $\eta_p^2 = 0.82$), with a longer reaction time under the incongruent condition than that under the congruent condition ($p < 0.001$) (Figure 1(a)).

3.2.2. Accuracy. Two-way ANOVA revealed a main effect of Group ($F_{2,57} = 4.06$, $p < 0.02$, $\eta_p^2 = 0.16$) and a main effect of Stroop congruency ($F_{1,57} = 43.33$, $p < 0.001$, $\eta_p^2 = 0.43$) that was superseded by a Group × Stroop congruency interaction ($F_{2,57} = 8.25$, $p < 0.001$, $\eta_p^2 = 0.23$). Post hoc comparison indicated higher accuracy in the AE and CE groups than that in the control group under the incongruent condition ($p < 0.02$ for both), whereas no difference in accuracy was found among the three groups under the congruent condition. In addition, higher accuracy was observed under the congruent condition than under the incongruent condition in the control and CE groups ($p < 0.02$ for all), but not in the AE group (Figure 1(b)).

3.2.3. Correlation Analysis. Table 3 summarizes the Pearson product-moment correlations between the fitness variables and the behavioral measures. Generally, VO_{2peak}, muscular strength, muscular endurance, and power were negatively correlated with reaction time under both the congruent and incongruent conditions ($p < 0.02$ for all). Agility and body composition were positively correlated with reaction time under both the congruent and incongruent conditions ($p < 0.004$ for all). However, no significant relationship between flexibility and reaction time was observed.

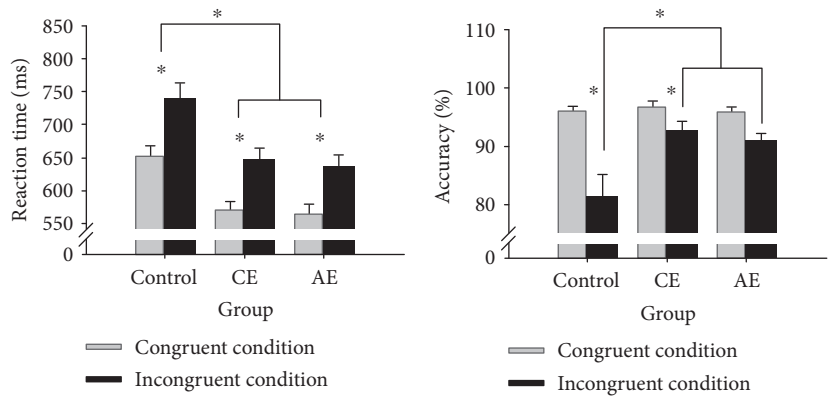

Figure 1: A comparison of the behavioral measures according to Stroop congruency for the three groups: (a) reaction time; (b) accuracy. The data are presented as the means ± SEM. $^{*}p < 0.05$. CE = coordination exercise; AE = aerobic exercise.

Table 3: Pearson product-moment correlation matrix for the fitness variables and the behavioral measures.

Measures	1	2	3	4	5	6	7	8	9
(1) VO_{2max}	1								
(2) Muscular strength (+)	0.48**	1							
(3) Muscular endur./press-up (+)	0.47**	0.58**	1						
(4) Muscular endur./CCU 30 (+)	0.41**	0.65**	0.64**	1					
(5) Muscular endur./CCU 60 (+)	0.44**	0.61**	0.6**	0.96**	1				
(6) Flexibility (+)	0.22*	0.25*	0.29*	0.32**	0.3*	1			
(7) Agility (−)	−0.48**	−0.43**	−0.49**	−0.62**	−0.62**	−0.4**	1		
(8) Power (+)	0.62**	0.81**	0.59**	0.7**	0.72**	0.2	−0.6**	1	
(9) Body composition (−)	−0.53**	−0.57**	−0.47**	−0.41**	−0.42**	0.03	0.49**	−0.72**	1
(10) Accuracy (%) Cong. (+)	0.16	0.04	−0.09	−0.14	−0.15	−0.04	−0.14	0.08	−0.23*
(11) Accuracy (%) Incong. (+)	0.29*	0.21	0.25*	0.1	0.15	0.18	−0.28*	0.28*	−0.34**
(12) Reaction time (ms) Cong. (−)	−0.27*	−0.32**	−0.45**	−0.36**	−0.39**	−0.16	0.37**	−0.39**	0.42**
(13) Reaction time (ms) Incong. (−)	−0.24*	−0.27*	−0.41**	−0.31**	−0.36**	−0.09	0.34**	−0.35**	0.34**

Cong.: congruent condition; Incong.: incongruent condition. $^{*}p < 0.05$; $^{**}p < 0.01$.

3.3. ERP Measures. Figure 2 illustrates the grand average ERP waveform of each Stroop congruency for each group and the interaction between Stroop congruency and Group. Figure 3 illustrates the topographical distribution of each ERP component (i.e., N1, N2, P3, and N450) across the global scalp for the three groups.

3.3.1. Mean N1 Amplitude. Three-way ANOVA revealed a main effect of Site ($F_{2,102} = 32.98$, $p < 0.001$, $\eta_p^2 = 0.39$), which was superseded by a Site × Stroop congruency × Group interaction ($F_{4,57} = 3.55$, $p < 0.02$, $\eta_p^2 = 0.12$). Post hoc comparisons indicated greater N1 amplitude for Cz and Pz than that for Fz in the three groups ($p < 0.008$ for all) and under both congruency conditions ($p < 0.001$ for all). No other significant main effects or interactions were revealed.

3.3.2. Mean N2 Amplitude. Three-way ANOVA revealed main effects of Group ($F_{2,51} = 9.03$, $p < 0.001$, $\eta_p^2 = 0.26$) and Site ($F_{2,102} = 23.83$, $p < 0.001$, $\eta_p^2 = 0.32$), which were superseded by a Group × Stroop congruency interaction ($F_{4,102} = 4.20$, $p < 0.007$, $\eta_p^2 = 0.14$). Post hoc comparisons indicated a smaller N2 amplitude in the AE group than in the CE and control groups under both congruency conditions ($p < 0.004$ for both). No other significant main effects or interactions were revealed.

3.3.3. Mean P3 Amplitude. Three-way ANOVA revealed main effects of Group ($F_{2,51} = 39.16$, $p < 0.001$, $\eta_p^2 = 0.61$) and Stroop congruency ($F_{1,51} = 18.89$, $p < 0.001$, $\eta_p^2 = 0.27$), which were superseded by a Group × Stroop congruency interaction ($F_{4,102} = 7.89$, $p < 0.001$, $\eta_p^2 = 0.24$). Post hoc comparisons indicated that the greatest P3 amplitude was observed in the AE group, followed by the CE group ($p < 0.005$) and the control group ($p < 0.005$), under both congruency conditions. However, a difference in P3 amplitude between the congruent and incongruent conditions was only observed in the AE and CE groups ($p < 0.05$ for both), not in the control group. No other significant main effects or interactions were revealed.

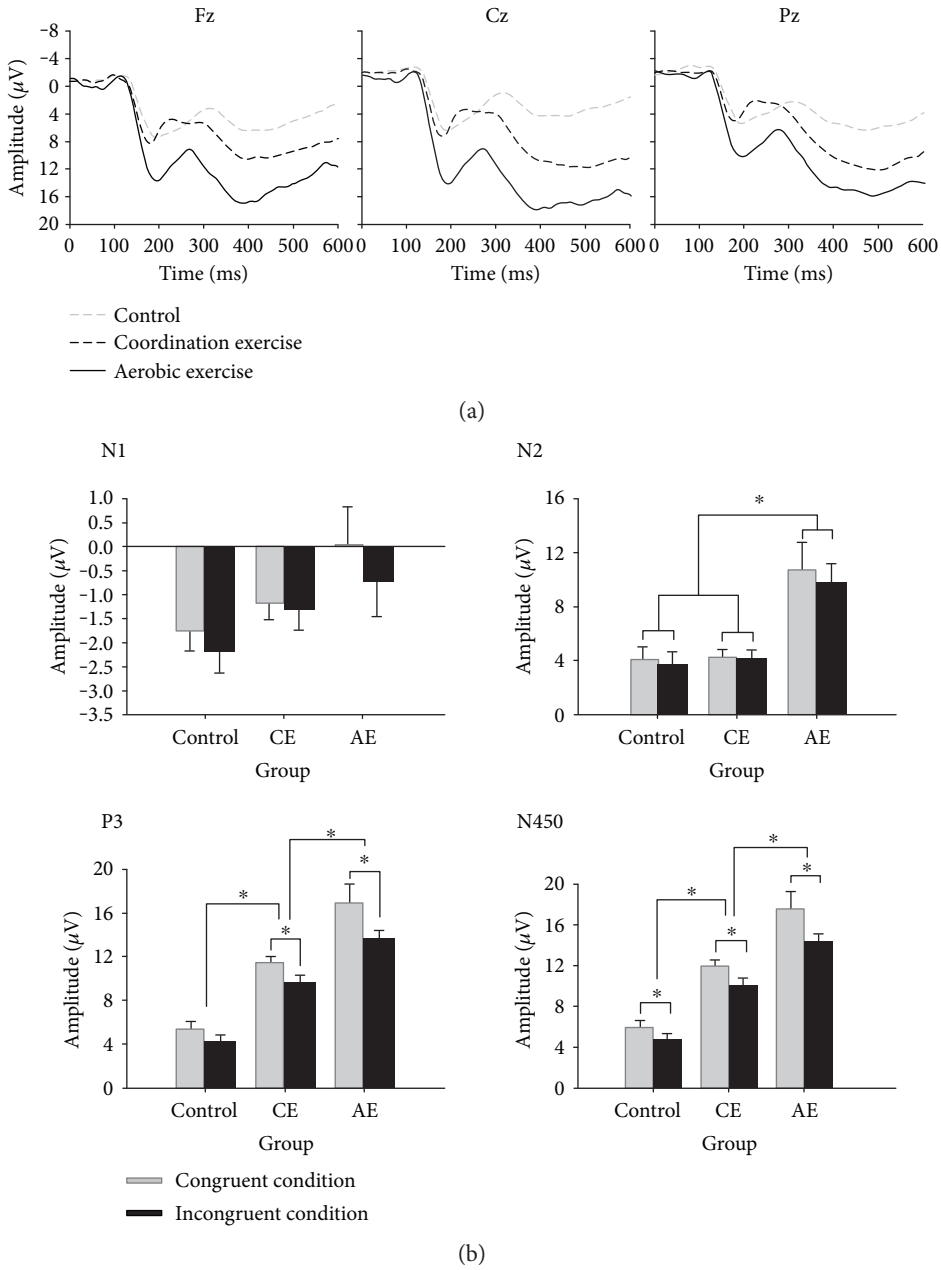

Figure 2: (a) Grand average ERP waveform of averaged Stroop congruency in each group at the Fz, Cz, and Pz electrode sites. (b) Interaction effect between Stroop congruency and group for each ERP component on N, N2, P3, and N450. CE = coordination exercise; AE = aerobic exercise. $^{*}p < 0.05$.

