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Master Thesis

運動對具心血管危險因子之中老年人的心血管危險因子、心肺適能、腦結構與活化、及轉換任務表現的效果及效果間之關係

Effects of Exercises on Cardiovascular Risks, Cardiorespiratory Fitness, Brain Structures and Activation, Task-switching Performance, and Their Interrelationships in Middle-aged and Older Adults with Cardiovascular Risks

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中文摘要

研究背景與目的:規律運動可能可預防心血管危險因子對腦結構、腦活化、與認知功能的負面影響。本研究的目的為探討對具心血管危險因子的中老年人，有氧、太極拳、與伸展運動對四類成效參數－心血管危險因子、心肺適能、腦結構及活化、與認知轉換任務表現－的效果，及運動訓練後腦部結構與功能之改變是否為改善之心血管危險因子與心肺適能與進步之轉換任務表現間的中介因子。

研究方法：本研究資料來自一個評估者單盲之隨機對照臨床試驗（NCT 試驗編號：NCT03275038），有 70 位(45 至 79 歲)具心血管危險因子的中老年人參與該試驗。受試者被隨機分配至有氧組、太極組、或伸展組，接受每週三次，每次一小時，為期十二週之監督下輕至中強度運動訓練。運動訓練前後，受試者均進行抽血檢測、心肺運動功能測試、腦部磁振照影、及認知轉換表現測試。以二因子重複測量變異數分析比較三組間各參數訓練效果之差異。使用各參數後測數值減去其前測數值計算訓練前後各參數改變量。使用淨相關分析，探討心血管危險因子及心肺適能改變量與腦部體積與活化改變量及轉換任務表現改變量間的相關性，控制年齡、性別、教育程度。使用中介分析，探討腦結構及活化的改變，是否顯著中介訓練後改善的心血管危險因子或提升的心肺適與進步的轉換任務表現間的關係，控制年齡、性別、教育程度。與腦結構相關的分析則增加控制估計全顱內體積。此論文採完成者分析法，完成全程研究者之資料才會納入分析

結果: 總共 56 位受試者（平均年齡 64.3 ± 7.4 歲，37 位女性）完成此研究。三種運動，不論運動類別，均可有效降低部分心血管危險因子、一致性的提升心肺適能、與提升轉換任務表現，並降低左側運動輔助區轉換情境下之活化（p 均<0.05）。因三種運動對成效參數之效果多無組間差異，本研究之淨相關與中介分析是將三組

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資料合併後作的分析。運動訓練後，同半胱胺酸降低量與轉換任務表現進步量呈顯著正相關（r= 0.345, p= 0.011）；舒張壓下降量與轉換任務下海馬迴（r= 0.438, p= 0.001）與杏仁核活化（r= 0.419, p= 0.002）下降量呈顯著正相關。心肺適能上升量與左側額下回體積（r= 0.309, p= 0.026）上升量呈顯著正相關。運動訓練後，右側海馬迴腦活化下降量可完全中介並促進舒張壓下降及轉換任務進步間的關係（間接效果= 0.020, 95%CI= [0.001, 0.047]）。運動訓練後，左側額下回腦體積上升量可完全中介並增強心肺適能上升及轉換任務進步間的關係（間接效果= -0.124, 95%CI= [-0.347, -0.005]）。

討論:三個月規律之中至輕度運動，無論是有氧、太極、或伸展，對具心血管危險因子的中老年人，均可改善其部份心血管危險因子，提升其心肺適能及轉換任務表現。改善的心血管危險因子或提升的心肺適能可分別透過腦活化下降及腦體積上升中介轉換任務表現的進步。透過非必要腦活化下降的中介，亦即更有效的腦血管耦合機制，可使改善的心血管危險因子促進轉換任務表現。透過增加特定前額葉腦體積之中介，上升的心肺適能可提升轉換任務表現。

結論:在具心血管危險因子的中老年人，規律運動後，其腦活化及腦體積之變化可有效中介其心血管危險因子與心肺適能之改善與轉換任務表現之進步間的關係。

關鍵字：心血管危險因子、心肺適能、腦部結構、腦部活化、轉換任務表現、運動、磁振造影

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Abstract

Background and purposes: Engaging in regular exercises may prevent the negative impacts of cardiovascular risks (CVRs) on brain structures, brain activation, and cognitive functions. This study examined the effects of aerobic training (AT), Tai Chi Chuan (TCC), and stretching (ST) exercises on four types of outcome measures, including measures of CVRs, cardiorespiratory fitness (CRF), brain structures and functional activation, and task-switching performances; and investigated whether changes in brain structures and brain activation would mediate the relationships of the changes in CVRs and CRF with the changes in task-switching performances after exercise training in middle-aged and older adults with CVRs.

Methods: Data analyzed in this study came from an assessor-blind randomized controlled clinical trial (Trial no: NCT03275038), in which 70 sedentary middle-aged and older adults with CVRs (aged 45-79 years) were enrolled and were randomly assigned to the AT, TCC, or ST group. All three groups underwent one-hour supervised mild-to-moderate intensity exercise triweekly for 12 weeks. Blood tests for measuring CVRs, cardiorespiratory exercise tests for measuring CRF, MRI scans for collecting brain structures and functional images, and task-switching performances were all performed before and after the 12-week exercise training. The changes in all outcome measures were calculated as post-test values minus the pre-test values. Two-way (group x time) repeated measures ANOVA was used to compared group differences in training effects on outcome measures. Partial correlations were applied for the associations of the changes in CVRs and CRF with the changes in brain volumes and activation and in task-switching performances. Mediation analysis was applied to determine whether the changes in brain volumes and activation would mediate the relationships between the

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changes in CVRs and CRF with the changes in task-switching performances, controlling for age, sex, and education. Brain volumetric related analysis was additionally adjusted for the estimated total intracranial volume. The completer analysis approach was used in this study Only data of participants who completed the trial were used in this study.

Results: Fifty-six participants (64.3 ± 7.4 years old, 37 women) completed the trial. After training, all three groups significantly improved CRF, some CVRs, and task-switching performances, and decreased brain activation at the left supplementary motor area while performing task-switching after the 12-week training (all $p< 0.05$). Because there were no group differences in training effects on most outcome measures, data from the three groups were pooled for correlation and mediation analyses. Greater reductions in the homocysteine level was correlated with greater improvement in task-switching performance ($r= 0.345$, $p= 0.011$). Greater reductions in diastolic blood pressure was correlated with greater reductions in brain activation at the right hippocampus ($r= 0.438$, $p= 0.001$) and the right amygdala ($r= 0.419$, $p= 0.002$) for task-switching. Greater increases in CRF was correlated with greater increases of the left inferior frontal gyrus volume ($r= 0.309$, $p= 0.026$). Reduced brain activation at the right hippocampus mediated and facilitated the positive relationship between the improved CVR and the improvement in task-switching performances (Indirect effect= 0.020, 95%CI= [0.001, 0.047]). The enlarged brain volume at the left inferior frontal gyrus fully mediated and strengthened the beneficial relationship between the increased CRF and the improvement in task-switching performances (Indirect effect= -0.124, 95%CI= [-0.347, -0.005]).

Discussion: Three-month regular mild-to-moderate exercises, whether being aerobic, TCC, or stretching, resulted in some improvements in CVRs and robust improvement in

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CRF and cognitive task-switching in middle-aged and older adults with CVRs. Changes in brain activation and structures mediated the relationships between changes in CVR and CRF with changes in task-switching performance, respectively. Through decreasing unnecessary brain activation, which may imply a more efficient cerebrovascular coupling mechanism, improved CVR promoted task-switching performances. Through enlarging a specific prefrontal volume, increased CRF enhanced task-switching performances.

Conclusions: In middle-aged and older adults with CVRs, after engaging in regular exercises, their changes in brain activation and structures could effectively mediate the relationships between their improvement in CVRs and CRF with their improvement in task-switching.

Keywords: Cardiovascular risks, cardiorespiratory fitness, brain structures, brain activation, task-switching, exercises, MRI

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Chapter 1 Introduction

1.1 Background

Cardiovascular risks (CVRs) are considered as risk factors associated with the increased incident of cardiovascular diseases (CVDs) and stroke (Cannon, 2007; O'Donnell and Elosua, 2008; Payne, 2012; Wolf et al., 1991). While the prevalence of CVRs is high in the general population already, the prevalence of CVRs is even higher in middle-aged and older adults (McDonald et al., 2009; Ostchega et al., 2007). Research has shown that middle-aged and older adults with CVRs have worse cognitive functions compared with those without CVRs (Beeri et al., 2022; Desideri and Bocale, 2021; Qin and Basak, 2020), suggesting that CVRs may do harms to brain structures and affect brain activation (Friedman et al., 2014; Gu et al., 2019; Qin and Basak, 2020; Williamson et al., 2018). Results from cross-sectional studies also show that brain structures could be the mediators of the adverse relationship between CVRs and cognitive functions in middle-aged and older adults (Luo et al., 2019; Moran et al., 2019; Wang et al., 2017). However, there is little research using brain activation as mediators to investigate the relationships between CVRs and cognitive functions.

Research has provided evidence for the protective roles of cardiorespiratory fitness (CRF) on CVRs, cognitive functions, and the structure and functions of the brain

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(Bertoli et al., 2003; Cooper et al., 1976; Juraschek et al., 2014; LaMonte et al., 2000; Rauramaa et al., 1995; Wei et al., 1999). Indeed, regular exercises have shown positive effects not only on CRF, but also on cognitive functions, brain structures and brain activation (Agarwal, 2012; Fong et al., 2014; Kramer et al., 2001; Lin et al., 2015; Voss et al., 2013; Zheng et al., 2015). Among the many types of exercise forms, aerobic training (AT) exercises, Tai Chi Chuan (TCC) exercises, and stretching training (ST) exercises are commonly practiced by older adults. Based on several studies, aerobic and TCC exercises consistently show positive effects on improving cognitive functions in middle-aged and older adults, but stretching exercises do not (Fong et al., 2014; Kramer et al., 1999; Kramer et al., 2001; Wu et al., 2018). Several intervention studies using MRI have also shown consistently positive effects of aerobic and TCC exercises on improving brain structures and effectiveness of brain activation in middle-aged and older adults, but not for stretching exercises (Colcombe et al., 2004; Mortimer et al., 2012; Tao et al., 2017; Voss et al., 2013; Wu et al., 2018).

Though the above-mentioned literature has shown various effects of exercises on CVRs, CRF, brain structures and functions, and cognitive functions, little research has examined correlations of changes in CVRs and CRF with changes in task-switching related brain structures and brain activation after different types of exercise training in middle-aged and older adults with CVRs. Furthermore, it remains unknown whether

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changes in task-switching-related brain structures and brain activation would mediate the relationships of changes in CVRs and CRF with changes in task-switching performance after exercise training. Therefore, this study was aimed to compare the training effects on CVRs, brain structures, brain activation, and task-switching performances of the AT, TCC, and ST exercises in middle-aged and older adults with CVRs, and to investigate the interrelationships among the exercise-induced changes in CVRs, CRF, brain, and task-switching performance.

1.2 Operational definitions

The operational definitions of outcome measures used in this study were defined below.

1. CVR-related outcomes:

In this study, there were three types of CVR-related outcome measures: (1) people with CVRs and people with specific CVR; (2) number of CVR factors (CVRF); (3) CVR indices. First, people with CVRs was defined as people having at least one of these three CVRs— hypertension (HTN), diabetes mellitus (DM), and dyslipidemia. People with HTN was defined as people whose resting systolic blood pressure (SBP) was ≥ 140 mmHg or diastolic blood pressure (DBP) was ≥ 90 mmHg, averaged from two blood pressure measures took from the screening test and the physical examination for each participant, or who was receiving antihypertensive medication (Chobanian et

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al., 2003). People with DM was defined as people whose fasting plasma glucose (GLU-AC) was ≥ 126 mg/dL, or glycated hemoglobin (HbA1c) was ≥ 6.5%, or who was taking any antidiabetics treatment orally or by injection (American Diabetes Association, 2010; Petersmann et al., 2019). People with dyslipidemia was defined as whose total cholesterol (TCHO) > 200 mg/dL or triglyceride (TG) > 150 mg/dL based on the criteria of Taiwan Health Promotion Administration, or who are receiving lipid-lowering medication (National Cholesterol Education Program, 2001). Second, numbers of CVRF was defined as the sum of presence of any of the five vascular CVRs (HTN, dyslipidemia, heart disease, stroke, and smoking) and two metabolic CVRs (DM, and obesity) (Ruthirakuhan et al., 2022). Third, the CVR indices included the resting SBP, resting DBP, and the levels of the homocysteine, TCHO, TG, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), glycated hemoglobin (HbA1c), and fasting blood glucose (GLU-AC). In this study, improved CVR-related outcomes meant reductions in resting SBP, DBP, homocysteine, TCHO, TG, LDL-C, HbA1c, GLU-AC, and increases in high density lipoprotein cholesterol (HDL-C).

2. Cardiorespiratory fitness (CRF):

In this study, the CRF of all participants was measured with a cardiopulmonary

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exercise test (CEPT). Two parameters from the CPET were used to represent CRF in this study— the peak oxygen uptake ($\dot{V}O_{2peak}$, ml/min/kg) and the $\dot{V}O_{2peak}$ in percentage of age- and sex-adjusted predicted reference values ($\dot{V}O_{2peak}$ in percentage of reference value), the latter compared the $\dot{V}O_{2peak}$ obtained with that of healthy persons at the same age and of the same sex (Bisschop et al., 2012; Itoh et al., 2013). The higher values these two parameters are, the better the CRF is. Therefore, improved CRF in this study meant increased $\dot{V}O_{2peak}$ and $\dot{V}O_{2peak}$ in percentage of reference value after the 12-week training.