3.3.4. Mean N450 Amplitude. Three-way ANOVA revealed a main effect of Group ($F_{2,51} = 37.11$, $p < 0.001$, $\eta_p^2 = 0.59$), which was superseded by a Group × Site interaction ($F_{4,102} = 7.16$, $p < 0.001$, $\eta_p^2 = 0.22$). Post hoc comparisons indicated that the smallest N450 amplitude was observed in the AE group, followed by the CE group ($p < 0.02$ for all) and the control group ($p < 0.02$ for all), for all three sites. In addition, although no differences in N450 amplitude were found among the three sites in the CE group, Fz and Pz displayed higher N450 amplitudes than did Cz in the AE and control groups. The analysis also revealed a main effect of Stroop congruency ($F_{1,51} = 22.70$, $p < 0.001$, $\eta_p^2 = 0.31$), with a greater N450 amplitude under the incongruent condition than under the congruent condition ($p < 0.001$). No other significant main effects or interactions were revealed.

4. Discussion

The current study, which investigated exercise-cognition relationships in older adults, is among the first to examine the modulatory role of exercise modality on cognitive function, as assessed by the Stroop Test, from behavioral and neuroelectrical perspectives. The major finding was that

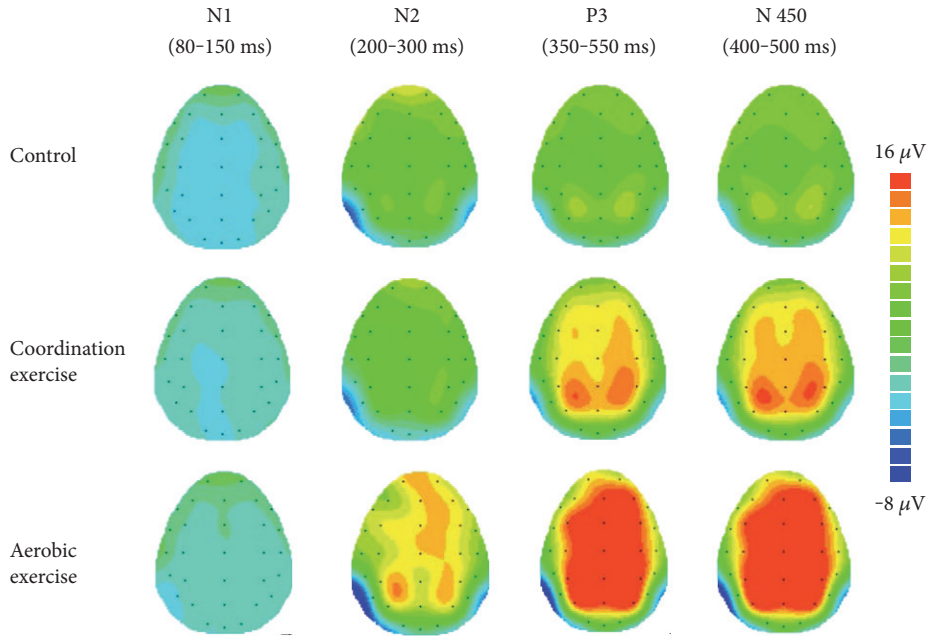

Figure 3: Topographic distribution of each ERP component (i.e., N1, N2, P3, and N450) across the global scalp for the three groups.

the AE and CE groups both demonstrated shorter reaction times than those of the control group in both the congruent and incongruent trials. In addition, higher ratings on all the health- and skill-related fitness indices except flexibility were positively associated with cognitive performances, and positive relationships between fitness and cognition were observed regardless of the type of cognitive function assessed. Examination of the time course of the ERP components indicated that the AE group exhibited the largest P3 amplitude and the smallest N2 and N450 amplitudes compared with the corresponding amplitudes of the other two groups. The CE group exhibited a larger P3 amplitude and a smaller N450, but not N2, amplitude than did the control group. However, no difference in N1 amplitude was observed among the three groups.

Our first aim was to test whether exercise modality was associated with cognition either generally or specifically. The prolonged reaction times and reduced accuracies observed in the incongruent trials suggest that these trials require greater cognitive demand than do the congruent trials, possibly due to interference. The observed differences between the congruent and incongruent trials not only represent the typical "Stroop interference effect" but also demonstrate the appropriateness of our task manipulation. Additionally, along with the finding of an increase or no change in accuracy between each exercise group and the control group, the association of superior cognitive performance with exercise in both types of congruency trials excludes the possibility of a speed-accuracy tradeoff. Although these results contrast to some degree with the specific improvement hypothesis, our findings agree with empirical studies that showed similar improvements in performance on the flanker task for congruent and incongruent trials [20] and on working memory task with different loads [21], suggesting a general improvement associated with AE.

However, a novel finding of the present study was that CE elicited similar positive effects as AE on the behavioral measures. That is, general improvements in behavioral cognitive performance were exhibited by older adults in the CE group as well as those in the AE group. These findings from the Stroop Test extend the findings of previous studies that focused on the effect of CE on performance on the flanker task [14, 32] and the effects of open-skill exercise and light-intensity CE on performance on a task-switching test [10, 21]. These results might be particularly important because Stroop Test performance has been revealed to decline with age [33]. CE that involves a variety of exercise characteristics may enable environmental enrichment to increase cognitive performance. An extensive rodent study has shown that environmental enrichment consisting of repeated exercise, complex motor skills, cognitive stimulation, and/or social interaction has a positive effect on neurogenesis, neurotrophin expression, and synaptic plasticity involved in memory and learning [34]. Furthermore, an enriched environment leads to more cell proliferation than running exercise alone [34], suggesting an association between complex exercise modalities and cognition. Taken together, these findings suggest that the positive associations between exercise and cognition in older adults are independent of cognitive function type, executive function type, and exercise modality.

Although both exercise groups demonstrated better fitness index values than the control group, the AE and CE groups exhibited higher cardiovascular fitness and greater flexibility, respectively. These findings suggest that the relationship between exercise modality and cognition may be interpreted from the perspective of fitness type [16, 32], which was our second aim. Our findings demonstrated that cognitive function, as assessed by the Stroop Test, was positively correlated with each of the cardiovascular,

muscular (i.e., strength and muscular endurance), body composition, and agility fitness indices. Thus, our study provides the first demonstration that, with the exception of flexibility, fitness is associated with improved cognitive performance regardless of whether the measures are health- or skill-related fitness indices. Although both types of fitness demonstrated similar positive effects on cognition, the brain plasticity associated with the fitness indices and cognition might differ. For example, greater hippocampal volume was observed in older adults with high cardiovascular fitness [35] or high motor fitness [16] compared with the volume in their less-fit counterparts. In contrast, the volume of basal ganglia, which is responsible for the early stages of motor learning and the processes of executive function, was positively associated only with motor fitness and mediated the association between motor fitness and executive function [16]. Similarly, physical fitness (i.e., cardiovascular and muscular fitness) is primarily related to the activation of sensorimotor cortical areas, whereas motor fitness indices are primarily related to the activation of visuo-motor and visuo-spatial networks [14, 32]. In contrast, older adults who follow long-term resistance exercise interventions demonstrate better cognitive performance but display smaller frontal and temporal brain volumes [36]. These findings suggest differential neuromodulation with respect to the type of fitness. Future study is warranted, including the simultaneous examination of health- and skill-related fitness and cognitive functions using a neuroimaging approach.

Another novel aspect of the current study was the monitoring of the time course of ERPs, including both late (i.e., P3 and N450) and early components (i.e., N1 and N2). Our P3 findings replicate and extend previous results showing a positive association between P3 and exercise [17, 18, 20, 21]. In the present study, older adults in the AE group exhibited a larger P3 amplitude than those in the control group. Notably, the P3 amplitudes of the CE group were also larger than those of the control group but were smaller than those of the AE group. This result is in accordance with studies that examined either open-skill exercise or Tai Chi Chuan [10, 11]. These findings suggest that in addition to improving cognitive performance, participation in exercise, regardless of the exercise modality, induces an increase in attentional resource allocation during cognitive processing.

Interestingly, N450, another late component, showed a similar pattern to that of P3. The AE group had the smallest N450 amplitudes, followed by the CE group, and, finally, the control group. N450, a specific component induced by the Stroop Test, is believed to originate in the anterior cingulate cortex (ACC) and to reflect conflict detection processes [37]. Our finding of greater N450 amplitudes following incongruent trials than following congruent trials support evidence of a role of N450 in conflict monitoring activity [38]. The association between N450 activity and the ACC provides an alternative explanation for the beneficial effect of exercise. Colcombe et al. indicated that both older adults with higher cardiovascular fitness and those performing AE training exhibit better executive function, with lower activation in the ACC [39]. Accordingly, from a neuroelectrical perspective, our finding of a decrease in N450 amplitude due to exercise is consistent with the superior performance of the AE and CE groups on the Stroop Test because of the reduction of ACC activation, extending these findings from AE to CE.

The early ERP components displayed largely distinct activity from that of the late ERP components. Specifically, a reduced N2 amplitude was observed only in the AE group, and no differences in N1 were observed among the three groups. N2 amplitude is susceptible to the degree of conflict and is believed to be associated with conflict monitoring by the ACC [40]. Previous studies that investigated the association between N2 and fitness have predominately focused on younger or older children, and our findings demonstrate that the association of reduced N2 amplitude with AE extends to older adults [41, 42]. These N2 findings, along with the reduction in the N450 amplitude in the AE group, suggest that AE is positively associated with improved top-down executive control and reduced conflict processing. However, CE failed to show this N2 alteration, and this result is inconsistent with our prior expectations. Despite their similar origin in the ACC and reflection of conflict processing, N2 and N450 may be distinguishable. N2 is believed to represent conflict detection, adjustment, and resolution [24, 40], whereas N450 reflects only conflict detection within conflict monitoring processes [40]. Our data reflect that the effects of each exercise modality may be modulated by the relationship between exercise and conflict monitoring; specifically, AE likely affects a variety of subprocesses within conflict monitoring, and CE specifically impacts conflict detection. Future research is required to replicate these findings and to test this hypothesis.

The current study failed to identify a difference in N1 among the three groups. N1 is an exogenous ERP component that reflects stimulus discrimination and is primarily controlled by the physical characteristics of the event. To date, only a few studies have examined N1. Chang et al. [21] reported that N1 amplitudes were larger in older adults with more physical activity than in those with less physical activity, conflicting with our findings. However, their study utilized a working memory task in which the memory response of the retrieval phase depended on the stimulus in the preceding encoding phase, whereas the cognitive inhibition of the Stroop Test utilized in the current study might require less effort at the early stage of information processing. Therefore, the lack of an observed association of alteration in N1 activity with exercise in the present study may indicate that the effect of exercise on effortful stimulus discrimination at the early stage of the Stroop Test is limited.

Although the present study extends current knowledge by examining the relationships among exercise, fitness, and cognitive function using behavioral and neuroelectrical approaches, caution must be taken when interpreting the findings. The positive associations among exercise modalities, fitness indices, and cognitive function observed in the current study were based on cross-sectional evidence, which limits the interpretation of causal relationships. However, along with recent neuroimaging studies that

used longitudinal interventions to show that exercise leads to modifications of brain function and structure [15, 16], our findings indicate that further exploration of the effects of different exercise modalities and fitness measures on cognitive function is warranted, using randomized controlled trials and neuroelectrical approaches. Although the older adults in the CE group exhibited lower cardiovascular fitness and greater flexibility than those in the AE group, the two groups exhibited similar ratings on the other health- and skill-related fitness indices. To determine the effectiveness of an exercise modality and the importance of a specific fitness index, exercise designed to involve high muscular demand in addition to intense motor and coordination demand is required in older adults. A potential confounding factor in the present study is the gender ratio, which differed among the groups. Although we found no significant gender differences regarding the three measures of the WAIS-III, our findings should be interpreted with caution. Finally, although the emphasis on inhibitory control and the selection of the Stroop Test were appropriate, exercise might differentially affect specific aspects of executive function (e.g., working memory and task switching), or its effects may depend on the neuropsychological assessment utilized [6]. Thus, further investigation of the exercise-cognition relationship by comparing different types of executive function using a variety of tasks is suggested.