3. Task-switching-related brain structures:

In this study volumes of specific brain regions were used to investigate the effects of exercise on brain structures in middle-aged and older adults with CVRs. Task-switching-related brain regions were taken as the regions of interest (ROIs), including the superior frontal gyrus (SFG), middle frontal gyrus (MFG), dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus (IFG) (or ventrolateral prefrontal cortex (vlPFC)), orbitofrontal gyrus (OFG) (or ventromedial prefrontal cortex (vmPFC)), hippocampus, anterior cingulate cortex (ACC), thalamus, caudate, putamen, pallidus, and amygdala (Adolfsdottir et al., 2014; Prehn et al., 2019; Steffener et al., 2016). In this study, improved brain volume meant increased brain volumes after the 12-week training.

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4. Brain activation during switching tasks:

The ROIs to examine brain activation while performing switching task in this study were the left IFG, supplementary motor area (SMA), and superior medial frontal gyrus (SMFG), and the right SFG, MFG, amygdala, hippocampus, and thalamus. In this study, improved brain activation was considered if the changes in brain activation correlated with improved task-switching performances.

5. Task-switching behavioral measures:

In this study, three types of neuropsychological assessments were used to assess task-switching performances— the Color Trails Tests (CTT) (D'Elia et al.) parts 1 and 2, the intra-extra dimensional set shift (IED) of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins et al., 1994), and the modified numerical Stroop task (Huang et al., 2012; Wu et al., 2018). Task-switching measures included the time (seconds) from initiation to the completion of the CTT, the number of stages completed in the IED test (IED $\text{stage}_{\text{completed}}$), and the error rate (ER) and reaction time (RT) on the modified Numerical Stroop task. The modified Numerical Stroop test included Non-switch and Switch trials. Switch cost meant the difference in performance between switch trials and Non-switch trials within mixed-task blocks, which meant the

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additional cost from Non-switch to switch trials. Switch cost was calculated as the average performance (ER and RT) from the Switch trials minus the average performance in the Non-switch trials in the modified Numerical Stroop task. The lesser the Switch cost, the lesser the additional effort to pay off.

In this study, improved task-switching performances meant decreased ER/RT on the modified Numerical Stroop task, and decreased time to completed the CTT, and increased the IED $stage_{completed}$.

6. Changes of outcome measures

In this study, the changes of outcome measures were calculated as the post-test values minus the pre-test values.

1.3 Research questions and hypotheses

Purposes

The purposes of this study were:

1. To compare the effects of 12-week AT, TCC and ST exercises on CVRs, CRF, brain structures, brain activation, and task-switching performance in middle-aged and older adults with CVRs.
2. To examine whether changes in CVRs and CRF were correlated to changes in task-

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switching related brain structures and brain activation, and change in task-switching performance after each type of exercise training in middle-aged and older adults with CVRs.

3. To examine whether changes in task-switching related brain structures and brain activation would mediate the relationships between changes in CVRs and changes in task-switching performance after exercise training in middle-aged and older adults with CVRs.

4. To examine whether changes in task-switching related brain structures and brain activation would mediate the relationships between changes in CRF and task-switching performance after exercise training in middle-aged and older adults with CVRs.

The research questions and hypotheses were as follows:

1. Would 12-week of the AT, TCC, and ST exercise interventions have different effects on CRF, CVRs, brain structures and brain activation related to task-switching, and task-switching performance in middle-aged and older adults with CVRs?

   1.1 Hypothesis about CRF: The exercise effects on improving CRF (increases in $\dot{V}O_{2peak}$ and $\dot{V}O_{2peak}$ in percentage of reference value) would be greater for the AT and TCC exercise groups compared to the ST exercise group.

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1.2 Hypothesis about CVRs: The exercise effects on improving CVRs (decreases in SBP, DBP, LDL-C, TCHO, TG, homocysteine, HbA1c, and GLU-AC; and increases in HDL-C) would be greater for the AT and TCC exercise groups compared to the ST exercise group.

1.3 Hypothesis about brain structures related to task-switching: The exercise effects on volumes of brain regions related to task-switching (increases in the MFG and ACC) would be greater for the AT and TCC exercise groups compared to the ST exercise group.

1.4 Hypothesis about brain activation related to task-switching: The exercise effects on activation of brain regions during conducting task-switching (increases in SFG and MFG) would be greater for the AT and TCC exercise groups compared to the ST exercise group.

1.5 Hypothesis about task-switching performance: The exercise effects on task-switching performance (decreases in RT and ER on the modified numerical Stroop task, increases in the number of stage completed on the IED test, and reductions in the completing the CTT) would be greater for the AT and TCC exercise groups compared to the ST exercise group.

2. Would changes in CVRs be significantly correlated with changes in task-switching

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related brain structures and brain activation and change in task-switching performance after 12-week AT, TCC and ST exercise training in middle-aged and older adults with CVRs?

2.1 Hypothesis about CVRs and task-switching related brain structures: There would be significant negative correlations between improvements in CVRs (decreases in SBP, DBP, LDL-C, TCHO, TG, homocysteine, HbA1c, and GLU-AC and increases in HDL-C) and increases in brain volumes of the SFG, MFG, and IFG for the AT and TCC groups, but not for the ST group.

2.2 Hypothesis about CVRs and task-switching related brain activation: There would be significant positive correlations between improvements in CVRs (decreases in SBP, DBP, LDL-C, TCHO, TG, homocysteine, HbA1c, and fasting glucose and increases in HDL-C) and increases in brain activation of the SFG, MFG, and IFG for the AT and TCC groups, but not for the ST group.

2.3 Hypothesis about CVRs and task-switching performances: There would be significant positive correlations between improvements in CVRs (decreases in SBP, DBP, LDL-C, TCHO, TG, homocysteine, HbA1c, and GLU-AC and increases in HDL-C) and improvements in task-switching performances (decreases in ER and RT on the modified numerical Stroop task, increases in the number of stages completed on IED, reductions in time completing CTT2)

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for the AT and TCC groups, but not for the ST group.

3. Would changes in CRF be significantly correlated with changes in task-switching related brain structures and brain activation and change in task-switching performance after 12-week AT, TCC and ST exercise training in middle-aged and older adults with CVRs?

   3.1 Hypothesis about CRF and task-switching related brain structures: There would be significant positive correlations between increases in CRF ($\dot{V}O_{2peak}$ and $\dot{V}O_{2peak}$ in percentage of reference value) and increases in volumes of the SFG, MFG, and IFG for the AT and TCC groups, but not for the ST group.

   3.2 Hypothesis about CRF and task-switching related brain activation: There would be significant positive correlations between increases in CRF ($\dot{V}O_{2peak}$ and $\dot{V}O_{2peak}$ in percentage of reference value) and increases in activation of the SFG, MFG, and IFG for the AT and TCC groups, but not for the ST group.

   3.3 Hypothesis about CRF and task-switching performances: There would be significant correlations between increases in CRF ($\dot{V}O_{2peak}$ and $\dot{V}O_{2peak}$ in percentage of reference value) and improvements in task-switching performances (decreases in RT and ER on the modified numerical Stroop task, and increase in the number of stage completed on the IED test) for the AT and TCC groups, but not for the ST group.

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4. Would changes in task-switching related brain structures and brain activation mediate the relationships between changes in CVRs and changes in task-switching performance after each type of exercise training in middle-aged and older adults with CVRs?

   4.1 Hypothesis about task-switching related brain structures: The exercise-induced changes in brain volumes would mediate the relationships between changes in CVRs and changes in task-switching performance found in answers to Question 2 for the AT and TCC groups.

   4.2 Hypothesis about task-switching related brain activation: The exercise-induced changes in brain activation during conducting task-switching would mediate the relationships between changes in CVRs and changes in task-switching performance found in answers to Question 2 for the AT and TCC groups.

5. Would changes in task-switching related brain structures and brain activation mediate the relationships between changes in CRF and task-switching performance after each type of exercise training in middle-aged and older adults with CVRs?

   5.1 Hypothesis about task-switching related brain structures: The exercise-induced changes in brain volume would mediate the relationships between changes in CRF and changes in task-switching performance found in answers to Question 3 for the AT and TCC groups.

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5.2 Hypothesis about task-switching related brain activation: The exercise-induced changes in brain activation during conducting task-switching would mediate the relationships between changes in CRF and changes in task-switching performance found in answers to Question 3 for the AT and TCC groups.

1.4 Significance

The findings of this study would not only provide important evidence for effects of different types of exercise interventions on improving CVRs, CRF, brain structures and activation, and task-switching performance, but also reveal the interactions between these changes after different types of exercises in middle-aged and older adults with CVRs. In particular, the correlation and mediation analyses results will help with advancing further understanding of the roles of the brain structures and activation in mediating the effects of different forms of exercises on improving cognitive task-switching.

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Chapter 2 Literature Review

2.1 Introduction of cardiovascular risks (CVRs)

Cardiovascular risks are considered risk factors associated with the increased incident of cardiovascular diseases and are significant independent predictors of developing CVDs and stroke (Cannon, 2007; O'Donnell and Elosua, 2008; Payne, 2012; Wolf et al., 1991). Generally, CVRs can be categorized into unmodifiable and modifiable ones (Cannon, 2007; Payne, 2012; Williamson et al., 2018). Unmodifiable CVRs mainly include age, gender, ethnicity, and family history, among which age is the strongest predictor of adverse cardiovascular outcomes (Cannon, 2007; Levy and Kannel, 1988; Rodgers et al., 2019). Modifiable CVRs, primarily including HTN, DM, dyslipidemia, and some behavior characteristics (e.g. smoking, physical inactivity), are considered as preventable through lifestyle modifications (e.g. regular exercises, healthy diet, quit smoking) and controllable through pharmacological treatment in the combination of lifestyle modifications (Barbaresko et al., 2018; Cannon, 2007; Green et al., 2008; Levy and Kannel, 1988; Mifsud et al., 2020; Staessen et al., 2001).

Epidemiologic studies indicate that having CVRs increases a person's likelihood of developing CVDs and stroke (Cannon, 2007; Fox et al., 2004; Kannel, 1996; O'Donnell and Elosua, 2008; Wolf et al., 1991). Reports from the Framingham Heart Study, a long-term, ongoing observational cohort study directed by the National Heart, Lung, and

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Blood Institute since 1948, have shown that HTN, DM, and dyslipidemia are strong predictors and risk factors for stroke and CVD (Wolf et al., 1991). According to the data collected over ten to thirty years of follow-up in the Framingham Heart Study, risks for developing CVD and stroke were 2- to 3-fold and 3- to 4-fold, respectively, for those with HTN compared to those without HTN, especially for men than women (Kannel, 1996; Wolf et al., 1991). Similarly, those with DM had 2- to 3-fold of likelihood of developing CVD compared to those without DM, especially in women (Cannon, 2007; Fox et al., 2004). Regarding LDL-C levels, an 18-year follow-up study showed that people with better LDL-C levels, the incidence of CVD decreased (Cannon, 2007). Likely, a pooled project research groups found that men with TCHO > 268 mg/dl had 2.4-fold of risks to getting CVD than men TCHO < 218 mg/dl (Pooling Project Research Group, 1978).

Globally, the prevalence of HTN was approximately 22% in 2015 (World Health Organization [WHO], 2017), which was lower than the prevalence of 31% reported in 2010 (Mills et al., 2020). Such a decline in the prevalence of HTN occurred in both sexes, but only in high-income countries (Zhou et al., 2021). The global prevalence of diabetes was estimated as 9% in 2019 (Saeedi et al., 2019), which was higher than the 8% reported in 2017 (WHO, 2017). The prevalence of dyslipidemia remained approximately 39% from 1980 to 2018 (Pirillo et al., 2021). While the prevalence of

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CVRs is generally high in the general population already, the prevalence of these CVRs is even higher in middle-age and older adults. According to the National Health and Nutrition Examination Survey done in the United States during 1999 – 2004, the prevalence of HTN, dyslipidemia, and DM in adults older than 65 year-old is approximately 70%, 60%, and 21%, respectively; and the prevalence of these risks in adults older than 65 year-old is three- to fifth-folds higher than those below 45 year-old and increasing with age (McDonald et al., 2009; Ostchega et al., 2007).

Hypertension is defined as a persistently elevated SBP ≥ 140 mmHg or DBP ≥ 90 mmHg based on the average of 2 or more measures in a seated position according to the Seventh Report of the Joint National Committee (JNC 7 Report) (Chobanian et al., 2003). Although the more recent guideline proposed by the American College of Cardiology/American Heart Association has recommended using SBP of 130–139 or a DBP of 80–89 mmHg as the cutoff to diagnose HTN (Whelton et al., 2018), the definition put forth by JNC 7 remains commonly used currently (Carretero and Oparil, 2000; Forouzanfar et al., 2017). The World Health Organization, American Diabetes Association, and German Diabetes Association have recommended the diagnosis of diabetes being made by meeting one of three criteria— GLU-AC concentration ≥ 126 mg/dl, 2-hour after meal plasma glucose ≥ 200 mg/dl, or HbA1c ≥ 6.5% (American Diabetes Association, 2010; Petersmann et al., 2019). The National Institutes of Health

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(NIH) defines dyslipidemia in the National Cholesterol Education Program Adult Treatment Panel III Guideline as TCHO ≥ 240 mg/dL, or LDL-C ≥ 160 mg/dL, or TG ≥ 200 mg/dL (National Cholesterol Education Program, 2001).