5. Conclusions

Previous studies examined the relationships among AE, cardiovascular fitness, and cognition. Our study extended this knowledge based on demonstrating the effectiveness of AE and CE for improving cognitive performance, irrespective of the aspect of cognitive function, as indicated by the results of the Stroop Test. Although we provided the first demonstration that the positive association between fitness and cognition is independent of the measure of health- or skill-related fitness assessed, different exercise modalities may differentially impact neuroelectrical activation. Specifically, both AE and CE induced enhanced allocation of attentional resources and improved conflict detection during conflict monitoring processes, although AE appeared to have an additional effect on conflict adjustment and resolution. In addition to clarifying the association between fitness and cognition and providing the potential mechanism underlying this relationship, the present research provides an important implication to serve as a reference for the selection of exercise modalities to improve cognitive function.

Conflicts of Interest

All authors declare no conflict of interest.

Acknowledgments

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Review Article

Nonpharmacological Interventions in Targeting Pain-Related Brain Plasticity

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Chronic pain is a highly prevalent and debilitating condition that is frequently associated with multiple comorbid psychiatric conditions and functional, biochemical, and anatomical alterations in various brain centers. Due to its widespread and diverse manifestations, chronic pain is often resistant to classical pharmacological treatment paradigms, prompting the search for alternative treatment approaches that are safe and efficacious. The current review will focus on the following themes: attentional and cognitive interventions, the role of global environmental factors, and the effects of exercise and physical rehabilitation in both chronic pain patients and preclinical pain models. The manuscript will discuss not only the analgesic efficacy of these therapies, but also their ability to reverse pain-related brain neuroplasticity. Finally, we will discuss the potential mechanisms of action for each of the interventions.

1. Introduction

Chronic pain is a heavy burden for the individual and society affecting 30% of the adult population in the USA [1] and presenting with multiple comorbid psychiatric disorders, including mood alterations [2] and cognitive impairment [3]. With its growing incidence and prevalence, chronic pain is associated with billions of dollars in expenditure related to both therapeutic efforts and costs linked to loss of productivity [4], thus becoming one of our most urgent unmet medical needs. Back pain, headache, and joint pain are some of the most prevalent types of chronic pain [5].

Due to its distressing and unpleasant nature, acute pain serves a protective role against tissue damage. However, under certain circumstances, it can become persistent, eventually presenting as a distinct pathology. One of the pivotal mechanisms that could explain the chronification of pain, as well as its resistance to classical forms of treatment, is the concept of pain centralization, where initial sensory events following trauma can gradually alter the central nervous system (CNS), resulting in amplified pain and/or aberrant pain that exists without peripheral tissue damage or sensitization. In particular, alterations in brain circuitry have been well reported across a wide spectrum of pain conditions, such as complex regional pain syndrome [6, 7], fibromyalgia [8, 9], neuropathic pain [10–13], and migraine [14], thus prompting the quest for treatments that could reset these systems.

Defining the exact circuitry of pain in the brain is complex, mainly because pain is a multidimensional experience that incorporates nociceptive, affective, and cognitive networks. In brief, the dorsal posterior insula, the primary and secondary somatosensory cortices, the anterior insula, the ventrolateral and medial thalamus, the hypothalamus, and the dorsal anterior cingulate cortex (dACC) have been implicated in the nociceptive processing of pain, while limbic systems including the nucleus accumbens, amygdala, and hippocampus could become involved with persistent nociceptive input, eventually engaging prefrontal cortical circuitry [15, 16]. It is important to note, however, that this pain "matrix" is not a static entity but rather a dynamic network that is characterized by specific spatiotemporal neural expression patterns in painful conditions [17].

Current analgesic therapies rely heavily on pharmacological agents and fail in providing relief to a substantial subset

of the chronic pain population. Despite the recent advances in understanding the neuroscience of pain and nociception, most drugs fall into a few narrow categories, including opioids which are widely used in patients with moderate to severe chronic pain [18]. With opioids falling increasingly out of favor due to concerns over poor efficacy and abuse, complementary and alternative medicine (CAM) approaches as safe and efficacious replacements or complements to pharmacotherapy are fast gaining popularity [19].

CAM encompasses an array of treatments that fall outside the radius of conventional therapies. It can be used together with conventional therapies (complementary) or in place of conventional therapies (alternative), with most patients receiving a coordinated care regimen that integrates mainstream medicine with complementary approaches to a healthy lifestyle. Despite an initial skepticism towards the analgesic efficacy of such interventions, there is now accumulating evidence regarding the utility of CAM treatments as well as potential underlying mechanisms that could demystify them. To date, there have been few studies directly addressing the effects of CAM analgesic treatments on pain-related neuroplasticity, in large part because the field of brain plasticity that is associated with chronic pain is itself rapidly evolving. This review aims at describing a few of the commonly used, feasible, efficacious, and safe CAM approaches to treating chronic pain and their associated neuroplastic mechanisms in the brain both in chronic pain patients and, where applicable, in preclinical models.

2. Attentional and Cognitive Interventions

Attentional and cognitive factors are key modulators in the experience of pain. Below we will discuss some of the most commonly used interventions that have been shown to influence both pain perception and the related brain alterations.

2.1. Distraction. This intervention is based on diverting attention from the painful stimulus, instead focusing on cognitively demanding tasks. Multiple functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) studies have shown the efficacy of distraction. For example, in response to the application of a noxious heat stimulus, distraction is associated with decreased pain intensity (as reported by the experimental subject) and decreased activity of the thalamus and insula [20], decreased activity in the somatosensory cortex, and increased activity in the prefrontal areas [21, 22]. Distraction might be particularly efficacious in patients who appear to be excessively attentive to their pain, including high pain catastrophizers [23]. Since distraction analgesia is based on "escaping" the reality of pain, it is therefore important to create distractions that are immersive. As such, we have seen a rise in the use of virtual reality (VR) as an analgesic tool, particularly in acute pain conditions. Unlike classic distraction methods that rely on audiovisual or narrative stimulation, VR relies on the use of a simulated three-dimensional virtual environment with which the patients can interact in seemingly "real" and physical manner, often with the use of a headset or goggles. Due to the simulated nature of these environments, there is a broad range of virtual scenarios that can be presented to the pain patient as a distraction. Much like more classical techniques, VR has been linked to reduced pain ratings as well as decreased brain activity in pain regions such as the ACC, primary and secondary somatosensory cortices, insula, and thalamus [24].

The effects of distraction have been tested in rodent models of pain. Mice were injected with formalin and then placed in a familiar arena containing a novel (nonaversive) object. Despite the fact that the formalin-evoked swelling remained unchanged by the distraction paradigm suggesting a lack of effects on peripheral mechanisms, formalin-injected "distracted" mice spent less time engaged in nocifensive behaviors (licking, biting, shaking, etc.) and demonstrated elevated levels of endogenous cannabinoids in the ventral hippocampus [25].

2.2. Mindfulness and Meditation. Mindfulness and meditation practice comprises a host of constructs that focus on mental exercises potentially beneficial in modulating painful stimuli [26]. Unlike distraction, mindfulness relies on being attentive to pain in a nonjudgmental way, with the consensus that openness and acceptance to pain, without attaching any cognitive appraisal to it, diminish pain unpleasantness. In a study of experimental pain in healthy control subjects, those who were given mindfulness and meditation training perceived noxious heat stimulation to be less unpleasant and less intense compared to control subjects [27]. In patients with diverse chronic pain conditions, acceptance and commitment therapy (ACT), emphasizing the willingness to live with the pain rather than expect its full resolution, resulted in reduced pain interference in daily functioning, as well as improvements in measures of anxiety and depression [28]. These differences in pain perception are accompanied by functional and anatomical brain changes. Functionally, expert meditators display low baseline activity in pain-related regions (such as the dorsal anterior insula and anterior mid-cingulate cortex) and the amygdala, in addition to enhanced activity in pain-related regions during painful stimulation [29]. In another study, expert (pain-free) meditators showed lower activity in the mid-cingulate cortex, secondary somatosensory cortex, and insula during the painful stimulus [30]. Anatomically, meditation was shown to be associated with increased gray matter thickness in the secondary somatosensory and dorsal anterior cingulate cortices [31]. These techniques are not only applicable to highly trained and long-term meditation practitioners. In a study employing pain-free subjects, a 4-day mindfulness/meditation training program was sufficient in reducing experimental pain unpleasantness and pain-related activation of the primary somatosensory cortex [27].

2.3. Cognitive Behavioral Therapy (CBT). One of the most common CAM approaches to the treatment of chronic pain is cognitive behavioral therapy (CBT). This psychosocial intervention relies on cognitive and behavioral approaches to maximize coping strategies and minimize unhelpful thoughts and attitudes towards chronic pain. These techniques include, but are not limited to, homework assignment (e.g., keeping

a pain journal), relaxation techniques (deep breathing, progressive muscle relaxation, etc.), positive affirmation, relapse prevention, operant behavioral therapy, and biofeedback (using monitoring devices) [32]. Despite the somewhat mixed reports for CBT efficacy [33–36], there is some evidence that it can affect pain-related cortical alterations. For example, in a cohort of patients with painful irritable bowel syndrome, a 10-week CBT course was linked to a reduction in pain and anxiety, in addition to reduced activation in brain regions thought to be involved in the emotional and cognitive modulation of pain [37]. In a cohort of female fibromyalgia patients, a 12-week CBT course was paralleled by improvements in depression and anxiety and increased activation in brain areas involved with executive cognitive control [38]. More recently, Seminowicz et al. reported that, following an 11-week long CBT course, chronic pain patients showed improved clinical outcomes in addition to increased gray matter density in the prefrontal and posterior parietal cortices [39].

3. Environmental Influences

Environmental influences play a significant role in the prevalence of chronic pain in humans, with low socioeconomic status being associated with higher prevalence of chronic pain conditions both in childhood and adolescence [40] and in adult populations [41]. In the absence of randomized controlled studies, we cannot discount the possibility that these findings reflect a general link between overall health and socioeconomic disadvantage. Nevertheless, there are a few reports of environmental manipulations modulating the perception of pain. In a study conducted in surgical patients, exposure to natural lighting was associated with diminished analgesic usage [42]. Furthermore, under experimental pain conditions, visual images of natural scenery were able to increase both pain thresholds and pain tolerance in control subjects [43]. It is unclear, however, whether these improvements are due entirely to an enriched environment or perhaps due in part to distraction provided by a novel environment. In contrast to the limited set of data available in human subjects, environmental manipulations in animal models of pain are well-studied. The subsequent paragraph will address the effects of environmental manipulations on reversing or preventing the neuroplastic changes that accompany chronic pain.

Similar to clinical observations, preclinical pain measurements are especially sensitive to environmental factors [44]. Housing conditions have been extensively studied, with the consensus that enriched environments are often associated with diminished pain, with slight variations between different reports. Most enriched environments aim to foster natural rodent behaviors and may include the presence of cagemates, textured bedding, activity wheels, various objects that the animals can interact with, and marbles and other similar items buried in the bedding. The effects of such enriched environments have been reported in multiple models: for example, in a rat model of inflammation, environmental enrichment (EE) was associated with reduced thermal, but not mechanical hyperalgesia [45], and in a model of chronic pain following spinal cord injury, rats housed in enriched environments after injury showed a rapid normalization of mechanical allodynia in addition to improved gross locomotor performance [46]. Similarly, in a mouse model of peripheral neuropathy, EE that was administered 3 months after injury attenuated mechanical and cold allodynia [47]. In addition to a standalone therapy, EE synergizes with pharmacological agents in targeting experimental pain. For example, the antinociceptive effects (tail withdrawal test) of both mu [48] and kappa opioids [49] are enhanced in EE rats. It is noteworthy that most EE paradigms rely on both social (cagemates) and physical (cage dimensions, inanimate objects within the cage, etc.) enrichment, with physical enrichment having a larger experimental (antiallodynic) effect under certain conditions [50].

Despite the abundance of studies pertaining to behavioral plasticity after EE in preclinical models of pain, there is a surprising paucity of data regarding the underlying brain neuroplasticity. A study from our group investigated the effects of EE on pain-associated aberrant epigenetic modifications in the prefrontal cortex (PFC) of the mouse and showed that global hypomethylation in the PFC, an epigenetic signature of chronic pain in the brain, is absent in the EE group, although the specific genes regulated by methylation in EE were not identified [51]. In another study, Terada et al. demonstrated that EE-induced hippocampal neurogenesis is hampered in chronic pain, although the effects of EE on pain measures were not considered [52]. Finally, in a model of peripheral neuropathy, Norman et al. showed social isolation to be associated with depression and IL1-β upregulation in the frontal cortex, both of which were reversed by central oxytocin administration [53]. These results provide preliminary molecular and biochemical links between EE and pain-related brain neuroplasticity. While much of the published literature focuses on EE in chronic pain conditions and its role in ameliorating allodynia and hyperalgesia, there is some evidence that EE could increase nocifensive responses to inflammation. In a mouse model of formalin-induced inflammation, enriched animals demonstrated increased licking as well as increased response to a "safety" signal (dimly lit quarters). These behavioral changes were paralleled with increased plasticity in the ACC [54] and could reflect emotions of fear and safety that are associated with pain.

4. Exercise and Physical Rehabilitation

The chronic pain patient population is highly heterogeneous, with a wide range of physical abilities and levels of disability. Nonetheless, physical activity is highly recommended for most patients, with results being comparable to the use of nonsteroidal anti-inflammatory drugs (NSAIDS) and simple analgesics [55–58]. Below we review some evidence supporting the role of exercise in improving pain outcomes, as well as associated brain neuroplastic phenomena, in preclinical and clinical pain populations.

Clinically, chronic pain is often linked with motor disturbances, potentially due to physiological impairment, limb immobilization, or kinesiophobia. Such motor disturbances are associated with alterations in cortical networks perceiving and regulating motor function [59]. It is therefore not surprising that, in addition to neuroplasticity in the "pain matrix,"

multiple pain conditions are associated with alterations in the motor cortex, particularly if motor disability is comorbid with the pain. For instance, in patients with chronic low back pain, decreased excitability in the primary motor cortex (M1) [60] and diminished intracortical motor inhibition in M1 circuits [61] have been reported. It is therefore plausible that motor training and physical rehabilitation might be considered as therapeutic options. Indeed, in a study conducted by Tsao et al., low back pain patients exhibited a delay in the postural activation of deep abdominal muscles in addition to abnormal motor representation of this muscle group in the motor cortex, parameters that were both normalized following motor skill training of the muscle group [62]. Unfortunately, self-paced exercise failed to elicit similar improvements [62], suggesting the need for targeted physical rehabilitation.

The antinociceptive and analgesic effects of physical exercise have been shown in rodent models of pain as well, both as prophylactic [63] and therapeutic [64] interventions. While exercise has similarities to EE, it is nonetheless distinct since it not only fosters "natural" rodent behaviors, but actively aims to model aspects of physical rehabilitation commonly employed in the clinic. One of the few studies that addresses the topic of brain plasticity after exercise in animal models of pain comes from Sluka et al. where regular physical activity was shown to prevent the development of chronic muscle pain and to downregulate the phosphorylation of the glutamate receptor NMDA-R1 in the rostral ventromedial medulla, in the absence of any effects on acute nociception [65].

When discussing the "desirable" effects (antidepressive, antiallodynic, analgesic, antinociceptive, etc.) of physical exercise, we must distinguish between voluntary and forced activity. In rodent studies, it appears that the positive outcomes of innately driven exercise could be reversed if the animal subjects are forced to exercise. As such, forced exercise is associated with stress-induced hyperalgesia [66] (thus negating the desirable effects of exercise) or stress-induced analgesia [67] (thereby obscuring the interpretation of the acquired data). These differential effects are also paralleled by brain alterations: for example, forced swimming in rats is associated with increased hyperalgesia after peripheral inflammation, in addition to biochemical and epigenetic marks of plasticity in the insular cortex [68]. It is possible that a similar scenario exists in pain patients as well: those who choose to lead an active lifestyle might benefit the most from it, while those who view it as an unpleasant obligation might profit from the addition of CBT or other intervention that changes their mindset regarding physical exercise.

5. Potential Mechanisms of Action

The interventions reviewed in this manuscript affect multiple organ systems in the body, and as such, it is difficult to trace the exact mechanisms by which it can alter pain-related brain plasticity. Below, we describe several potential routes by which CAM therapies can play a part.

5.1. Blood-Brain Barrier (BBB) Permeability. BBB compromise has been described in both preclinical [69, 70] and clinical [71, 72] pain conditions and is an attractive candidate for linking peripheral changes following a painful injury to behavioral changes associated with brain plasticity [73]. One possible mechanism by which exercise could prevent some of the maladaptive neuroplasticity observed in chronic pain is limiting BBB permeability after peripheral injury. For instance, data from an experimental model of autoimmune encephalomyelitis shows physical exercise to be associated with the reestablishment of tight junctions and the partial restoration of the BBB [74]. This is particularly relevant to pain-associated comorbidities: in both preclinical models and patients with chronic pelvic pain, pain and depression are associated with elevated levels of prostate-derived cytokines in the cerebrospinal fluid [75], suggesting a BBB breach.

5.2. Normalization of Endogenous Neuroplasticity and Neurogenesis. In addition to alterations in motor areas, motor deficits that often parallel chronic pain can also hamper endogenous neurogenesis, in both mice and humans [76]. Furthermore, chronic pain itself is associated with altered neurogenesis, despite the presence of conflicting studies regarding the relationship between the two [77]. It is therefore possible that physical exercise and EE can restore some of endogenous neurorestoration, potentially through antineuroinflammatory mechanisms [78, 79], thereby altering the processing of nociceptive signals. Furthermore, both exercise and EE can have beneficial effects on anxiety and memory deficits that often coexist with pain. Clinical studies show that exercise induces neuroprotection and synaptic strengthening and improves cognitive function as well as motor control in Parkinson's disease [80]; preclinically, EE paired with exercise stimulates neurogenesis in transgenic mice with impaired neurogenesis and reverses the observed memory deficits [81] and, in WT mice, this exercise/EE paradigm reduces anxiety and improves memory. Additional observations demonstrate that EE/exercise modulates multiple gene targets with known involvement in synaptic plasticity [82].

5.3. Ascending Control of Nociceptive Signals. Nociceptive information travels from peripheral nociceptors and dorsal horn to the thalamus (spinothalamic tract) and brainstem and medulla (spinoreticular and spinomesencephalic tracts). Mindfulness therapy and other similar cognitive interventions could interfere with the ascending nociceptive signal, since they rely on a "bottom-up" approach that focuses on the pain sensation without appraising it in any way. To date, there is some conflicting evidence for thalamic modulation in CAM therapies.

On one hand, there is evidence for thalamic activation in CAM-related pain amelioration. For instance, mindfulness practitioners have lower pain sensitivity in addition to increased thalamic activation and decreased connectivity between cognitive (e.g., dorsolateral PFC [dlPFC]) and pain-related (e.g., ACC) cortices [83]. Additionally, it is possible that thalamic activation during exercise could hinder the relay of nociceptive signals. This hypothesis is supported by both the robust and direct anatomic connections between the motor cortex and the thalamus, by clinical data showing effective neuropathic pain relief by motor cortex stimulation [84],

and by preclinical data where chronic exercise was paralleled by an increased activation of the cerebellar-thalamic-cortical circuit in rats [85], thus providing additional incentive for ongoing physical activity in pain patients. For those patients with reduced mobility, ascending noxious signals can be modulated via guided imagery. For instance, motor imagery under hypnotic trance results in thalamic activation [86].

On the other hand, some studies have found thalamic inhibition to be linked with decreased nociception. In a study conducted by Pagano et al., motor cortex stimulation (without any physical exercise) was shown to result in increased nociceptive thresholds and the inhibition of thalamic hyperactivity in naïve rats [87].

The seeming discrepancy between these sets of findings could be due to multiple factors, including the pain-free versus chronic pain state of the subjects (thalamic activity varies significantly between these two groups [88]), the type of intervention, and the alternate mechanisms that could be at play. For example, it is possible that motor imagery is efficacious, at last in part, through its ability to function as a distraction agent. Finally, the thalamus is part of a complex set of circuits and pathways that constitute the pain matrix. As such, it is an oversimplification to assume thalamic activation alone as a proxy for pain relay and processing.

5.4. Descending Modulation of Pain. In addition to controlling ascending signals, the brain exerts control over nociception via a descending brain network that encompasses the dlPFC, ACC, insula, hypothalamus, rostral ventromedial medulla (RVM), and the periaqueductal gray (PAG) [89]. These "top-down" regulators may be disrupted in chronic pain conditions and may be rectified by nonpharmacological means: For example, distraction, by the virtue of being a "top-down" pain regulator, could possibly act through the modulation of descending pain [22]. It is even arguable that classic descending noxious inhibitory control (DNIC) paradigms are efficacious due to the element of distraction (distracting one type of pain by another) [90]. By the same token, descending pain modulation is a likely mechanism of action for CBT as well, where improved clinical outcomes could be due to enhanced top-down control of pain (pain modulation) and altered experience of noxious stimuli (pain perception), as evidenced by CBT-associated increase in gray matter density in the dlPFC and posterior parietal cortex [39]. Finally, this top-down regulation of pain can be modulated through exercise: in a study conducted in a cohort of fibromyalgia patients (compared to control subjects), a brief bout of exercise was shown to modulate pain and stimulate the anterior insula and the dlPFC [91].

Serotonergic, dopaminergic, and noradrenergic pathways are all involved in modulating the facilitatory and inhibitory pain drives. In brief, serotonin (5-HT) and dopamine (D) can exert both pro- and antinociceptive effects, depending on the type of pain and the expression of its receptors (5-HT1, D2, and D3 being antinociceptive and 5-HT2, 5-HT3, and D1 being pronociceptive), and noradrenergic pathways have been shown to be mainly antinociceptive (for review, please see [92]). The balance between these various drives is altered in chronic pain. For instance, nerve injury is accompanied by an overall enhancement of the descending 5-HT facilitatory drive [93] and chronic peripheral inflammation is paralleled by increased activity in the descending dopaminergic pathway [94]. The pain-related alterations in these monoaminergic pathways can be modulated by physical exercise. In rodents, peripheral neuropathy was ameliorated by low intensity aerobic exercise and was associated with increased 5-HT and 5-HT receptor content, reduced 5-HT turnover, and decreased proinflammatory cytokine levels in the brainstem [95].