Due to the high prevalence and burden of CVRs in middle-aged and adults, prevention of development and progression of these CVRs are important. Before the manifestations of clinically significant cerebrovascular damages and CVDs, adequate management of these modifiable CVRs, through pharmacological and non-pharmacological approaches such as exercises, may prevent the development of irreversible deleterious diseases.

2.2 Influences of CVRs on cognition, brain structure, and brain function

In the past decades, researchers have found that presence of CVRs would affect brain health and cognitive performance in adults. The following review introduces the influences of CVRs on cognition, brain structures, and brain activation.

2.2.1 Influences of CVRs on cognitive functions

Research on middle-aged and older adults have shown that people with HTN have worse cognitive performance compared to those without (Budge et al., 2002; Kuo et al., 2004). Older adults (aged 65-85 years) with resting, supine SBP ranging from 136-145 mmHg and 146-185 mmHg had 3.7-folds and 8.6-folds, respectively, of risks of

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showing impairment in psychomotor speed and set shifting measured with the Trail-making Part-B test compared to those without HTN (Kuo et al., 2004). In middle-aged and older adults who already had at least one CVR, higher resting SBP was associated with worse global cognitive function measured with Cambridge Examination for Mental Disorders of the Elderly (r= -0.195, p= 0.02) (Budge et al., 2002).

Reports from the Atherosclerosis Risk in Communities (ARIC) Study, a multicenter longitudinal study of CVDs and their consequences since 1987, have shown the presence of DM and HTN is associated with greater declines in attention, executive function, and psychomotor processing speed in middle-aged and older adults with CVRs (Knopman et al., 2001; Knopman et al., 2009). A 6-year follow-up study performing cognitive assessments on 10,963 participants enrolled in the ARIC showed that the presence of DM at baseline was associated with greater declines in scores on both the Digit Symbol Subtest (DSS) and first-letter Word Fluency (WF) tests (both $p < 0.05$); the presence of HTN at baseline was associated with greater decline on the DSS alone ($p < 0.05$) in adults over 58 years-old. However, there was no significant decline in cognitive performance in those with dyslipidemia in the 6-year follow-up (Knopman et al., 2001). The same research team used logistic regression analysis to investigate the relationships of CVRs with cognitive change over a 14-year follow-up period in the participants recruited in their middle age (Knopman et al., 2009). Results showed that

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DM was an independent predictor of declines in performance on the DSS ($p < 0.001$) and WF tests ($p = 0.003$), and HTN was an independent predictor of declines in performance on the WF test ($p = 0.002$) over the 14-year period (Knopman et al., 2009). Both DSS and WF test can measure attention, executive function, and psychomotor processing speed (Cerhan et al., 1998).

In addition to the presence of CVRs, greater numbers of CVRs have been found to be associated with faster cognitive declines in adults with CVRs (Wang et al., 2017). Wang et al. (2017) found that in cognitive normal older adults (aged 60–72 years), people with higher Framingham general cardiovascular risk (FGCR) scores had faster declined on the Mini-Mental State Examination (MMSE) at a 9-year follow-up period. The FGCRS reflects the burden of CVRs by summing up the number of CVRs, with one point being given to each of the included 46 CVRs. The results showed that per 1-point increment in the FGCR scores was significantly associated with a 0.03-point faster annual decline on the MMSE score ($\beta = 20.03$, $p < 0.01$) (Wang et al., 2017).

2.2.2 Influences of CVRs on brain structures

Not only have CVRs been found to influence cognitive functions or cause declines, research has found that middle-aged and older adults with HTN, DM, or dyslipidemia have greater loss of total brain volume, grey matter volume, and cortical thickness, and

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poorer white matter (WM) integrity, compared to age-matched adults who do not have these CVRs (Alosco et al., 2014; de Bresser et al., 2010; den Heijer et al., 2003; Heijer et al., 2003; Leritz et al., 2011; Moran et al., 2019; Musen et al., 2006; Raz et al., 2003; Reiman et al., 2010; Schwarz et al., 2018; Whalley et al., 2003; Williams et al., 2013; Zhang et al., 2014). Several cross-sectional studies have shown that middle-aged and older adults with HTN have smaller gray matter volumes of the frontal, temporal, and parietal lobes or of the entire brain, a thinner cortical thickness and density, a decreased integrity of WM, especially in the prefrontal region, and an increased volume of white matter hyperintensities (WMHs), compared with age-matched counterparts without HTN, after controlling for confounding factors (Alosco et al., 2014; Heijer et al., 2003; Leritz et al., 2011; Raz et al., 2003; Schwarz et al., 2018). A longitudinal cohort study on 1077 nondemented older adults (baseline aged 40-70 years; n= 513) found that those who had higher baseline DBP (≥ 90 mmHg) and without taking antihypertensive medication (n= 434) had more severe entire cortical atrophy over a 20-year follow-up period than those with stable baseline DBP levels (65-75 mmHg) and taking antihypertensive medication (n=79) (0.17 versus 0.03 unit of decrease in cortical volume per 10mmHg increase in DBP). Furthermore, they also found an U-shape association between DBP levels and degree of cortical atrophy at follow-up tests. People whose DBP was > 75 or < 65 mmHg had greater cortical atrophy than those whose DBP

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ranged between 65-75 mmHg at follow-up (Heijer et al., 2003), suggesting that lifetime controlling of DBP at an optimal level (65-75 mmHg) is important to prevent cortical atrophy in later life. Another longitudinal cohort study showed that among 190 participants (aged 60-81 years at follow-up), those with HTN at the 28-year follow-up tests, especially those with poorly controlled HTN, had smaller right hippocampal volumes and more deep WMHs than the normotensive group (Allan et al., 2015). In this same study, higher mean arterial pressure (= ⅓ SBP + ⅔ DBP) averaged across 5 repeated measures during the first 24-year period was found to significantly predict increased WMHs at the 28-year follow-up of brain MRI, highlighting the importance of lifetime good control of HTN to prevent brain atrophy and development of WMHs (Allan et al., 2015).

Similar to HTN, having DM is also associated with lower brain gray matter volume and cortical thickness and density in middle-aged and older adults (de Bresser et al., 2010; de la Torre, 2012; Heijer et al., 2003; Moran et al., 2019; Musen et al., 2006; Zhang et al., 2014). In cross-sectional studies, smaller volumes of many brain gray or white matter regions have been found in cognitively normal middle-aged and older adults with DM compared to those without DM. Three regions include the hippocampus, amygdala (Heijer et al., 2003), superior and middle temporal gyri, superior and medial frontal gyri (Moran et al., 2013; Zhang et al., 2014), middle

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occipital gyrus, precuneus, angular gyrus, bilateral cingulate regions (Zhang et al., 2014), and WM in the frontal and temporal regions (Moran et al., 2013). Whole brain analysis studies also reveal that patients with DM have a significantly smaller total brain volume (de Bresser et al., 2010; Friedman et al., 2014) or lower cortical thickness (Moran et al., 2019) compared with those without DM. In longitudinal studies, the presence of DM has been found to be associated with a greater rate of lateral ventricular volume expansion (3.6% larger increase in the diabetic than control group) over a 4-year follow-up period (de Bresser et al., 2010) and worsening sulcal widening (OR 2.10, 95% CI 1.36–3.24.) over a 10-year follow-up period (Knopman et al., 2011).

Among the lipid profiles, LDL-C has been found to be the most important one related to brain structural changes (Reiman et al., 2010; Whalley et al., 2003; Williams et al., 2013). Whalley et al. (2003) studied non-demented older adults and found that higher LDL-C levels was associated with smaller total gray matter volumes. In middle-aged and older adults, Reiman et al. (2010) and William et al. (2013) found that higher LDL-C levels were associated with poorer WM integrity in many brain regions, including the anterior/superior corona radiata, the superior longitudinal fasciculus, deeper subcortical pathways, and WM tracts in the frontal, temporal, and fusiform regions. However, the relationships of other lipid profiles with brain structures are not conclusive (Reiman et al., 2010; Williams et al., 2013). High levels of homocysteine, a

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risk factor of developing dyslipidemia, has been found to be negatively associated with total gray matter volume in non-demented older adults (Whalley et al., 2003)

Studies also have investigated whether having a greater number of CVRs is associated with greater brain changes. Several cross-sectional studies have investigated the relationships between brain structures and the burden of CVRs, the little was the sum of the number of CVRs, in adults mostly with single or multiple CVRs of HTN, DM, or dyslipidemia. Their results showed that a larger number of CVRs was associated with a greater loss in brain volume, grey matter volume, cortical thickness, and poorer WM integrity in the entire brain or specific brain regions (Cox et al., 2019; Gu et al., 2019; Marebwa et al., 2018; Vemuri et al., 2018; Williamson et al., 2018).

In conclusion, the above-reviewed literature suggests that uncontrolled HTN, DM, and high LDL-C are either related to greater grey and white matter loss or poorer WM integrity or predict greater declines in brain structures over a longer period of follow-up. Therefore, it is important to prevent the occurrence or progress of these CVRs to maintain good brain structures as people get older.

2.2.3 Influences of CVRs on brain activation while performing cognitive tasks

Several reviews and cross-sectional studies have revealed that CVRs not only

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affect brain structures but also the brain activation while performing cognitive tasks in middle-aged and older adults (Chuang et al., 2014; Friedman et al., 2014; Macpherson et al., 2017; Marder et al., 2014; Naumczyk et al., 2017; Qin and Basak, 2020; Wood et al., 2016). Compared to middle-aged adults without HTN, people with HTN significantly recruited more brain regions in the frontal, parietal and occipital lobes and the limbic system while performing the Stroop color-word interference task, though there was no group difference in task performance (Naumczyk et al., 2017). This finding suggests that patients with HTN need to recruit additional compensatory activation to achieve behavioral performance comparable to those without HTN.

For middle-aged and older adults with DM, significantly reduced activation was found in the left temporoparietal regions (including the angular, supramarginal, and middle temporal gyri) while performing memory encoding (Wood et al., 2016); and in the dlPFC while performing encoding and recognition tasks (Marder et al., 2014). However, greater activation in the MFG was found in these people with DM while performing memory encoding task, suggesting that similar to patients with HTN, people with DM also have difficulty recruiting task-specific brain activation and need to select other brain regions for compensatory activation (Cabeza et al., 2018).

Furthermore, Chuang et al. (2014) found that older adults with higher scores on the FGCR Profiles showed greater task-related activation in the left inferior parietal region

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when doing the modified Eriksen flanker tasks in the high-executive demand contrast condition; however, this increased activation was associated with poorer task performance (r = 0.37, p = 0.004). This finding suggests that older adults with a greater burden of CVRs show ineffective compensatory brain activation while performing difficult cognitive tasks (Cabeza et al., 2018; Chuang et al., 2014).

2.2.4 Brain structures mediate the relationships of CVRs and cognitive functions

Given the known negative impacts of CVRs on cognitive performance and the brain, researchers have further explored the complex interrelationships among the presence of CVRs, cognitive performance, and brain structures by using mediation analysis with the parameters of brain structures as the mediators (Luo et al., 2019; Moran et al., 2019; Wang et al., 2017). Two longitudinal studies showed that baseline cortical thickness and volumes of WMH and total gray matter could mediate the association between CVRs and related cognitive declines (Moran et al., 2019; Wang et al., 2017). Wang et al. (2017) investigated the interrelationships among the baseline FGCRS, baseline volumes of WMH and total gray matter, and MMSE declines at a 9-year follow-up in older adults (aged > 60 years) using structural equation modelling (SEM) analysis. The results showed that while higher baseline FGCRS was associated

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with greater MMSE declines (β-coefficient (95%CI)= -0.019 (-0.030, -0.008)), this relationship was significantly attenuated after entering the WMH volume or total gray matter volume in the SEM, indicating that these two brain structural indices serve as important mediators on the effects of burden of CVRs on cognitive declines in older adults (Wang et al., 2017). Moran et al. (2019) studied the interrelationships among the presence of baseline DM, baseline cortical thickness, and cognitive declines over a 5-year follow-up period in middle-aged and older adults with DM. Results showed that while there was no direct effect of the presence of DM on cognitive declines, there was an indirect effect of DM on cognitive declines through the mediation of baseline cortical thickness ($\beta = -0.176$, $p = 0.022$). This results showed that the adverse relationship between DM and cognitive decline was significantly strengthened after entering baseline cortical thickness as the mediator, suggesting that the presence of DM adversely affected baseline cortical thickness and indirectly affected the cognitive function via baseline cortical thickness (Moran et al., 2019).

In addition to brain macrostructures, brain microstructures were also found to mediate the adverse relationships between CVRs and cognition. In a cross-sectional study, Luo et al. (2019) used the SEM to examine the interrelationships among HTN, WM microstructural integrity, and cognitive function in middle-aged and older adults with and without HTN. Results showed that there were poorer cognitive performances

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and lower WM integrity in hypertensive adults compared to non-hypertensive ones. Additionally, WM integrity of bilateral inferior frontal-occipital fasciculus was found to significantly mediate and emphasize the adverse association between HTN and multiple domains of cognitive functions, including processing speed, memory encoding, memory retention, and executive function. The results suggested that HTN-related WM disruptions underlined the negative link between HTN and cognitive functions (Luo et al., 2019).

Taken together, recent studies concurrently collecting data of CVRs, brain structures, and cognitive functions and using mediation analysis have permitted better elucidation of the adverse effects of CVRs on cognitive functions. Both macro- and micro-structural indices of the brain have been found to significantly mediate the effects of CVRs on multiple domains of cognitive function or global cognitive functional declines.