5.5. Opioid Regulation. Data from animal studies show the involvement of EE is regulating opioids, with somewhat conflicting results. While rodent data shows that EE is commonly associated with activated opioid signaling [96], data from porcine subjects shows that enriched housing environments are associated with decreased expression of opioid receptors in the amygdala [97].

In general, exercise is associated with increased endogenous opioids in healthy subjects [98]. In the chronic pain population, this link is less clear: On one hand, there is evidence of dysfunctional regulation of central (hypothalamus) and peripheral (pituitary) endogenous opioids following acute bouts of exercise [99]; on the other, motor cortex stimulation in chronic pain patients was linked to pain relief as well as the release of endogenous opioids in the anterior middle cingulate cortex and the PAG [100]. Preclinically, physical activity is commonly associated with increased endogenous opioid peptides, and increased μ-opioid receptors have been reported in the rat hippocampus following acute and chronic exercise [101]. Moreover, rats who were bred for high motivation for voluntary running showed elevated opioidergic signaling in the nucleus accumbens [102], and hyperalgesia following limb immobilization in rats was ameliorated by treadmill exercise and was linked with increased levels of β-endorphins in the hypothalamus and midbrain PAG [103].

The role of endogenous opioids in mindfulness/meditation is less clear: in a study conducted in healthy meditation practitioners, the analgesic effects of meditation were reversed by the administration of the opioid antagonist naloxone [104]. In contrast, in meditation-naïve healthy participants, a 4-day mindfulness/meditation training protocol resulted in analgesic effects that were naloxone independent [105]. It is therefore possible that the duration of meditation practice is key in recruiting various neuroplastic mechanisms for pain perception and regulation.

5.6. Endocannabinoid Mechanisms. The endocannabinoid system has recently emerged as a potential therapeutic target for multiple chronic pain conditions [106]. Similar to the aforementioned opioid-mediated analgesia, cannabinoid mediated analgesia and antinociception are mediated by brainstem circuits, including the inhibition of GABA release in the PAG and RVM [107]. In chronic pain, there is evidence from rodent studies showing that CB1R, one of the two main cannabinoid receptors, is downregulated in the RVM, with CB2R playing a compensatory role in GABA modulation [108].

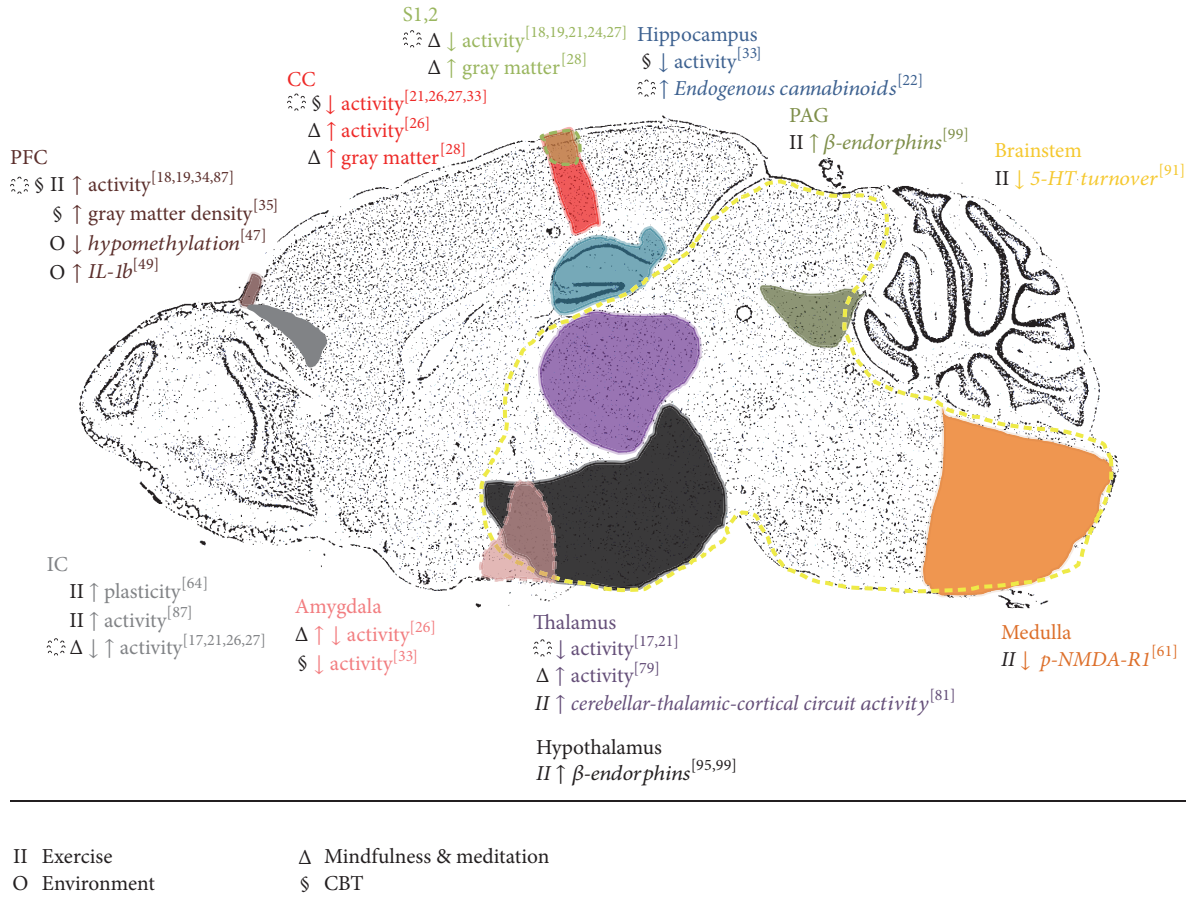

Figure 1: Illustrated summary of key CAM-responsive centers in the pain brain. Text in colors correspond to each painted brain region in that same color. Due to the single sagittal view of the brain, some areas may not be visualized in their entirety or may not be true to scale. CC: cingulate cortex; IC: insular cortex; IL-1b: interleukin 1-beta; PAG: periaqueductal gray; PFC: prefrontal cortex; S1,2: primary and secondary somatosensory cortices; 5-HT: 5-hydroxytryptamine/serotonin. Text in italics refers to findings from rodent studies.

Data from a rat model of formalin-evoked pain shows the endocannabinoid system to be involved in distraction-induced antinociception, where distraction is associated with increased levels of the endogenous ligands in the ventral hippocampus, and the administration of a CB1R antagonist attenuates distraction-induced analgesia [109]. Similarly, both aerobic exercise and resistance training in rats were shown to be associated with increased nociceptive thresholds as well as increased CB1R levels in the PAG [110, 111].

5.7. Placebo. Clinically, pain is usually measured as a subjective report and is particularly sensitive to the placebo effect through both opioid and cannabinoid systems [112–114]. However, it would be shortsighted to equate placebo treatments with the administration of an inert substance. Instead, the key to the measurable and physical effects that placebo has may lie in the treatment or care that the patient receives. Viewed in this light, it is plausible that various CAM modalities exert significant placebo effects in part because of expectations of alleviation of pain. Particularly in those patients where CAM is integrated alongside more traditional pharmacotherapy, a "preconditioning" effect could take place, where the pharmacological agent both relieves the pain and boosts the efficacy of the placebo [115], even reaching the extent of overriding the knowledge that the intervention is only a placebo [116].

6. Limitations and Future Directions

It is noteworthy that many of the studies reviewed here do not distinguish between the neuroplastic changes that occur indirectly through the amelioration of pain through CAM approaches versus the direct effect of these CAM interventions on the brain. Indeed, many of the described neuroplastic changes may not be unique to pain but could rather serve as a proxy for the plethora of pain-associated comorbidities, including memory deficits, anxiety, and depression. Additionally, much of the reviewed data was collected in pain-free control subjects under experimental pain conditions. These data may not be directly relevant to the chronic pain brain, since pain perception in healthy subjects is radically different from that in chronic pain patients. Finally, despite the multiple reports showing beneficial results of CAM treatments, we lack concrete evidence of their efficacy in different

pain conditions, especially since there are preclinical [117] and clinical [118] studies that fail to show any benefits. We anticipate that future research findings both from preclinical studies and from controlled clinical trials will provide us with an improved mechanistic understanding of the efficacy of CAM therapies in the treatment of chronic pain.

7. Conclusions

This review summarizes the effects of noninvasive treatments in preventing or reversing pain-related alterations in brain biochemistry, structure, and function in preclinical models as well as chronic pain patients (please refer to Figure 1 for an illustrated summary). The limited efficacy of traditional pharmacotherapy, along with our increased understanding of the mechanisms behind the action of complementary therapies, has led the shift towards a more holistic view of pain treatment, where long-lasting supra-spinal changes are targeted.

Competing Interests

The authors declare that they have no competing interests.

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Research Article

The Rapid Effect of Bisphenol-A on Long-Term Potentiation in Hippocampus Involves Estrogen Receptors and ERK Activation

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Bisphenol-A (BPA), a widely used synthetic compound in plastics, disrupts endocrine function and interferes with physiological actions of endogenous gonadal hormones. Chronic effects of BPA on reproductive function, learning and memory, brain structure, and social behavior have been intensively investigated. However, less is known about the influence of BPA on long-term potentiation (LTP), one of the major cellular mechanisms that underlie learning and memory. In the present study, for the first time we investigated the effect of different doses of BPA on hippocampal LTP in rat brain slices. We found a biphasic effect of BPA on LTP in the dentate gyrus: exposure to BPA at a low dose (100 nM) enhanced LTP and exposure to BPA at a high dose (1000 nM) inhibited LTP compared with vehicle controls. The rapid facilitatory effect of low-dose BPA on hippocampal LTP required membrane-associated estrogen receptor (ER) and involved activation of the extracellular signal-regulated kinase (ERK) signaling pathway. Coadministration of 17β-estradiol (E_2, the primary estrogen hormone) and BPA (100 nM) abolished both the BPA-induced enhancement of LTP and the E_2-induced enhancement of baseline fEPSP, suggesting a complex interaction between BPA- and E_2-mediated signaling pathways. Our investigation implies that even nanomolar levels of endocrine disrupters (e.g., BPA) can induce significant effects on hippocampal LTP.

1. Introduction

Bisphenol-A (BPA) is a widely used synthetic compound included in polycarbonate plastics and epoxy resins, for example, in food and beverage containers, dental prostheses, compact discs, and baby bottles. It is capable of acting as an endocrine disrupter and interferes with actions of endogenous gonadal hormones (e.g., estrogen or androgen) at low concentrations. BPA can bind to estrogen receptors (ERs) at low concentration and thus affects normal hormonal regulation and endocrine function [1]. A large number of studies have indicated that chronic exposure to the low-dose (nanomolar) BPA during fetal/neonatal stages inhibits sexual differentiation and nonreproductive behaviors of adult animals [2–4].

Although the widespread effects of BPA on reproductive function, brain structure, and social behavior have been investigated, recent studies reported controversial actions of BPA on learning and memory, ranging from deficits to no effect and to enhancements. In rodents, pre- and perinatal exposures to BPA at or below the TDI (tolerable daily intake; $\leqslant 50\,\mu$g/kg/day) have resulted in adverse effects on memory processes [4–9]. Adolescent exposure to BPA below the TDI impairs spatial memory in rats [5]. In contrast, other studies have shown that chronic oral exposure to BPA does not alter memory processes of adult male or ovariectomized (OVX) female rats [10, 11]. We previously found that acute exposure to BPA rapidly enhanced short-term passive avoidance memory in the developing rats [12]. The underlying mechanism is unclear. The role of BPA in synaptic remodeling in brain

areas involved in learning and memory is also controversial. Adolescent exposure to low-dose BPA inhibited spinogenesis and synaptic modification in hippocampi of rodents [13]. BPA inhibited 17β-estradiol (E_2)-induced formation of dendritic spine synapses in hippocampal CA1 area and prefrontal cortex of adult ovariectomized rats or nonhuman primates [14, 15]. However, other studies have shown the facilitatory effects of BPA on synaptic plasticity in neuronal development. Exposure to BPA at low doses (<100 nM) enhanced both dendritic and synaptic development in cultured hypothalamic cells [16, 17]. Exposure to BPA at 10–100 nM for 30 min rapidly increased the spine density dendritic filopodia mobility of the hippocampus [18]. Nanomolar doses of BPA rapidly modulated spinogenesis in adult hippocampal neurons [19]. Our previous study has also identified the facilitatory effect of BPA on dendritic morphogenesis of cultured hippocampal neurons through ER activation [12].

The long-lasting plasticity of synaptic transmission, as long-term potentiation (LTP) or long-term depression (LTD), is thought to be the cellular basis of learning and memory processes. Interestingly, it has been reported that exposure to BPA at low concentrations (10–100 nM) rapidly enhanced LTD in CA1 and CA3 but suppressed LTD in the dentate gyrus of the hippocampus [20, 21]. However, no studies have assessed the potential of BPA to influence LTP, and the underlying mechanisms are yet largely unknown.

The extracellular signal-regulated kinase (ERK) signal pathway is a component of a mitogen-activated protein kinase (MAPK) signaling cascade which regulates a variety of important cellular events. Recently, evidence highlights the ERK-mediated effects of estrogen and xenoestrogens in the brain [22]. Our previous studies have demonstrated that ERK signaling is involved not only in the chronic effect of BPA on dendritic morphogenesis in hippocampal neurons but also in the rapid effect of BPA on passive avoidance memory of young rats [12, 23].

In the present study, we investigated the dose-dependent effect of BPA on hippocampal LTP and explored the downstream intracellular pathways. In addition, we examined the synergistic role of BPA and E_2 in hippocampal LTP. Therefore our study provides additional information on possible mechanisms for the effects of BPA on synaptic plasticity in brains.

2. Materials and Methods

2.1. Animal and Drug Treatment. All experiments were carried out on male Wistar rats (Weight 120–140 g, age 5-6 weeks). The use of animals for experimental procedures was carried out in accordance with Guidelines for the Care and Use of the Laboratory Animals of Ningbo University, China.

2.2. Preparation of Slices. All experiments were conducted on transverse slices of the rat hippocampus. The brains were rapidly removed after decapitation and placed in cold oxygenated (95% O_2, 5% CO_2) artificial cerebral spinal fluid (ACSF). Slices were cut at a sickness of 350 μm using a VT 1000S vibroslicer (Leica, Germany) and placed in a storage chamber containing oxygenated medium at room temperature (20–22°C) for 1 h. The slices were then transferred to a recording chamber and continuously superfused at a rate of 5-6 mL/min at 30–32°C. The ACSF contained (mM) NaCl, 120; KCl 2.5, NaH_2PO_4, 1.25; $NaHCO_3$ 26; $MgSO_4$, 2.0; $CaCl_2$, 2.0; D-glucose 10. All solutions contained 100 μM picrotoxin (Sigma, St Louis, MO, USA) to block $GABA_a$-mediated activity.

2.3. In Vitro Electrophysiological Techniques. The electrophysiological techniques were applied according to our previous reports [24, 25]. Presynaptic stimulation was applied to the medial perforant pathway of the dentate gyrus using a bipolar insulated tungsten wire electrode, and field excitatory postsynaptic potentials (fEPSPs) were recorded at a control test frequency of 0.033 Hz from the middle one-third of the molecular layer of the dentate gyrus with a glass microelectrode. The inner blade of the dentate gyrus was used in all studies. In each experiment, an input-output curve (afferent stimulus intensity versus fEPSP amplitude) was plotted at the test frequency. For all experiments, the amplitude of the test EPSP was adjusted to one-third of maximum (~1.2 mV). LTP was evoked by high-frequency stimulation (HFS) consisting of two trains (each of two stimuli at 100 Hz for 1 s, intertrain interval 15 s) with the stimulation voltage increased during the HFS so as to evoke an initial EPSP of the train of double the normal test EPSP amplitude.

2.4. Statistics. Recordings were analyzed using pCLAMP 10.3 software (Axon Instruments, Foster City, CA, USA). Values are the means ± SEM for n slices. All brain slices in the same group were from different animals. In most experiments, the amplitude of fEPSPs measured 40 min after HFS (post-HFS) was shown, unless indicated otherwise. Two-tailed Student's t-test and one-way ANOVA were used for the detailed statistical analysis where appropriate; $p < 0.05$ was considered statistically significant.

2.5. Agents. All drugs were applied through the perfusion medium. BPA was purchased from Shanghai Chemical Reagent Research Institute (Shanghai, China). 17β-E_2 and U0126 were purchased from Cell Signaling (Boston, MA, USA). ICI182,780 was purchased from Tocris (Ballwin, MO, USA). All reagents were dissolved in dimethyl sulphoxide (DMSO, from Sigma, St. Louis, MO, USA) and then diluted in ACSF (0.05% vehicle). Control levels of LTP were measured on slices perfused with vehicle (DMSO) alone.

3. Results

3.1. The Facilitatory Effect of Low-Dose BPA on LTP in the Dentate Gyrus. We first investigated the dose-dependent effect of BPA (10, 100, and 1000 nM; added to the ASCF 60 min before HFS) on synaptic plasticity of perforant path-granule cell synapses induced by HFS in the dentate gyrus (DG). We found that application of 10 nM BPA did not have any effect on LTP (140.8 ± 5.2% of baseline, $n = 8$) compared with vehicle controls (143.7 ± 7.6% of baseline, $n = 8$, $p > 0.05$, Figures 1(a) and 1(b)). However, 100 nM BPA increased LTP (193.1 ± 8.3% of baseline, $n = 8$) compared to control

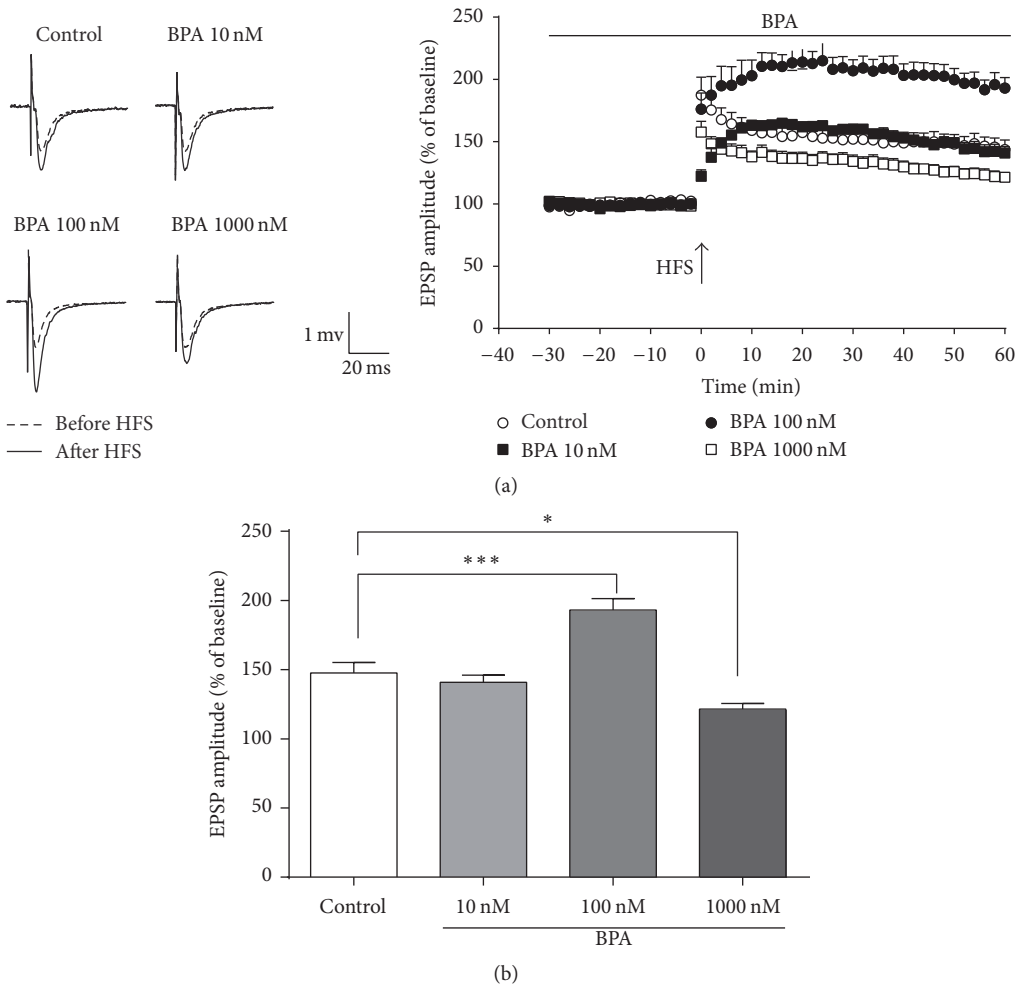

Figure 1: The biphasic effect of BPA on LTP in rat dentate gyrus in vitro. (a) High-frequency stimulation induced LTP in the medial perforant path of the dentate gyrus of acute rat hippocampus slices (open circles, $n = 8$). Applications of BPA are indicated at concentrations of 10 nM (filled squares, $n = 8$), 100 nM (filled circles, $n = 8$), and 1000 nM (open squares, $n = 8$), respectively. All hippocampal slices were preperfused with ACSF, 30 min before HFS, to obtain baseline EPSP amplitude. (b) Summary of the major experimental outcomes. The average fEPSP amplitudes at 60 min after HFS in separate perfusion of different concentration BPA. Applications of BPA 100 nM and BPA 1000 nM have significant effects on LTP, $^{*}p < 0.05$, $^{***}p < 0.001$ as compared to controls. Solid and dashed example traces before HFS and after HFS, respectively.

(143.7 ± 7.6% of baseline, $n = 8$, $p < 0.001$, Figures 1(a) and 1(b)). In contrast, application of BPA 1000 nM resulted in an inhibition of LTP in DG (121.1 ± 4.0% of baseline, $n = 8$, $p < 0.05$, Figure 1(b)), indicating a biphasic effect of low-dose (100 nM) and high-dose (1000 nM) BPA on hippocampal LTP.

3.2. The BPA-Enhanced LTP Requires Activation of ERs. To examine whether the enhancement of LTP by 100 nM BPA involves ERs, we add a high-affinity nonselective ER antagonist ICI 182,780 (100 nM) into bath solution 30 min before BPA application. Application of ICI 182,780 had no effect on LTP (120.6 ± 3.7% of baseline, $n = 8$, controls: 140.8 ± 5.2% of baseline, $n = 8$. $p > 0.05$, Figure 2(b)) but blocked BPA-enhanced LTP (123.4 ± 6.2% of baseline, $n = 8$, $p < 0.001$, Figure 2(b)), suggesting that the facilitatory effect of BPA (100 nM) on LTP in hippocampal dentate gyrus requires the activation of ERs.