2.3 Introduction of CRF

Cardiorespiratory fitness, as a component of physical fitness, is defined as the ability to supply oxygen during sustained physical activity by the circulatory, respiratory, and muscular systems (Albouaini et al., 2007; Itoh et al., 2013; Rankinen et al., 2007). Cardiorespiratory pulmonary exercise test (CPET), the gold standard to

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measure CRF, is an overall assessment of cardiocirculatory, pulmonary, and metabolic responses to exercises. Results of the CPET also could serve as useful health indicators for both symptomatic and asymptomatic patients in clinical practice (Albouaini et al., 2007; Balady et al., 2010). There are different protocols of conducting a CPET, in which a stationary bicycle or a motorized treadmill is used. The common protocol includes warm-up, workload progression, termination of workload progression, and cool down. The warm-up period usually lasts for 5-10 minutes with the exercise intensity set at comfortable speed for a participant (Ross et al., 2016). Then, the workload will increase every 10~60 seconds by 10 watts, called ramp protocols. The termination of workload progression would be determined by the presence of fatigue-related symptoms, dyspnea, or any abnormal exercise responses in participants due to safety considerations (Mezzani et al., 2013; Ross et al., 2016).

The underlying assumption of CPET is that during exercises, the cardiovascular system will deliver oxygen to the respiratory system and the exercising skeletal muscles; then the exercising muscles will extract oxygen and remove the carbon dioxide and other metabolic products from the blood. When the exercise intensity reaches maximal exercise capacity of a person, every minute of oxygen uptake and carbon dioxide output measured from the mouth will be equal to the amount of oxygen utilization and carbon dioxide generation in exercising muscle cells, respectively. In

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healthy adults, a plateau in $\dot{V}O_2$ could be observed when the exercise reaches the maximal intensity in the final stage of a CPET. The $\dot{V}O_2$ value averaged over 20 to 30 seconds after the $\dot{V}O_2$ value achieves a plateau is called the maximal oxygen uptake ($\dot{V}O_{2max}$) (ml/min/kg), indicating the maximal exercise capacity of a person (Albouaini et al., 2007; Balady et al., 2010a). However, in clinical testing, a sustained plateau of maximal achievable $\dot{V}O_2$ usually may not be observed before fatigue-related symptoms in people with cardiorespiratory problems. In this situation, the $\dot{V}O_2$ value reaches a peak and then declines as the workload continues to rise and therefore the peak value of $\dot{V}O_2$ ($\dot{V}O_{2peak}$) is used to serve as an estimate of $\dot{V}O_{2max}$ (Forman et al., 2010). Many researchers agree that both $\dot{V}O_{2max}$ and $\dot{V}O_{2peak}$ could represent the maximal oxygen utilization and exercise capacity of a person during CPET, and serve as the most important indicators of CRF (Forman et al., 2010).

Epidemiological studies show that age, gender and lifestyle could affect $\dot{V}O_{2peak}$ (Herdy and Uhlendorf, 2011; Koch et al., 2009). In a large-scale study from Brazil, 3922 participants (aged 15-74 years) were recruited, including active men (n = 1818), active women (n =1019), sedentary men (n = 570) and sedentary women (n = 515). All participants performed the CPET on a ramp protocol according to guidelines of the Brazilian Cardiology Society of Cardiology. The $\dot{V}O_{2peak}$ values of active young (aged 15-24 years) men and women were 50.6 ± 7.3 and 38.9 ± 5.7 ml/min/kg, respectively;

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and those of active older (aged 65-74 years) men and women were 30.0 ± 6.1 and 25.1 ± 4.4 ml/min/kg, respectively. The $\dot{V}O_{2peak}$ values of sedentary young men, young women, older men, and older women were 47.4 ± 7.9, 35.6 ± 5.7, 23.1 ± 6.3, and 21.2 ± 3.4 ml/min/kg, respectively (Herdy and Uhlendorf, 2011). Similarly, a German study on healthy adults (aged 25-80 years) also showed that $\dot{V}O_{2peak}$ values were higher in men than women and in younger than older adults (Koch et al., 2009).

In Asian countries, a Japanese study conducted by Itoh et al. (2013) collected $\dot{V}O_{2peak}$ values from 749 healthy adults (aged 20-78 years) using bicycle and treadmill protocols of CPET. Since age and sex were found to affect $\dot{V}O_{2peak}$ values in this study, Itoh et al. (2013) further established separate linear relationships between $\dot{V}O_{2peak}$ values and age for each sex for CPET conducted under the bicycle and treadmill protocols. The relationships under the bicycle protocol were: $\dot{V}O_{2peak}$ (ml/min/kg) = - 0.272*age + 42.29 for men and $\dot{V}O_{2peak}$ (ml/min/kg) = - 0.196*age + 35.38 for women. The relationships under the treadmill protocol were: $\dot{V}O_{2peak}$ (ml/min/kg) = - 0.509*age + 61.06 for men and $\dot{V}O_{2peak}$ (ml/min/kg) = - 0.208*age + 40.65 for women (Itoh, H. et al., 2013). These equations could serve to establish the estimated $\dot{V}O_{2peak}$ reference values for healthy Asian adults across a wide range of ages for men and women.

2.4 Protective roles of better CRF on CVRs

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Cross-sectional studies have shown that in adults with or without CVRs, those with higher CRF would present better CVR indices (Bertoli et al., 2003; Cooper et al., 1976; LaMonte et al., 2000; Rauramaa et al., 1995). Cooper et al. (1976) divided 2924 males (mean age 44 years) into five age-adjusted CRF categories (excellent, good, fair, poor, very poor) according to their CPET results. They found that men who were in the excellent CRF category had lower resting SBP, DBP, fasting blood glucose, TCHO, and TG than those in the very poor CRF category (all $p < 0.05$). Rauramaa et al. (1995) examined the relationships of CVRs and CRF in 163 middle-aged (aged 50-60 years) men with or without CVRs using Pearson correlations. They found that CRF was negatively correlated to TG (r = -0.41, $p < 0.001$), insulin (r = -0.49, $p < 0.001$), and positively correlated to HDL-C (r = 0.43, $p < 0.001$) in these middle-aged men. Hence, higher CRF was associated with better indices of CVRs.

In longitudinal studies, higher baseline CRF has been associated with the lower risks of developing CVRs in adults after years of follow-up (Juraschek et al., 2014; Wei et al., 1999). Juraschek et al., (2014) divided 22109 adults without HTN at baseline into four CRF categories (very low-, low-, moderate-, and high-fit) based on their performance on CPET and then followed the participants' development of HTN 5 years later. The results showed that high-fit group had a 27% lower odd of having a diagnosis of HTN compared to the very low-fit group, after adjusting for age, sex, race, baseline

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resting SBP and DBP (Juraschek et al., 2014). In middle-aged adults without DM at baseline, it was observed that the people whose fitness ranked at the bottom 20% of the cohort had a 1.9-fold risk of impaired fasting glucose and a 3.7-fold risk for developing DM at the 6-year follow-up, compared with those whose baseline fitness ranked on top 40 % of the cohort (Wei et al., 1999).

Therefore, results from both cross-sectional and longitudinal studies have suggested that higher CRF may play a protective role in reducing CVRs or preventing the development of CVRs (Bertoli et al., 2003; Cooper et al., 1976; Juraschek et al., 2014; LaMonte et al., 2000; Rauramaa et al., 1995; Wei et al., 1999). However, the above-reviewed cross-sectional studies pooled people with and without CVRs together and the longitudinal studies included people without CVRs at baseline. Large-scale epidemiological studies are still needed to understand whether in people who already have CVRs, better CRF at baseline or during lifetime follow-up also could have a protective effect on reducing CVRs or prevent the progression of CVRs in later life.

2.5 Relationships of CRF with cognitive functions, brain structures, and brain activation

Over the past two decades, with the development of neuroimaging technology, research has provided evidence for the protective roles of high CRF on cognitive

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function and the structures and functions of the brain.

2.5.1 Relationships between CRF and cognitive functions

In cross-sectional studies, higher CRF levels have been found to be associated with better executive function, visuospatial ability, psychomotor speed, and spatial working memory in middle-aged and older adults (Brown et al., 2010; Edwards and Loprinzi, 2017; Freudenberger et al., 2016; Weinstein et al., 2012). Brown et al. (2010) examined the relationships of CRF measured with $\dot{V}O_{2max}$ and cognitive functions in 42 middle-aged and older women (aged 50–90 years), a group mixing those who lived in active and sedentary lifestyles, using Pearson correlations. The results showed that CRF was positively correlated with better overall cognitive function (r= 0.41, p = 0.008), cognitive speed (r= 0.391, p = 0.013), and perception (r= 0.351, p = 0.026). Even in sedentary older adults, studies have found that better CRF levels were associated with better executive functions (Freudenberger et al., 2016; Weinstein et al., 2012), spatial working memory (Weinstein et al., 2012), visuospatial function (Edwards et al., 2017), processing speed (Edwards et al., 2017), and memory (Freudenberger et al., 2016).

Similarly, longitudinal studies have shown that better baseline CRF levels are related to better verbal memory, psychomotor speed, and executive function at long-

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term follow-up tests, as well as less memory decline during the follow-up period (Wendell et al., 2014; Zhu et al., 2014). In the 25-year longitudinal follow-up results from the Coronary Artery Risk Development in Young Adults Study, Zhu et al. (2014) found the significant relationships of baseline CRF levels, measured with symptom-limited maximal treadmill tests, with multiple domains of cognitive function measured 25 years later in 2747 adults aged 18-30 years at baseline. Results of the multiple linear regression analyses showed that higher baseline CRF levels significantly predicted better verbal memory (Rey Auditory Verbal Learning Test, $\beta = 0.12$, $p < 0.0001$), psychomotor speed (DSST, $\beta = 0.86$, $p < 0.0001$), and executive function (Stroop Test, $\beta = -0.38$, $p = 0.002$) after adjusting for age, sex, race, and education (Zhu et al., 2014). In another longitudinal follow-up study on people aged 19-94 years, baseline CRF levels and cognitive assessments were performed approximately every 2 years. Results showed that greater baseline CRF was associated with less prospective memory declines on the Benton Visual Retention Test ($\beta = 0.15$, $p < 0.05$) and immediate free recall test ($\beta = -0.31$, $p < 0.05$) across the lifespan (Wendell et al., 2014).

2.5.2 Relationships between CRF and brain structures

Early research investigating the relationships between CRF and brain structures in

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middle-aged and older adults has found that brain regions that are most affected by aging benefit from better CRF the greatest (Colcombe et al., 2003; Gordon et al., 2008; Jonasson et al., 2016). Colcombe and colleagues (2013) measured both $\dot{V}O_{2max}$ and brain tissue density using MRI in 55 middle-aged and older adults. They found that although there were age-related declines in gray matter density of the prefrontal (Brodmann areas 46, 9, 6), superior parietal (Brodmann areas 40, 21, 5), and middle/inferior temporal (Brodmann areas 21, 38) cortices, these age-related declines could be ameliorated by having higher $\dot{V}O_{2max}$ (Colcombe et al., 2003). In another cross-sectional study on healthy older adults, higher $\dot{V}O_{2max}$ was also found to be associated with greater gray matter volumes in the prefrontal cortex, superior/inferior frontal lobe, motor cortex, cingulate gyrus, anterior parietal lobe, and temporal lobe (Gordon et al., 2008). Jonasson et al. (2016) found that better baseline CRF was related to greater thickness in dlPFC in 60 sedentary healthy older adults (aged 64–78 years). All these studies suggest that better CRF may have a protective role against age-related declines in brain structures. However, intervention studies are needed to understand the causal relationships between CRF and brain structures.

2.5.3 Relationships between CRF and brain activation

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Regarding the relationships between CRF and brain activation, research has shown that healthy middle-aged and older adults with better CRF show better behavioral performances on executive functions and meanwhile greater activation in brain regions relevant to performing these cognitive tasks (Colcombe et al., 2004; Prakash et al., 2011). In a cross-sectional study, Colcombe et al. (2004) discovered that older adults with higher CRF demonstrated significantly greater activation in several cortical regions associated with inhibition control- the right MFG, the SFG, and the superior parietal lobules while performing the modified Flanker tasks (Colcombe et al., 2004). Meanwhile, these participants also performed better on the modified Flanker tasks. In another cross-sectional study on 70 community-dwelling older adults, Prakash et al. (2011) conducted fMRI scans when these participants were performing modified Stroop tasks. The results showed that higher CRF levels were associated with better Stroop performance and increased recruitment of the prefrontal and parietal cortices, areas relevant to performing the Stroop tasks (Prakash et al., 2011). Therefore, both of these earlier studies provide important evidence for the positive relationships between CRF and greater recruitment of relevant brain regions while performing high-level cognitive tasks. Although both studies also reported higher CRF being associated with better executive functions, studies are still needed to examine the correlations between magnitude of brain activation and cognitive performances in order to understand

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whether the increased activation observed in older adults are effective activation.