3.3. BPA-Enhanced LTP Involves ERKs. To explore the downstream signaling pathway of the BPA-enhanced LTP in rat hippocampus, we examined whether the ERK pathway is involved. Application of 100 nM U0126 (a MEK1/2 or ERK inhibitor) 60 min before HFS did not alter the baseline fEPSP but inhibited the hippocampus LTP in rat dentate gyrus compared with vehicle controls (103.1 ± 3.5% of baseline, $n = 8$, $p < 0.001$, Figures 3(a) and 3(c)). In addition, pretreatment of 100 nM U0126 added 30 min before BPA application completely blocked BPA-enhanced LTP (102.8 ± 6.1% of baseline, $n = 8$, $p < 0.001$, Figure 3(c)). However, pretreatment of BPA (added 30 min before U0126 application) resulted in partial inhibition of BPA-enhanced LTP (151.0 ± 4.7% of baseline, $n = 8$, $p < 0.001$, Figure 3(d)). These results indicate that activation of ERK pathway is not only required for physiological LTP but also necessary for the facilitatory effect of BPA on LTP in the dentate gyrus.

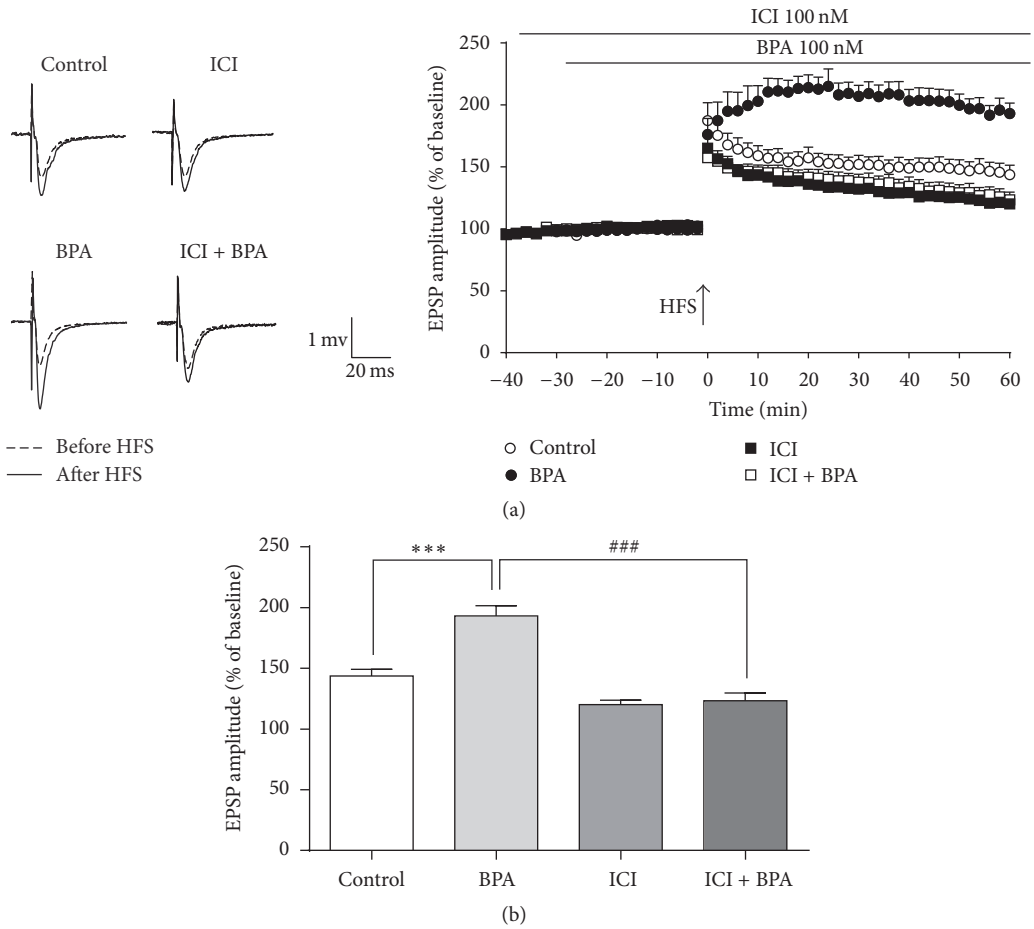

Figure 2: The enhancement of BPA on hippocampal LTP was ER-dependent. (a) Administration of ICI 182,780 10 nM (an antagonist of ERs, filled square, $n = 8$) remarkably decreased the 100 nM BPA-induced enhancement of LTP. Pretreatment with the ERs antagonist ICI 182,780 30 min before BPA 100 nM (open squares, $n = 8$) application completely blocked BPA-enhanced LTP compared with BPA alone. (b) Figure columns express the average fEPSP amplitudes after HFS in separate perfusion or coperfusion of BPA 100 nM and ICI 182,780 100 nM, $^{***}P < 0.001$ as compared to the control, $^{###}P < 0.001$ as compared to the BPA 100 nM. Solid and dashed example traces before HFS and after HFS, respectively.

3.4. The Effects of BPA and E_2 on Baseline fEPSP and LTP Enhancement. Previous studies have reported the facilitatory effect of E_2 on both baseline fEPSP and LTP induction [26]. Here, we applied 10 nM E_2 on rat brain slice and observed a significant increase (~20–30%) of baseline fEPSP compared with vehicle controls (Figures 4(a) and 4(b)). However, coapplication of BPA (100 nM) and E_2 reversed the enhancement of baseline fEPSP induced by E_2 (Figure 4(b)). In terms of LTP enhancement, E_2 treatment did not enhance LTP while comparing fEPSP before HFS (at 0 min) and after HFS (at 60 min) in the dentate gyrus (Figures 4(b) and 4(c)). Unexceptionally, coapplication of E_2 and BPA blocked both the BPA-induced enhancement of LTP and the E_2-induced enhancement of baseline fEPSP (Figures 4(b) and 4(c)).

4. Discussion

4.1. The Rapid Facilitatory Effect of Low-Dose BPA on Hippocampal LTP Is ER-Dependent and Involves Activation of ERK Pathway. The rapid effect of BPA on synaptic plasticity has been investigated by several studies. It is shown that low-dose BPA (10 nM) increases Ca influx, enhances filopodia flexibility in cultured hippocampal neurons, and rapidly modulates spinogenesis in adult hippocampal slices [18, 19]. These effects have been reported to relate to ERs and MAPK activation [19]. In the terms of memory-related synaptic plasticity (e.g., LTP and LTD), the effect of BPA has been less investigated. Hasegawa et al. [21] have reported the BPA-induced enhancement of LTD in CA1 region of rat hippocampus, but this effect does not require ER activation [21]. However, we here demonstrate that low-dose BPA (100 nM) significantly enhances LTP in rat DG region and this facilitatory effect of BPA on LTP depends on ER activation since E_2 antagonist ICI 182,780 completely abolishes the BPA enhancement on LTP.

There are two types of ERs: one type is nuclear estrogen receptors (nERs), which are members of the nuclear receptor family of intracellular receptors, including ERα and ER; the other type is membrane estrogen receptors (mERs), which are mostly G protein-coupled receptors, including Gq-coupled

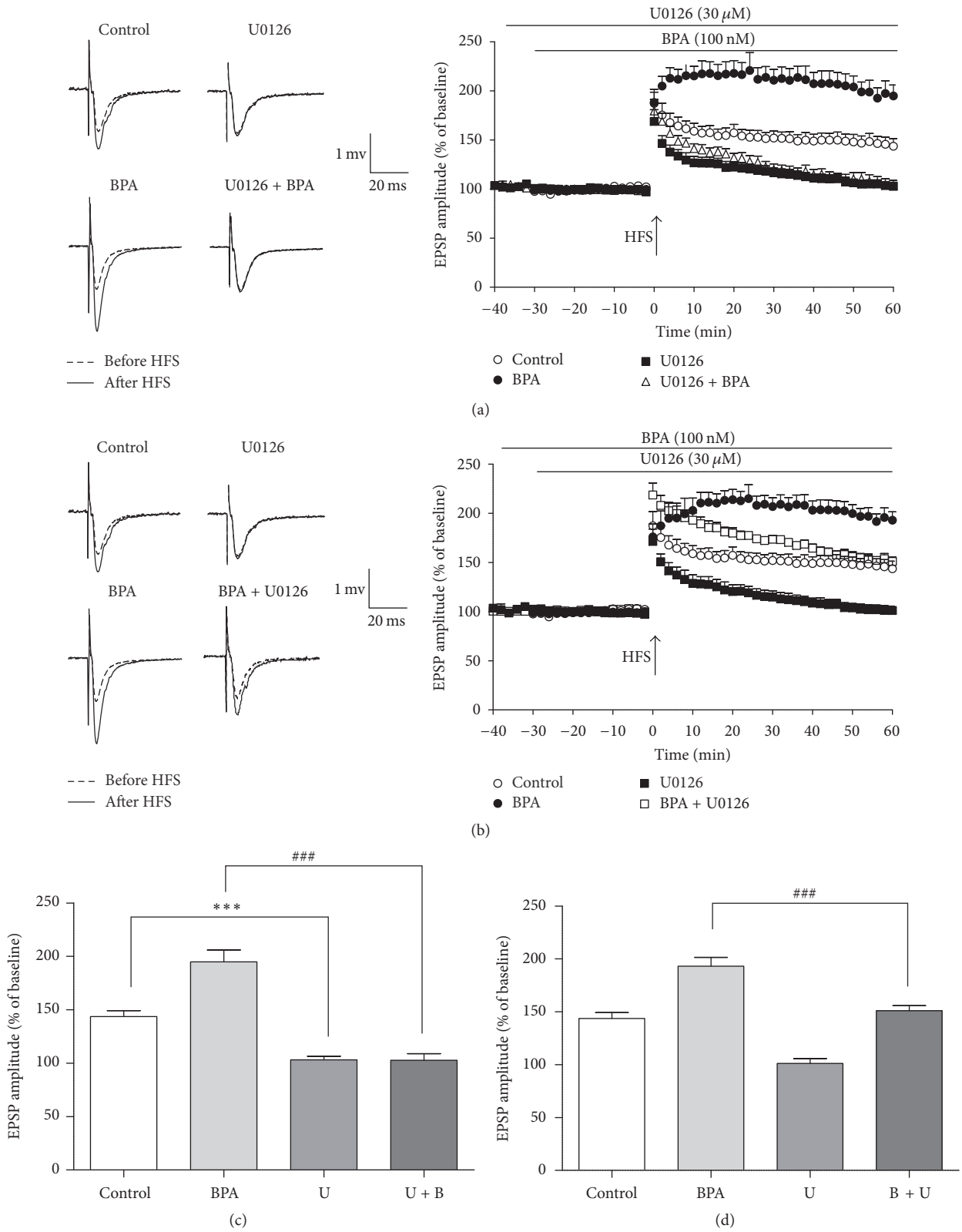

Figure 3: ERK signal pathway was involved in BPA-enhanced LTP. Pretreatment with ERK inhibitor U0126 for 30 min before BPA 100 nM (open triangles, $n = 8$) completely blocked LTP compared with controls. (b) Pretreatment with BPA 100 nM 30 min before the ERK inhibitor (open squares, $n = 8$) application remarkably decreased the BPA effect as compared with BPA 100 nM alone (open squares). (c, d) Figure columns showing the average fEPSP amplitudes at 60 min after HFS in separate perfusion or coperfusion of BPA 100 nM and U0 126 30 μM, $^{***}P < 0.001$ as compared to the control, $^{\#\#\#}P < 0.001$ as compared to the BPA 100 nM. Solid and dashed example traces before HFS and after HFS, respectively.