2.5.4 Brain structures and brain function mediate the relationships between CRF and cognitive functions

More recent studies concurrently collecting data of CRF, cognitive functions, and brain structures or brain activation have further delineated the complex relationships among fitness, cognition, and the brain in cognitively normal middle-aged and older adults using mediation analyses (Freudenberger et al., 2016; Verstynen et al., 2012; Weinstein et al., 2012). Weinstein et al. (2012) found that higher CRF was associated with better performance on both the Stroop and spatial working memory tasks, and also with greater gray matter volume in the prefrontal cortex, the parietal lobe, and the temporal lobe. The right IFG volume was found to mediate the relationship between CRF and the Stroop performance (indirect effect= -0.128, 95% CI = [-0.336, -0.011]); and the bilateral MFG volume mediated the association between CRF and spatial working memory performance (right side indirect effect= 0.114, 95 % CI = [0.007, 0.343]; left side indirect effect= 0.116, 95 % CI = [0.010, 0.307]). This suggested that higher CRF was associated with better executive functions by the way of greater IFG and MFG volume in older adults (mean age= 66.6 years) (Weinstein et al., 2012). Verstynen et al. (2012) found that higher CRF was positively correlated with

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performance on the Stroop task and volumes of bilateral caudate nucleus, putamen, and pallidum. Results of bootstrapped mediation analysis showed that the caudate nucleus volume was a significant mediator of the relationship between CRF and task switching performance (Indirect effect= 0.0037, 95% CI = [0.0009, 0.0085]). These findings suggested that better CRF predicts greater task-switching performance through larger caudate nucleus volume in older adults (Verstynen et al., 2012). Another cross-sectional study supported that higher $\dot{V}O_{2max}$ was associated with better cognitive functions (global, $p < 0.001$; memory, $p < 0.001$; executive function, $p = 0.003$; motor skills, $p = 0.018$) and smaller volume of WM lesions, but not with lacunes or brain atrophy, However, WM lesions did not mediate the effects of CRF on cognitive performance in middle-aged and older adults (Freudenberger et al., 2016). Based on the evidence of these cross-sectional studies, right IFG, bilateral dlPFC, and caudate nucleus volume could mediate the association between CRF and cognitive function in middle-aged and older adults; while WM lesions did not (Freudenberger et al., 2016; Verstynen et al., 2012; Weinstein et al., 2012).

In addition to brain structures, brain activation were also found to mediate the relationships between CRF and cognition in cognitively normal middle-aged and older adults (Hayes et al., 2017; Wong et al., 2015). Using cognitive dual-tasks, Wong et al. (2015) found that higher CRF was associated with better dual-task performance and

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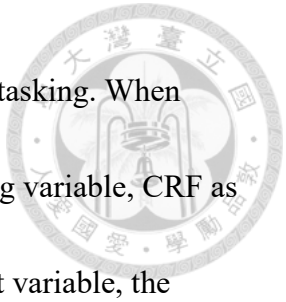

greater brain activation in the ACC, thalamus, and MFG during dual-tasking. When brain activation during dual-task processing was used as the mediating variable, CRF as the independent variable, and dual-task performance as the dependent variable, the results showed that greater ACC activation mediated the relationship between CRF and dual-task performance, controlling for age, sex, and education (indirect effect = −0.043; 95% CI = [−0.082, −0.012]). These findings suggested that greater activation within the ACC helped to facilitate the positive relationship between CRF and cognitive performance (Wong et al., 2015). Hayes et al., (2017) discovered that higher CRF was positively associated with higher accuracy on a face-name associative encoding task and greater activation in the bilateral prefrontal cortex, medial frontal cortex, bilateral thalamus and left hippocampus while performing this task in middle-aged and older adults. Results of mediation analysis showed that the activation in the medial frontal cortex mediated the relationship between CRF and the encoding performance (Indirect effect= 0.004, 95% CI= [0.0004, 0.0092]). Positive indirect effect suggested that greater activation in the medial frontal cortex assisted to facilitate the association between CRF and improved encoding performance (Hayes et al., 2017).

The evidence mentioned above mainly comes from cross-sectional studies. To further understand the mediation effects of brain structures or activation for the relationships between change in CRF and changes in cognitive functions, exercise

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intervention studies aimed to improve CRF were needed.

2.6 Effects of different exercises on CRF, CVRs indices, task-switching performance, and the brain

As reviewed above, cross-sectional studies have shown beneficial effects of high CRF on reducing CVRs, preserving better cognitive functions, better brain structures, and effective brain activation while performing cognitive tasks to counteract age-related declines in these aspects. The next important steps are to examine exercise intervention studies and ask: (1) whether engaging in regular exercises, which are known to improve a person's CRF and reduce CVRs, also improve cognitive function and help preserve better brain structures and effective brain activation, (2) which type of exercise would be most effective to improve all these four aspects of health-related measures, and (3) what are the interrelationships among these four aspects of measures after engaging in regular exercises in middle-age and older adults. Among the many exercise forms, aerobic exercises, Tai Chi Chuan exercises and stretching exercises are commonly practiced in older adults. Therefore, a brief introduction of these three types of exercises are given below.

Aerobic exercises, defined as engaging in continuous rhythmic activities of sufficient intensity, duration, or frequency aimed to improve CRF by using large muscle groups, include various forms, such as brisk walking, cycling, jogging, and swimming

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(Dimeo et al., 2012; Gaitán et al., 2020; McDonnell et al., 2011). Most meta-analysis results have shown that effective aerobic exercise programs that improve CRF usually are set at moderate intensity and last for 8 to 52 weeks, with 2-7 sessions per week and each session lasting for 20 to 60 minutes (Cornelissen et al., 2013; Cornelissen and Smart, 2013; Murtagh et al., 2015). Tai Chi Chuan (TCC), referred to as "meditation in motion," is composed of not only sequential multi-segmental body movements but also concentration and breathing control. Many studies have shown benefits of practicing TCC on cardiorespiratory function, muscle strength, balance, and coordination of whole-body movements (Lan et al., 1996; Wang et al., 2001). Due to the diverse forms, the number of practice time, practicing speed, and the depth of semi-squat posture, the exercise intensity of TCC could not be strictly regulated, but ranges from light-to-moderate (Lan et al., 2013b; Wang et al., 2013). Stretching exercises are known to have positive effects on reducing passive stiffness, relaxing the muscle, and increasing joint flexibility and muscle extensibility (Avela et al., 1999; Knudson et al., 2000; Page, 2012). The recommended dose of stretching exercise is at least three sessions per week, four to five stretches for each major muscle group per session, with each stretch being held for 15 to 30 seconds (Knudson et al., 2000). The following paragraphs will introduce three types of exercises: aerobic, TCC, and stretching exercises, and their effects on CRF, CVRs, brain, and cognition.

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2.6.1 Effects of different types of exercises on CRF

Based on several studies, effects on improving CRF in middle-aged and older adults are consistently positive for aerobic and TCC, but not for stretching exercise (Hotting et al., 2012; Kramer et al., 1999; Tworoger et al., 2003; Zheng et al., 2015). Hötting et al. (2012) conducted an RCT and compared effects of 6 months of aerobic cycling exercise and stretching exercises in sedentary middle-aged adults (40-56 years old). Both exercises were given twice a week for six months with a total of 48 sessions. The training intensity was set at 85% maximum heart rate (HRmax) for the aerobic group, but was not set for the stretching. The results showed that the participants' $\dot{V}O_{2peak}$ was improved by 15% (from 28.30 ml/min/kg to 32.53 ml/min/kg, $p < 0.001$) in the aerobic group but was not significantly changed in the stretching group after 6-month training (Hötting et al., 2012). Similar results were shown in another 6-month randomized controlled trial (RCT) study in older adults (aged 60–75 years). Participants in the aerobic walking group showed a significant improvement in $\dot{V}O_{2peak}$ (+5.1%), but the stretching/toning group did not (-2.8%) (Kramer et al., 1999).

Research findings support that TCC exercises could improve CRF in middle-aged and older adults (Zheng et al., 2015). A systematic review and meta-analysis that examined the effects of 12-month TCC training on $\dot{V}O_{2peak}$ in older adults, included

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three intervention trials using the RCT design (Zheng et al., 2015**)**. An effect size of 1.33 on $\dot{V}O_{2peak}$ was found for TCC exercises **(**Zheng et al., 2015**).** Stretching or toner exercises have not been shown effective in increasing CRF in middle-age and older adults (Hötting et al., 2012; Kramer et al., 1999). An RCT study comparing effects of a yearlong moderate-intensity aerobic exercise and stretching intervention in postmenopausal women showed that the $\dot{V}O_{2peak}$ was increased only by 1% in the stretching group, but by 10% in the aerobic group (Tworoger et al., 2003).

2.6.2 Effects of different types of exercises on indices of CVRs

Review articles on RCTs have shown that regular physical exercises, regardless of the type, are effective in reducing CVRs (Agarwal, 2012; Lin et al., 2015; Shephard and Balady, 1999). Therefore, regular physical exercises, regardless of the type, have been highly recommended by current therapeutic guidelines for controlling CVRs (Futterman and Lemberg, 2006). In the following paragraphs, the effects of exercises not specific to particular type and those of aerobic, TCC, and stretching exercises on improving CVRs will be reviewed.

A meta-analysis on 160 RCT studies examined effects of regular exercises, regardless of type, on many indices of CVRs in sedentary adults. All of the included RCT studies had one exercise intervention group, in which the participants received any

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type of exercise intervention for at least 2 weeks (median exercise duration= 12 weeks, maximum= 2 years), and a control group, in which the participants were not engaged in regular exercises. The results showed that regular exercises could significantly lower fasting insulin levels by 1.03 μIU/mL (95% CI= [-1.69 to -0.37]), HbA1c by -0.28% (95% CI= [-0.42 to -0.14]), and TG by 5.31 mg/ dL (95% CI= [10.63 to 0.89]) and increase HDL-C by 2.32 mg/dL (95% CI= [1.16 to 3.87]) (Lin et al., 2015). These findings suggest that engaging in any form of regular exercises is beneficial for reducing indices of CVRs in sedentary adults.

A systematic review on 15 RCTs showed that aerobic training (duration ranging from 6 to 52 weeks, mostly at moderate intensity) was effective in decreasing SBP by 3.2 mmHg (95% CI= [-5.0 to -1.3]) and DBP by 2.7 mmHg (95% CI= [-3.9 to -1.5]) in sedentary adults aged 25-68 years (Cornelissen et al., 2013). An RCT study by Dimeo et al. (2012) found that 8- to 12- week moderate-to-high intensity treadmill exercise program could significantly decrease SBP and DBP by 6±12 and 3±7 mmHg, respectively, in middle-aged and older adults with resistant HTN, who had concurrently taken 3 types of antihypertensive medicines (Dimeo et al., 2012). Yoshida et al. (2010) used a pre-post design and found that after receiving 16-week supervised aerobic exercise training (60 min/day, 2 to 3 times/week) with intensity set as 60−80% HRmax, 25 participants with dyslipidemia had a significant reduction in LDL-C at week 8 (by

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45%) and week 16 (by 50%), but no significant changes in TG and HDL-C (Yoshida et al., 2010). In another study also using the pre-post design, 51 patients with DM had a significant reduction in LDL-C and increase in HDL-C after 25-week light-to-moderate intensity supervised aerobic exercise training (Shakil-Ur-Rehman et al., 2017).

A meta-analysis by Liang et al. (2020) showed that in adults with essential HTN, regular (2-8 sessions/week with each session lasting about 30 to 60 mins) TCC training of 6 weeks to 18 months could significantly lower SBP by 12.47 mmHg (95% CI= [-16.00, -8.94]), DBP by 6.46 mmHg (95% CI= [-8.28, -4.64]) (Liang et al., 2020). A RCT of 9-month moderate-intensity TCC in 246 middle-aged and older adults with at least two CVRs showed that compared to the non-intervention control group, the TCC group presented significantly greater reduction in SBP by 13.33 mmHg, DBP by 6.45 mmHg, fasting blood glucose by 0.72 mmol/L, and HbA1c 0.39% (Chan et al., 2018). In summary, regular practice of TCC exercises for at least 6 weeks have shown promising effects on improving indices of CVRs in people who already have CVRs.

Although effects of stretching exercise on CRF are not significant, emerging evidence suggests that engaging in regular stretching exercises for at least 4 weeks could improve indices of CVRs (Bisconti et al., 2020; Kato et al., 2020; Park, 2015). A meta-analysis also showed that stretching exercises of at least 4 weeks could significantly reduce arterial stiffness (measured with pulse-wave velocity) and DBP by

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2.72 mmHg (95% CI= [-4.01, -1.43] mmHg) and improve vascular endothelial function in middle-aged and older adults (Kato et al., 2020). An RCT study by Bisconti et al. (2020) found that a 12-week stretching exercise program could decrease arterial stiffness by 25%, SBP by 4%, and DBP by 8% in healthy adults (Bisconti et al., 2020). In another 8-week RCT study in middle-aged and older adults with DM, HbA1c levels decreased significantly (from 7.4% to 6.8%) in the static stretching group (Park, 2015). It has been speculated that stretching exercises could improve CVRs through the mechanical deformation of the vascular bed, coupled with stimulation of group III muscle afferent fibers (Medeiros and Lima, 2017; Sobrinho et al., 2021). These mechanical inputs initiate a cascade of events resulting in peripheral vasodilation, increased muscle blood flow, reduced arterial stiffness, and improved endothelial function (Hotta et al., 2013; Kato et al., 2017; Kruse and Scheuermann, 2017).

2.6.3 Effects of different exercises on task-switching performance

Task-switching, a high-level executive function involving processes of attention, classification, inhibition, updating, memory retrieval and response to stimulus, allows a person to flexibly adapt behaviors among multiple task rules (Bae and Masaki, 2019; Jolly et al., 2017; Tsai and Wang, 2015; Wu et al., 2018). A task-switching research paradigm typically includes NS and switch conditions. In the NS condition, participants

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choose the correct behavioral responses according to the same single rule. In the switch condition, participants have to switch attention between different rules across trials and choose the correct behavioral responses according to the rule in each trial. Performance in the S condition usually becomes slower and less accurate compared to that in NS condition. The difference in performances between the S and NS conditions is called the switch cost (Bae and Masaki, 2019; Guiney and Machado, 2013).

Based on several studies, effects on improving task-switching performance in middle-aged and older adults are consistently positive for aerobic and TCC exercises, but not for stretching exercise (Fong et al., 2014; Kramer et al., 1999; Wu et al., 2018). An RCT in 124 sedentary older adults (aged 60-75 years) showed that those who receiving 26-week regular aerobic exercise (three times a week, 40 mins for each session) significantly improved task-switching performance compared to those in the stretching group (Kramer et al., 1999). An RCT on 58 sedentary older adults (aged 60-75 years) engaged in either aerobic exercise (brisk walking) or stretching and toning training for 6 months showed that the aerobic exercise group had a significantly greater reduction of behavioral measures of switching cost, compared to those in the stretching and toning group (Kramer et al., 2001). In sedentary older adults (65-75 years old), those who were engaged in regular Yang-style Tai Chi exercises for at least 5 years (three sessions a week, 30 mins each session) had shorter reaction time, lower switching

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cost, and higher accuracy while performing modified switching tasks (Fong et al., 2014). Wu et al. (2018) revealed that 12-week TCC exercises significantly reduced errors on the task-switching performance from pre- to post-intervention in older adults (Wu et al., 2018). However, the training effects on task-switching performance in middle-aged and older adults with CVRs remained unknown.

2.6.4 Effects of different types of exercises on brain structures and effectiveness of brain activation

Several intervention studies using MRI have shown consistently positive effects of aerobic and TCC exercises on improving brain structures and effectiveness of brain in middle-aged and older adults, but not of stretching exercises (Colcombe et al., 2006; Mortimer et al., 2012; Niemann et al., 2014; Tao et al., 2017; Voss et al., 2013; Wu et al., 2018). In the following paragraphs, the effects of aerobic exercises will be reviewed first, followed by those of TCC exercises.

Niemann et al. (2014) found that 12-month aerobic exercises with the vigorous intensity set at 60% $\dot{V}O_{2peak}$ could increase hippocampal volume significantly by 3.60% in healthy older adults. Colcombe et al. (2006) found that 6-month vigorous aerobic training at the intensity of 60-70% heart rate reserve (HRR) could increase volumes of the bilateral dorsal ACC and MFG, right IFG, and left superior temporal gyrus in older

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adults. Jonasson et al. (2017) studied the effects of 6-month aerobic training on cortical thickness in frontal regions and hippocampus volume in 60 sedentary healthy older adults (64–78 years). Results revealed that greater changes in cognitive scores were associated with greater increases in cortical thickness in dlPFC (Jonasson et al., 2016). An RCT on older adults showed that although there was no significant group difference in WM integrity between 12-month walking aerobic and stretching exercises, the increases in aerobic capacity after aerobic exercises were positively correlated with the increased WM integrity in the prefrontal, parietal, and temporal cortice (Voss et al., 2013).

Colcombe et al. (2004) found that older adults who received 24-week aerobic training at moderate-to-vigorous intensity (60–70% heart rate reserve) showed better cognitive performance and significantly greater activation in the right MFG, bilateral SFG, bilateral superior parietal lobules and reduced activation in the bilateral ACC while performing Ericksen Flanker tasks, compared to the stretching and toning group (Colcombe et al., 2004). However, Voelcker-Rehage et al. (2011) studied the effects of 48-week aerobic training at vigorous intensity (60% $\dot{V}O_{2peak}$) in older adults (aged 62–79 years) and found that after aerobic training, older adults decreased activation in the left MFG, ACC, middle temporal gyrus, and parahippocampal gyrus, and the right superior temporal gyrus. Both studies showed improvements in cognitive performance

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after aerobic training in older adults. However, the relationships between improved cognition and changed brain activation after aerobic exercises were not investigated.

In summary, 6- or 12-month aerobic exercises could not only improve cognitive performances in older adults, but also increase gray matter volume and cortical thickness in several prefrontal, parietal, and temporal regions, but not WM integrity. It might be possible that the methods used to measure WM integrity are not sensitive enough to detect its changes or WM integrity is more difficult to be changed with exercises than cortical regions in older adults. More intervention research is needed in this regard. Although there were no consistent findings of how aerobic exercises affect the amplitude of brain activation over task-switching relevant brain regions, given the concurrent findings on improved task-switching behavioral performances, it appears that older adults may become more able to use the strategies of greater activation or more efficient activation (with reduced activation) on task-relevant brain regions to achieve better executive functions after aerobic training. Both functional neural strategies are successful for older adults. However, correlation analyses between changes in behavioral gains and changes in cortical activation are needed to validate which strategy older adults use.

Regarding effects of TCC exercises on cognitive performances, an RCT showed that 12-week TCC exercises could significantly increase grey matter volumes of the left

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insula, putamen, hippocampus, amygdala, and inferior temporal gyrus with improved memory functions in middle-aged and older adults (aged 50-70 years) (Tao et al., 2017). Another RCT study using 40-week TCC exercises found increased total brain volume and executive functions in older adults (aged 60-79 years) (Mortimer et al., 2012). Wu et al. (2018) also found positive effects of 12-week 24-form Yang style TCC exercises on improving switching function (reduction of switching errors) and increasing brain activation in the task-relevant regions, including the left SFG, the left IFG, the left inferior parietal gyrus, and right MFG in cognitively normal middle-aged and older adults. More importantly, it was found that people who showed greater increases in the activation over the left SFG also showed greater improvement on task-switching performance after TCC training.

Evidence has shown that stretching exercises have no significant effects on changing brain structures and functional activation (Colcombe et al., 2006; Voss et al., 2013;Voelcker-Rehage et al., 2011). Voelcker-Rehage et al. (2011) investigated the changes in brain activation patterns after 12-month exercises of three types- aerobic, coordination, and stretching training. There showed decreased activation in prefrontal areas when performing Flanker tasks for the aerobic and coordination groups with improved cognitive performance, but there were no changes in cognitive functions and brain activation in the stretching group after training (Voelcker-Rehage et al., 2011).

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2.7 Knowledge gaps

After reviewing the above-mentioned literature, four major knowledge gaps are identified:

1. Little research has concurrently compared effects of aerobic, TCC, and stretching exercises on CVRs, CRF, brain structures, brain activation, and task-switching performance in middle-aged and older adults with CVRs.
2. Little research has examined correlations of changes in CVRs and CRF with changes in task-switching related brain structures and brain activation after exercise training in middle-aged and older adults with CVRs.
3. It remains unknown as to whether changes in task-switching related brain structures and brain activation would mediate the relationships between changes in CVRs and CRF and changes in task-switching performance after exercise training in middle-aged and older adults with CVRs.

Therefore, this study was proposed to address these issues.

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Chapter 3 Methods

3.1 Study design

This was an assessor-blind RCT (Figure 1).

3.2 Participants

Sedentary middle-aged and older adults with CVRs were recruited from the communities in the Taipei metropolitan region through advertisements posted at National Taiwan University Hospital. Each participant signed a consent form approved by the Research Ethics Committee of the National Taiwan University Hospital. The inclusion criteria were: (1) age between 45 and 80 years old, (2) literacy and intact cognition (Montreal Cognitive Assessment Taiwan version > 26) (Tsai et al., 2012), (3) with at least one of three CVRs (HTN, DM, or dyslipidemia), (4) being physically inactive (being engaged in physical activities less than 90 minutes per week) in recent one year (Fletcher et al., 1996), and (5) had no prior experiences with TCC or other meditative forms of exercises. In this study, HTN was defined as having resting SBP ≥ 140 mmHg, or resting DBP ≥ 90 mmHg, or receiving antihypertensive medication (Chobanian et al., 2003). Having DM was defined as GLU-AC being ≥ 126 mg/dL, or HbA1c ≥ 6.5%, or taking any antidiabetics treatment orally or by injection (American Diabetes Association, 2010; Petersmann et al., 2019). Having dyslipidemia was defined

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as TCHO > 200 mg/dL, or TG > 150 mg/dL, or who was receiving lipid-lowering medication (National Cholesterol Education Program, 2001; Taiwan Health Promotion Administration, 2003). The exclusion criteria were: (1) having any contraindications for MRI, (2) serious or uncontrolled cardiac or metabolic conditions, (3) severe renal failure, (4) symptoms or history of neurological diseases, including transient ischemic attack, (5) severe musculoskeletal disorders which would affect their mobility, (6) inability to follow instructions, (7) depression or psychiatric disorders (Geriatric Depression Scale-15 > 8) (Lee et al., 1993; Sheikh and Yesavage, 1986), and (8) having contraindications for doing exercises.

The sample size was estimated by using the G∗Power 3.1.9.2 software (Faul et al., 2009). Based on the effect size of 0.412 of TCC on cognitive performance reported by a previous study (Tao et al., 2017) and the 3 (groups- the AT, TCC, and ST groups) by 2 (time points) two-way repeated measures ANOVA design, a power of 0.8, and a significant level at α=0.05, the estimated total sample size was 60. Estimating a drop-out rate of 20%, 72 participants were needed for this study.

3.3 Procedures

All participants were signed the consent form. All potential participants underwent health/medical history surveys for screening first. All eligible participants were then

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stratified by age (45-64 vs 65-80 years of age) and sex, and randomly assigned to the AT, TCC, and ST groups. Blood tests, tests of psychological and physical functions, and brain image scans were performed at two time points: before training (pre-test) and after training (post-test). After finishing the pre-test, there were 12-week supervised exercise training for each exercise group. Finally, the post-test would be conducted after 12-week exercise training.

3.4 Exercise Training Programs

Participants in the three exercise groups undertook three one-hour (10 mins of warming up, 40 mins of exercises, and 10 mins of cool down) light (ST group) or light-to-moderate (AT and TCC groups) intensity exercise sessions for 12 weeks. The entire 12 weeks of exercises were supervised by an experienced TCC coach for the TCC group and by trained specialists for the AT and ST group. In the AT group, participants walked on a treadmill (832T, Horizon Fitness) or ride on a stationary bike (Horizon, USA) in each exercise's session. Intensity of the AT group was set at light intensity (57-64% HRmax) in the first two weeks; then light-to-moderate (57%-76% HRmax) in week 3 and week 4, and progressed to moderate intensity (65%-76% HRmax) from week 5 to week 12. In the TCC group, 24 forms of the Yang-style TCC was practiced, with three new forms taught per week. In the ST group, stretching exercises for the whole body

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muscle groups, including upper limbs, lower limbs, and the trunk, were applied. Each stretch hold for 20-30 sec, for 5-10 repetitions. The heart rate of all participants in all three groups was monitored using a Polar watch (Polar Electro Oy, RS300X, Kempele, Finland) to make sure they achieve predetermined target HR.

3.5 Equipment

The equipment used for measuring the task-switching performances

1. Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition Ltd., Bottisham, Cambridge, UK) was used to assess the task-switching performance through the intra-extra dimensional set shift (IED) test, a subtest from CANTAB (Robbins et al., 1994).
2. E-prime 2.0 (Psychology Software Tools, Pittsburgh, PA, USA) was used to implement the task-switching fMRI paradigm. The modified numerical Stroop task was used to assess the task-switching performance through E-prime 2.0 in this study

The equipment used for measuring the physical functions and CRF

1. Electronic sphygmomanometer (HEM-7210, Omron expertlink Co., Japan) was used to measure the resting SBP and DBP in sitting position during the screening test and the physical examination at pre- and post-tests.
2. Handheld dynamometer (Lafayette Instrument Co., Lafayette, IN, USA) was used to measure the muscle strength of bilateral knee extensors, which represent the muscle strength of lower extremities in this study.
3. Digital Hand Dynamometer (TTM Instrument Co., SKU: PE016, TKY, Japan) was

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used to measure the muscle strength of bilateral hand grip, which represent the muscle strength of upper extremities in this study.

4. Stationary cycle ergometer (Ergometrics ER800, Ergoline GmbH, Bitz, Germany) and the Breath-by-Breath system (MetaMax 3B, Cortex Biophysik GmbH, Germany) were used to measure CRF in the CPET.

The equipment used for MRI scans

All image data were acquired by using a 3-Tesla Trio MRI with a 32-channel head coil (Siemens Healthcare, Erlangen, Germany) at the National Taiwan University Hospital.

3.6 Assessment Tools

All participants underwent health/medical history surveys for screening and demographics. Blood tests for CVRs, tests of psychological and physical functions, and brain image scans were performed at two time points: before training (pre-test) and after training (post-test).

Demographics

The health/medical history surveys included participants' age, sex, education years, health condition, surgical history, and anthropometric measures (body weight, body height, waist circumstance). The general cognitive function was assessed with the

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Montreal Cognitive Assessment Taiwan version (Nasreddine et al., 2005; Tsai et al., 2012), level of depression was assessed with the Chinese version of Geriatric Depression Scale-15 (Lee et al., 1993; Sheikh and Yesavage, 1986). Daily physical activity level in the previous work was assessed with Physical Activity Scale for the Elderly (PASE) (Washburn et al., 1993).

Cardiovascular risks

The blood samples of all participants were collected to measure their CVR indices of fasting blood glucose, TCHO, TG, LDL-C, HDL-C and homocysteine before and after training. The measurement of resting SBP and DBP were conducted at the beginning of the physical examination by using the Electronic sphygmomanometer (HEM-7210, Omron expertlink Co., Japan) on the upper arm in the sitting position after 5-10 minutes of rest for each participant. The presence of CVRs was coded according to the values of the CVR indices and the medical conditions based on the criteria mentioned in operational definitions. Number of CVRF was calculated as the sum of the presence of any of the five vascular CVRF (HTN, dyslipidemia, heart disease, stroke, and smoking) and two metabolic CVRF (DM, and obesity) (Ruthirakuhan et al., 2022).