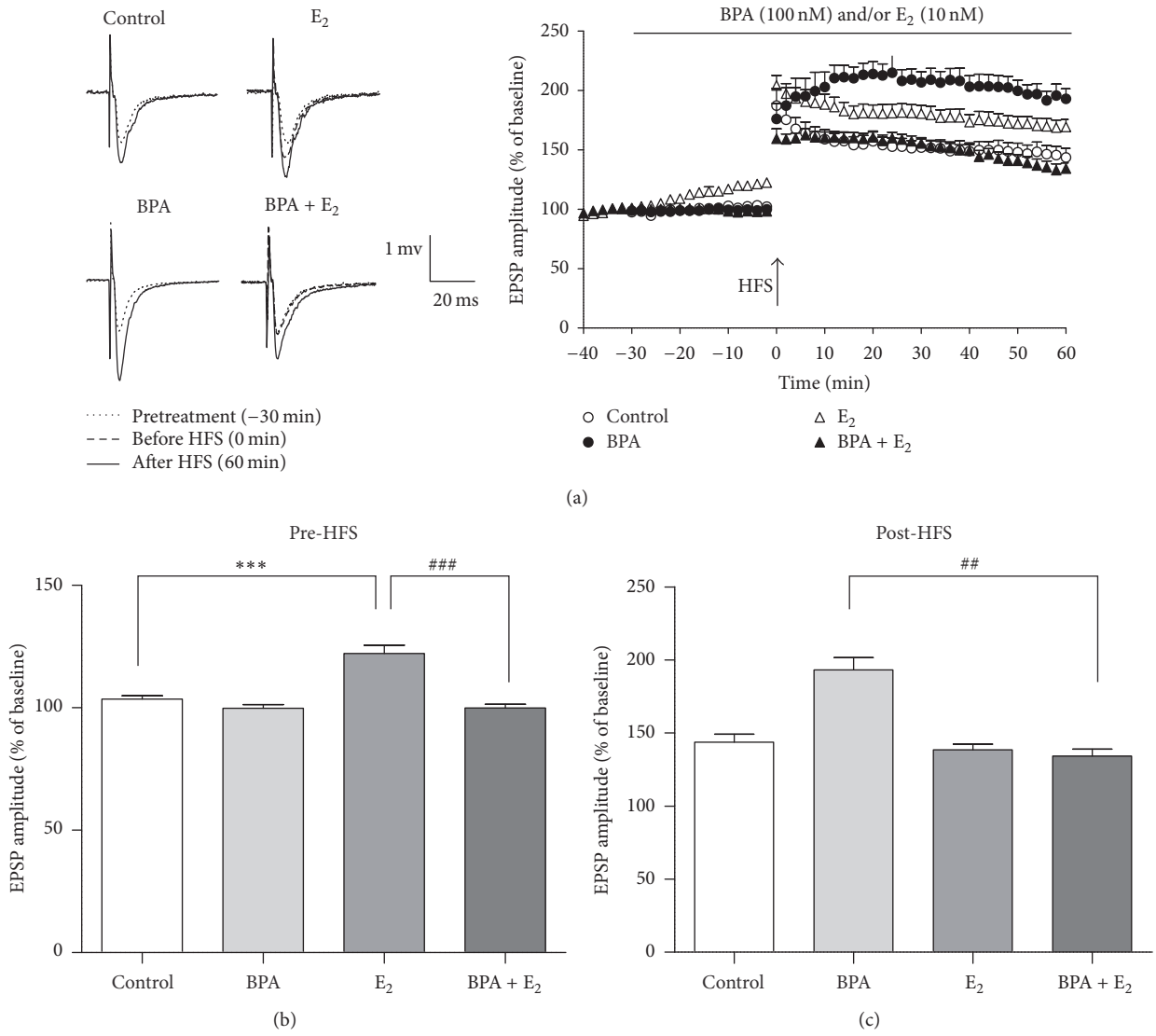

Figure 4: The enhancement of BPA on hippocampal LTP was abolished by E_2 treatment. Enhanced LTP by E_2 (10 nM) in hippocampal area DG (open triangles, $n = 8$). Coadministration of BPA 100 nM with E_2 (filled triangles, $n = 8$) had no effect on LTP compared with untreated controls. (b) Pretreatment by E_2enhanced the pre-HFS EPSP amplitudes, $^{***}p < 0.001$ as compared to controls, $^{###}p < 0.001$ as compared to the E_2 10 nM. (c) Comparison of different groups the fEPSP amplitudes at 60 min. E_2 had no effect on LTP compared with untreated controls without baseline increase in EPSP amplitude (before the HFS). $^{***}p < 0.001$ as compared to the control, $^{##}p < 0.01$ as compared to the BPA 100 nM. Solid and dashed traces are examples of before treatment, after treatment, and after HFS, respectively.

mER (Gq-ER), GPER1 (formerly GPR30), and ER-X [27]. In the genomic mechanism, E_2 binds to ERα and ERβ in the cytoplasm, and then the E_2-ER complex translocates into the nucleus, binds to an estrogen response element on the DNA, and finally facilitates gene transcription. The nongenomic mechanism involves actions of mERs at the plasma membrane: ERα and ERβ interact with mERs to rapidly activate extracellular signal-regulated kinase (ERK) cell signaling, which further triggers epigenetic processes, gene expression, and other cell signaling pathways [22]. Although it is not clear which type of ER(s) is involved in the facilitatory effect of BPA on LTP because ICI 182,780 blocks both nERs and mERs, the rapid effect of BPA (within 1 h) indicates a greater contribution of the nongenomic mER signaling to the BPA-induced enhancement of hippocampus LTP. Considering the essential roles of glutamate receptors (AMPA, NMDA, and metabotropic glutamate receptor) in the hippocampal LTP and the interactions between glutamate receptors and mERs, the glutamate receptors may also be involved in BPA-induced enhancement of LTP.

Growing evidence demonstrates that the hippocampal ERK signaling is necessary for E_2 to enhance hippocampal memory consolidation [28, 29]. Here our results confirm that ERK activation is also required for the BPA-induced enhancement of LTP. It is interesting that the blockade of ERK pathway did not completely inhibit BPA-enhanced LTP while the slices were preincubated with BPA for 30 min before U0126 treatment. The reason may be due to the rapid effect of

BPA on LTP since preincubation of BPA may already launch certain rapid downstream effects to enhance EPSP amplitude after high-frequency stimulation, whereas some slow effects of BPA requiring ERK activation are inhibited by following the application of U0126. These results are consistent with our previous findings on cultured rat hippocampal neurons that exposure to BPA for 30 min rapidly enhances the motility and the density of dendritic filopodia through the ER-mediated pathway [30]. Finally, our results also show that high-dose BPA (1000 nM) could severely inhibit hippocampal LTP, indicating a complex mechanism of BPA actions on neuroplasticity in hippocampi.

4.2. BPA and E_2 Differently Influence Hippocampal LTP and There Might Be a Complex Interaction between Them. Estrogen (e.g., E_2) is also locally synthesized within the hippocampus in addition to the gonads. Mounting articles demonstrate that E_2 influences hippocampal memory [31, 32]. A number of studies have reported rapid effects of E_2 on LTP, LTD, and spinogenesis in the hippocampus. Low concertation of E_2 (1 nM) rapidly enhances LTD in CA1, CA3, and dentate gyrus of the hippocampus. The density of thin type spines increases in CA1 pyramidal neurons within 2 h after application of 1 nm estradiol and this enhancement of spinogenesis requires ERs and MAPK signals [33]. Vedder et al. have demonstrated that E_2-induced enhancements in both spatial memory and LTP occur within a similar time frame, linking E_2-induced changes in LTP with hippocampal memory formation [34]. Our previous study also confirms that E_2 (10 nM) significantly increases the total dendritic length and enhances motility and density of dendritic filopodia in cultured hippocampal neurons [12]. In the terms of hippocampal LTP, although application of E_2 (1–10 nM) does not directly enhance LTP, it induces a baseline increase of the excitatory postsynaptic potential (EPSP) in CA1 neurons [26, 35].

Consistently, in the present study, we have shown a significant increase (~20–30%) of baseline fEPSP induced by application of E_2. Molecular mechanisms of modulation through synaptic estrogen receptor (ER) and its downstream signaling are still unknown. It may involve a complex kinase network based on a recent study investigating the induction of LTP by the presence of E_2 upon weak theta burst stimulation (a subthreshold stimulation that did not induce full-LTP) in CA1 region of the adult male hippocampus [36]. This E_2-induced LTP is ER-dependent and requires activation of multiple kinases including ERK, protein kinase A (PKA), protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K), and calcium calmodulin kinase II (CaMKII) [36].

It is worth noting that although exposure to either low-dose BPA or E_2 alone enhances LTP suppression of these effects is observed when low-dose BPA and low-dose E_2 are administrated together. Our findings are consistent with a previous in vivo study showing that the E_2-induced increase in synapse density is inhibited by the simultaneous application of BPA (40 ug/kg) and E_2 (60 ug/kg) in ovariectomized rats for 30 min [37]. The underlying mechanism is still unclear and requires further exploration. A possible explanation might be the influence of the allosteric effect of BPA on ERs. Binding of BPA to ERs may change the structure of E_2 binding sites and affect the affinity of E_2 to ERs. However, recent studies highlight another possibility that fluctuations of local E_2 levels during a learning event may be a key factor in learning and memory [32]. A study in adult nonhuman primates reported that elevated E_2 level by applying exogenous E_2 interferes with a cognitive function on the delayed response task in female monkeys [38]. Nevertheless, a study in finches has found that dynamic suppression of E_2 synthesis during a learning event may be a critical component of learning processes [39]. Possibly, low-dose BPA alone may act as the ER modulator and has estrogen-like effects on synaptic plasticity in the hippocampus, whereas high-dose BPA alone may act as the ER disrupter and impair hippocampal LTP, LTD, and spinogenesis. However, in physiological states, if we take into account the locally synthesized E_2 in the hippocampus and the importance of fluctuations of local E_2 levels in cognitive circuits, a small amount of BPA could disturb the subtle regulation of E_2 level and then influence hippocampal LTP.

5. Conclusions

In summary, we demonstrated biphasic effects of BPA on LTP in DG region of rat hippocampus: exposure to BPA at a low dose (100 nM) enhances LTP while to a high dose BPA (1000 nM) inhibits LTP. The rapid facilitatory effect of low-dose BPA on hippocampal LTP requires membrane-associated ER and involves activation of ERK signaling pathway. Coadministration of E_2 and BPA (100 nM) abolishes BPA-induced enhancement of LTP and E_2-induced enhancement of baseline fEPSP, suggesting a complex interaction between BPA- and E_2-mediated downstream pathways. Our investigation about hippocampal LTP implies that even nanomolar low doses of endocrine disrupters (e.g., BPA) could induce significant effects on hippocampal synaptic plasticity.

Competing Interests

All authors declare that they have no conflicts of interests.

Authors' Contributions

Xiaowei Chen and Yu Wang contributed equally to this study.

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