Task-switching performances

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Three types of neuropsychological assessments were used to assess task-switching performance in this study: the Color Trails Tests (CTT-1 and -2) (D'Elia et al.), intra-extra dimensional set shift (IED) of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins et al., 1994), and the modified numerical Stroop Test (Huang et al., 2012; Wu et al., 2018).

The CTT is composed of two parts- CTT- 1 and -2. The CTT-1 required the participant to quickly and correctly link sequential numbers from 1 to 25 with a pen. All odd numbers were embedded within circles that had a pink background, while all even numbers were embedded within circles that had a yellow background. Scoring consisted of time in seconds from initiation to completion of the task. The number of errors made were also recorded. The CTT-2 contains duplicates of each number from 1 to 15 embedded within pink and yellow circles. The participants were asked to work as quickly as possible and to try and not lift the pencil from the paper. In other words, the participant quickly connected Pink 1 with Yellow 2 then to Pink 3 and so on so forth from number 1 to number 25, alternating between pink and yellow colors. Scoring consisted of time in seconds from initiation to completion of the task. The number of errors committed were also recorded.

The IED is a subtest of CANTAB and is a 7-minute test on rule acquisition and rule changes. It features visual discrimination and attentional set formation,

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maintenance, shifting and flexibility of attention. Every trial of the IED was composed of unregular pink shapes and white lines, and the participant must use the feedback from the CANTAB to conceptualize the rule about which stimulus was correct. After six correct responses, the rule automatically changed. Initially, the IED task involves simple stimuli which were made up of just one of the pink shapes or white lines. Later in the task, compound stimuli were used with white lines overlapping on the pink shapes. The three parameters of IED used in this study were the number of total errors made, the number of trials completed, and the number of stages completed.

A modified Numerical Stroop test were used during the event-related task-switching fMRI paradigm to measure the task-switching behavioral performances as well as brain activation during task-switching. The paradigm was implemented using the E-prime 2.0 (Psychology Software Tools, Pittsburgh, PA, USA). Each participant received two runs of this paradigm before and after 12-week exercise interventions. Each run (approximately 7 min/run) includes two Non-switch blocks (physical size and numerical magnitude blocks in counterbalanced order across subjects, 12 trials for each block) first, followed by a Switch block (24 trials). In each trial, participants will see a pair of digits on screen and be asked to distinguish the size of digits by following the instructions given before each block. In the physical size block, participants had to distinguish which digit of the two was physically larger than the other, ignoring their

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numerical magnitude. In the numerical magnitude block, they needed to distinguish which of the two digits was numerically larger than the other, ignoring their physical size. Digit pairs were colored green and red in physical size and numerical magnitude blocks, respectively. In the Switch block, participants had to distinguish the physical size or numerical magnitude of the two digits according to stimulus color, with green indicating physical size distinction and red indicating numerical magnitude distinction. Each trial lasted 3 seconds and participants were asked to respond as soon and as account as possible in 3 seconds. Physical size and numerical magnitude of the two digits could be congruent or incongruent in a given trial, with half of the trials being incongruent in each block. Before starting the fMRI scanning, participants had two practice sessions to make sure they understood this task. An accuracy of ≥ 60% was needed before the participants could undertake the scanning. The RT and ER in Non-switch and Switch conditions and the Switch cost were measured in this study.

Physical examination

The pre- and post-training physical function tests of muscle strength, balance, mobility, and CPET. The muscle strength of bilateral knee extensors and hand gripping were measured twice with a handheld dynamometer (Lafayette Instrument Co., Lafayette, IN, USA; Wang et al., 2002) and a digital hand dynamometer (TTM

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Instrument Co., SKU: PE016, TKY, Japan), respectively. The best performances in twice measurements was chose to represent the strength of upper and lower extremities. Balance ability was assessed with the eyes-open one-legged stance test up to 30 s (Bohannon et al., 1984) and the Time Up and Go test. The average of the best trial performance of the bilateral leg from one-legged stance test and the shortest time from the Time Up and Go test were recorded. Mobility was assessed with two trials each of the Four Square Step Test (Dite and Temple, 2002). The better performance of the two trials was recorded. Cardiorespiratory endurance was assessed with one trial of the 6-Minute Walk Test (Brooks et al., 2003). The walked distance in the 6-Minute Walk Test was recorded.

Cardiopulmonary exercise testing

The cardiopulmonary exercise testing (CPET) was conducted at the Department of Physical Medicine and Rehabilitation of National Taiwan University Hospital under the supervision of physiatrists specialized in cardiac rehabilitation. Stationary cycle ergometer (Ergometrics ER800, Ergoline GmbH, Bitz, Germany) was used in this symptom-limited CPET. A non-rebreathing valve was connected to a mouthpiece with continuous 12-lead ECG and blood pressure monitoring to collect the gas exchange, heart rhythm, and BP of a participant during the CPET. Participants' body weight, body

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height, waist circumference, and resting SBP and DBP while sitting were measured before the CPET starts. In the first 3 minutes of the CPET, the resistance of the cycle remained 10 watts. Then the participant was asked to maintain the pedaling speed at 60-80 revolution per minute when the workload increased by 10 watts every minute. Rating of perceived exertion (RPE) was collected every 2 minutes by a researcher. The CPET would be terminated when the participant's $\dot{V}O_2$ and heart rate could not increase further as the workload continued to increase or when the participant had any of the following conditions: feeling exhausted or RPE ≥ 18 scores or abnormal exercise responses (including abnormal ECG, BP, heart rate, etc.) (Howley et al., 1995; Mezzani et al., 2013). Two parameters from the CPET were used in this study— the normalized $\dot{V}O_{2peak}$ and % predicted value (Itoh et al., 2013).

Brain Image data acquisition

Brain imaging data were acquired using a 3-Tesla Trio MRI scanner system with a 32-channel head coil (Siemens, Erlangen, Germany) at NTUH. Three types of brain images will be collected: a T1-weighted image using Magnetization-Prepared Rapid Acquisition Gradient Echo sequence with repetition time (TR) = 2000 ms, echo time (TE) = 2.98 ms, flip angle (FA) = 9°, 192 coronal slices, thickness = 1.0 mm, field of view (FOV) = 256 mm, matrix size = 192 × 256 × 208; a T2-weighted image in axial

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orientation parallel to the anterior and posterior commissures with TR = 7240 ms, TE = 101 ms, FA = 90°, 34 slices, thickness = 4.0 mm, FOV = 192 mm, matrix size = 256 × 256; and two runs of $T2^*$ weighted echo planar images (EPI), each with 209 volumes and coplanar with the T2 images, that measured blood-oxygenation-level dependent (BOLD) contrast with TR = 2000 ms, TE = 24 ms, FA = 90°, 34 slices, thickness = 4.0 mm, FOV = 192 mm, matrix size = 64 × 64, resolution = 3 × 3 × 4 mm^3.

3.7 Brain image data analysis

Volumetric analysis of the brain structural data analyzed using the Freesurfer (version 7.1.1, available at http://surfer.nmr.mgh. harvard.edu/) to segment the whole brain structures obtained from T1-weighted images (Fischl et al., 2002). The recon-all pipeline was run for every subject and two time points with standard settings. In the Freesurfer, T1-weighted images were averaged to increase signal-to-noise (SNR), reoriented into a common space, bias field corrected in which the intensity at each voxel was divided by the estimated bias field at that location, the skull was stripped using a deformable template model (Segonne et al., 2004). Then, the brain tissues were classified based on intensity gradients and anatomical positions between white and grey matter regions. Images were then automatically edited slice-by-slice for different brain area reconstructions. The output files from Freesurfer were used to calculate volumes of

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the bilateral SFG, MFG, dlPFC, IFG, OFG, hippocampus, ACC, thalamus, caudate, putamen, pallidum, and amygdala in this study.

The fMRI data analysis included preprocessing and general linear model (GLM) specification and estimations for first level and second level analysis. The brain image data analyzed by using Statistical Parametric Mapping (SPM 12; Wellcome Trust Centre for Neuroimaging, London, UK), which implemented in MATLAB version 16.0 (The MathWorks, Natick, MA, USA) software. Blood-oxygen level dependent (BOLD) signal represented the brain activation while performing switching task.

For the preprocessing of functional images, first, the reorientation, using the line from anterior commissure to posterior commissure of the first slice from T1-weighted images as the origin, was applied to all the functional images. Second, realignment for head motion correction was performed to minimize the influence of movement on image data by aligning the data to a reference time volume. All image data met the criteria of head motion < 3 mm in translation and < 3 degrees in rotation. Third, slice time correction was performed to decreased the effects the time differences between the slice acquisitions by realigning the images to the first image of each time series. Forth, co-registration was applied on functional images to co-planar T2 images, which was then co-registered to T1-weighted images. Fifth, normalization was then performing on the co-registered images to the Montreal Neurological Institute (MNI) template using

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the segmentation approach in SPM12. Sixth, spatially and temporally smoothed by using an 8-mm full-width half-maximum isotropic Gaussian kernel.

For the first-level whole brain analysis, we applied a general linear model for each session and each run with four task regressors, with six motion covariates, and a constant. Four task regressors included three regressors based on the vectors of onsets with the hemodynamic responses function for trials with correct responses in two Non-switch blocks (physical size blocks and numerical size blocks), and Switch blocks, and one regressor based on the onsets of incorrect trials across all blocks with the hemodynamic responses function. Six motion covariates included three translation parameters and three rotation parameters.

Individual contrast maps for Non-switch and Switch conditions and Switch > Non-switch contrasts were then provided as the dependent variable in a second-level group analysis with group (AT, TCC, and ST) and time (pre- and post-intervention) as independent variables. Then, the Switch > Non-switch contrasts generated from the whole-brain analysis for each group and each time point, a total of six contrasts, were used for creating disjunction map, and the threshold was set as voxel-wise $p < 0.001$ with FWE correction and at least of clusters $k \geq 50$ voxels.

To compare the group differences of functional activation, the ROI approach with the disjunction analysis method (Smith et al., 2013; Wu et al., 2018) was used to reduce

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errors from multiple comparisons between group contrasts in fMRI data processing, and to fairly consider all brain functional activation sensitive to switch > Non-switch contrasts across groups. Using the AlphaSim from RESTplus (Resting-State fMRI Data Analysis Toolkit, http://www.restfmri.net) to calculate the minimum voxel for the cluster size and the xjView software (https://www.alivelearn.net/xjview/) to determine the threshold from the disjunction map, the threshold was set at a significance criterion of voxel-wise uncorrected $p < 0.0001$ and a cluster size at least 34 voxels. From disjunction map and based on the threshold mentioned above, functional ROIs with 5 mm-radius spheres surrounding the peak activation coordinates were delineated. Mean BOLD response relative to rest fixation estimates for the NS and switch conditions were then extracted from each participant's first-level contrasts from each functional ROI using the Marsbar toolbox (Brett et al., 2002).

3.8 Statistical Analysis

All statistical analyses were performed using IBM SPSS version 21 (IBM Corp., Armonk, NY, USA). Distribution normality was assessed with a Kolmogorov-Smirnov test first. Non-parametric analysis was used while the parameter violated the normality. Descriptive statistics were applied to portray the baseline characteristics of the participants. Chi-square and one-way ANOVA tests were used to compare the baseline

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group differences. The parameters with significant baseline differences, the baseline would be controlled. Only participants who had complete sets of all data were entered into statistical analyses became the completer analysis approach was used in this study. A 3 (groups: AT, TCC, ST) × 2 (time points: pre- and post-test) two-way repeated-measures ANOVA was used to investigate effects of the AT, TCC and ST exercises on participants' CVRs, CRF, physical examination outcome variables and task-switching performances. A 3 (groups: AT, TCC, ST) × 2 (time points: pre- and post-test) two-way repeated-measures ANCOVA was used to investigate effects of the AT, TCC and ST exercises on participants' brain volumes and activation, by controlling age, sex, and education. Volumetric measures were additionally adjusted for estimated total intracranial volume (eTIV) by using the ANCOVA approach (Buckner et al., 2004; O'Brien et al., 2006). There were no group differences on most of these variables from two-way repeated-measures ANCOVA across the three groups. Therefore, data from the three groups were pooled for correlation and mediation analyses. Partial correlation analyses were performed to investigate relationships between change in CVRs or change in CRF and changes in brain activation, and relationships between change in CVRs or change in CRF and task-switching performances after exercise, controlling for age, sex, and education. Partial correlation analyses involving brain volumes parameters were additionally adjusted for the estimated total intracranial volume (eTIV) by using

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the ANCOVA approach (Buckner et al., 2004; O'Brien et al., 2006). The threshold was set at an alpha level of 0.5 for all statistical analyses. Bonferroni corrections were used in *post hoc* analysis as needed.

To investigate the mediating effects of changes in brain, a bootstrapped mediation analysis was conducted by using the PROCESS v.4 macro designed for SPSS (Igartua and Hayes, 2021). In this analysis, 1000 bootstrapped samples were drawn with replacement from the dataset to estimate a sampling distribution for the indirect mediation pathway. In this study, the independent variables (X) were changes in CVR and changes in CRF, the mediating variable (M) were changes in brain volumes and changes in brain activation, the dependent variable (Y) was changes in task-switching performances (Appendix 1). The total effects (path c) means the effect of the X on the Y, equal to the sum of direct and indirect effects of X on Y. The direct effect (path c') means the effect of X on Y after adding the M. The indirect effect (path ab) mean the mediating effects of M on the relationships between X and Y. The main requirement for a significant mediation is that the indirect effect of the independent variable (changes in CVR or CRF) through the mediator (changes in brain volume or brain activation) on the dependent variable (changes in task-switching performance) is significant (Gelfand et al., 2009; Zhao et al., 2010). All models were controlled for age, sex, and education. Indirect effects and 95% confidence intervals were reported. There are three types of

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mediation models, including complementary (with significant path ab and c, and positive a*b*c), competitive (with significant path ab and c, but negative a*b*c), and indirect-only mediation (with significant path ab only). Indirect effects can be interpreted as the strength of the relationship between the X and Y when accounting for the M (Hayes, 2009; Hayes and Little, 2018; MacKinnon et al., 2000; Zhao et al., 2010).

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Chapter 4 Results

4.1 Demographics and baseline differences in outcome measures

Two hundred and six volunteers were screened. One hundred and thirty-six of them were excluded for failure to meet the inclusion criteria, having conditions listed in the exclusion criteria, or time conflict (Figure 1). A total of 70 eligible middle-aged and older adults with CVRs were initially enrolled in this study and were assigned to the AT (N= 23), TCC (N= 23), or ST (N= 24) groups through the stratified randomization procedures according to sex and age (45-64 vs 65-80 years of age) (Appendix 2). During the entire course of the study, 4, 6, and 4 participants dropped out or were excluded from the AT, TCC, and ST groups, respectively, due to problems of time conflict, worse health conditions, or poor data quality (Figure 1). Considering the exploratory nature of this study and the 20% drop out rate of the data (Armijo-Olivo et al., 2009), the completer analysis approach was used in this study to allow for focus on investigating the 12-week training effects on different outcome variables. Thus, 56 participants (19 male and 37 female, mean age = 64.3 ± 7.4 years, age range= 45-79 years) were included in the final data analysis of this study, with 19, 17, and 20 participants in the AT, TCC, and ST groups, respectively (Figure 1).

Appendix 2 shows that demographics and clinical characteristics of the original AT, TCC, and ST groups before removing outliers and data from participants who dropped

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out (N= 70). There were no baseline differences in most of the demographic and clinical characteristic variables, except for the distributions of the number of CVRF, the percentage of people presenting HTN, the resting heart rate, and the resting SBP. There were significant baseline group differences in the distributions of the number of CVRF [$X^2(6,70)= 16.7$, $p= 0.010$], the percentage of people presenting HTN [$X^2(2,70)= 6.6$, $p= 0.036$], the resting heart rate [$F(2,67)= 4.8$, $p= 0.011$], and the resting SBP [$F(2,67)= 5.9$, $p= 0.004$]. The *post hoc* analysis for the distributions of the number of CVRF revealed a significant difference between the AT and TCC groups [$X^2(3,46)= 11.4$, $p= 0.010$], and between the AT and ST groups [$X^2(3,47)= 10.6$, $p= 0.014$]. The *post hoc* analysis for the percentage of the people presenting HTN in the AT group was significantly higher than that of the TCC groups [$X^2(1,46)= 5.9$, $p= 0.016$], and tended to be higher than that of the ST groups [$X^2(1,47)= 5.4$, $p= 0.020$]. *Post hoc* analyses revealed that the resting heart rate of the AT group tended to be lower than that of the TCC and ST group ($p= 0.029$ and $p= 0.025$, respectively), and the resting SBP of the AT group was significantly higher than that of the TCC group ($p= 0.003$).

Table 1 shows the demographics and clinical characteristics of the completers in the AT, TCC, and ST groups at pre-tests included in the completer analysis. There were no baseline differences in most of the demographic and clinical characteristic variables. However, the distribution of the number of CVRF significantly differed from the three

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groups [$X^2(6,56)= 12.8$, $p= 0.047$]. The *post hoc* analysis revealed a significant difference in this distribution between the AT and TCC groups [$X^2(3,36)= 12.0$, $p= 0.008$], with the AT and TCC groups showing a zero percentage of CVRF= 0 and 4, respectively. The distribution of CVRF in the AT and ST also tended to be different as shown in the *post hoc* analysis [$X^2(3,39)= 9.0$, $p= 0.029$]. There were also significant group differences in resting heart rate [$F(2,53)= 4.7$, $p= 0.013$] and resting SBP [$F(2,53)= 4.5$, $p= 0.016$]. *Post hoc* analyses revealed that the resting heart rate of the AT group tended to be lower than that of the TCC and ST group ($p= 0.034$ and $p= 0.030$, respectively), and the resting SBP of the AT group was significantly higher than that of the TCC group ($p= 0.013$) (Table 1). Given the similar baseline demographic and clinical characteristic findings between the original participant samples and the samples included in the completer analyses, the following reports are based on results of completer analyses only.

There were no baseline group differences in resting DBP, most blood CVR biomarkers and percentage of people presenting HTN, DM, or DLP (Table 3), CPET and physical examination performances (Table 4), task-switching performances (Table 5), the BOLD magnitude over 9 ROIs while performing the Numerical Stroop test (Table 6), and most of the brain volumetric measures (Table 7) (all $p> 0.05$). However, there were baseline group differences in peak workload [$F(2,53)= 3.3$, $p= 0.043$] from

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CPET measures (Table 4) and brain volume of subcortical GM [$F(2,49)= 4.1$, $p= 0.023$] and right ACC [$F(2,49)= 4.9$, $p= 0.012$] (Table 7). The *post hoc* analysis revealed that the right ACC volume of the TCC group tended to be lower than that of the AT and ST groups ($p= 0.042$ and $p= 0.018$, respectively). Baseline values of these outcome measures with baseline differences (Resting SBP, peak workload, subcortical GM volume, and the right ACC volume) were controlled as the covariates in the subsequent two-way ANCOVA procedures, while comparing the training effects on those measures (Tables 3, 4, and 7).

4.2 Exercise adherence and intensity during training

Figure 2 shows the mean exercise intensity measured across the 36 exercise sessions for the AT, TCC, and ST groups. According to our protocol, the intensity of the AT group was set at light intensity (57-64% HRmax) in the first two weeks; then light-to-moderate (57%-76% HRmax) in week 3 and week 4, and progressed to moderate intensity (65%-76% HRmax) from week 5 to week 12. As shown in Figure 2A, the exercise intensity of the AT group indeed increased from light to moderate gradually over the 36 sessions. The average exercise intensity of the AT and TCC groups across the 12 weeks fell within the moderate intensity range (64-76% HRmax), and that of the ST group fell within the light intensity range (57-63% HRmax) (ACSM, 2022).

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Table 2 shows the exercise adherence to the entire 12 weeks of training and exercise intensity during different period of the 12-week training of the AT, TCC, and ST groups. There was no significant group difference in exercise adherence [$F(2,53)= 2.7$, $p= 0.073$], but there were significant group differences in exercise intensity during weeks 1-2 [$F(2,53)= 36.5$, $p< 0.001$] , weeks 3-4 [$F(2,53)= 23.1$, $p< 0.001$], weeks 5-12 [$F(2,53)= 14.0$, $p< 0.001$], and the entire 12 weeks [$F(2,53)= 21.1$, $p< 0.001$]. *Post hoc* analysis revealed that the exercise intensity of the TCC group was significantly higher than AT and ST groups during weeks 1-2, weeks 3-4, and the entire 12 weeks (all $p< 0.0167$), and the intensity of the TCC group was additionally significantly higher than the ST group during weeks 5-12. The intensity of the AT group was significantly higher than the ST group during weeks 5-12, and the entire 12 weeks (both $p< 0.0167$),

4.3 Training effects on all outcome measures

The following sections of the results from the two-way analyses were focused on the group x time interaction effects and time main effects for emphasizing training effects on all outcome measures. Four parameters with baseline differences (Resting SBP, peak workload, subcortical GM volume, and the right ACC volume) were controlled as the covariates in the corresponding subsequent two-way ANCOVA procedures, while comparing the training effects on those measures.

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4.3.1 Training effects on CVR indices

Table 3 shows no significant group x time interaction effects on all CVR indices (all $p > 0.05$). There were significant time main effects on the homocysteine, HDL-C, and GLU-AC levels, and resting SBP. For the pooled data of the three groups, from pre- to post-tests, the level of the homocysteine improved from 11.3 ± 2.9 to 10.4 ± 2.8 μmol/L ($F(1,53)= 16.6$, $p< 0.001$) and that of the HDL-C improved from 54.6 ± 13.2 to 58.1 ± 15.0 mg/dL ($F(1,53)= 21.5$, $p< 0.001$), but the level of GLU-AC increased from 106.5 ± 17.2 to 111.7 ± 24.3 mg/dL ($F(1,53)= 8.5$, $p= 0.005$) and the resting SBP increased from 127.1 ± 19.2 to 129.5 ± 15.2 mmHg ($F(1,52)= 35.9$, $p< 0.001$).

4.3.2 Training effects on CRF and physical functions

Overall, the results from CPET and physical examinations revealed that there were improvements in most of the CRF and physical function measures for the pooled data of the three exercise groups after 12-week exercise training.

Table 4 shows that there were no significant group x time interaction effects on all CRF measures (all $p > 0.05$), but significant time main effects on the $\dot{V}O_{2AT}$, $\dot{V}O_{2peak}$, and $\dot{V}O_{2peak}$ in percentage of reference value. For the pooled data of the three groups, from pre- to post-tests, the $\dot{V}O_{2AT}$ improved from 11.4 ± 1.9 to 12.2 ± 2.1 ml/min/kg

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[$F(1,53)= 14.1$, $p< 0.001$], that of the $\dot{V}O_{2peak}$ improved from 17.9 ± 3.5 to 19.1 ± 3.5 ml/min/kg [$F(1,53)= 24.6$, $p< 0.001$], and that of the $\dot{V}O_{2peak}$ in percentage of reference value improved from 77.0 ± 13.0 to 82.3 ± 13.0 % [$F(1,53)= 24.3$, $p< 0.001$].

As for the results of physical examinations, there was a significant group x time interaction effect on the Sit and Reach Test results [$F(2,53)= 7.7$, $p= 0.001$]. The *post hoc* analysis revealed that the ST group, but not the other two groups, significantly improved trunk and lower limb flexibility from the pre-test to post-test ($p< 0.001$). There were significant time main effects on the grip strength, 6MWT, Sit and Reach test, one-leg standing, Four Square Step Test, Time Up and Go Test, and Five Times Sit to Stand Test. For the pooled data of the three groups, from pre- to post-tests, the grip strength improved from 24.3 ± 8.6 to 25.3 ± 8.2 kilograms [$F(1,53)= 6.3$, $p= 0.015$], the 6MWT performance improved from 527.2 ± 62.2 to 553.3 ± 56.6 meters [$F(1,53)= 24.5$, $p< 0.001$], the Sit and Reach test performance improved from -1.3 ± 11.3 to 2.2 ± 11.2 centimeters [$F(1,53)= 9.4$, $p= 0.003$], the one-leg standing performance improved from 26.2 ± 7.2 to 27.7 ± 5.6 seconds [$F(1,53)= 8.1$, $p= 0.006$], the Four Square Step Test performance improved from 7.8 ± 1.3 to 7.3 ± 1.2 seconds [$F(1,53)= 6.6$, $p= 0.013$], the Time Up and Go Test performance improved from 9.2 ± 1.4 to 8.4 ± 1.1 seconds [$F(1,53)= 13.8$, $p< 0.001$], and the Five Times Sit to Stand Test performance improved from 8.5 ± 2.0 to 7.8 ± 1.6 seconds [$F(1,53)= 8.5$, $p= 0.005$].

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4.3.3 Training effects on task-switching performances

For the performance of CANTAB variables, there were no group x time interaction effects or group main effects, but a significant time main effect on the IED $Stage_{completed}$. The IED $Stage_{completed}$ improved from 8.3 ± 1.0 stages to 11.3 ± 6.7 stages for the pooled data from the three groups [$F(1,53)= 10.5$, $p= 0.002$]. As for the performances on the modified Numerical Stroop tests, there were also no group x time interaction effects, but significant time main effects on $ER_{Practice\_S}$, $ER_{Practice\_NS}$, ER_{Scan_S}, ER_{Scan_NS}, RT_{Scan_S}, and RT_{Scan_SC}. For the pooled data of the three groups, from pre- to post-tests, the $ER_{Practice\_S}$ improved from 12.9 ± 8.7 to 9.0 ± 6.2 % [$F(1,53)= 13.0$, $p= 0.001$], $ER_{Practice\_NS}$ improved from 6.2 ± 5.1 to 4.2 ± 3.8 % [$F(1,53)= 6.7$, $p= 0.012$], ER_{Scan_S} improved from 3.7 ± 3.2 to 2.6 ± 2.1 % [$F(1,53)= 9.1$, $p= 0.004$], ER_{Scan_NS} improved from 1.4 ± 1.9 to 0.7 ± 1.3 % [$F(1,53)= 6.9$, $p= 0.011$], RT_{Scan_S} improved from 1056.4 ± 104.0 to 1014.5 ± 107.2 seconds [$F(1,53)= 19.1$, $p< 0.001$], RT_{Scan_SC} improved from 212.6 ± 88.6 to 175.9 ± 67.0 seconds [$F(1,53)= 10.0$, $p= 0.003$]. There was a group main effect on RT_{Scan_SC} ($p= 0.043$), with the RT_{Scan_S} of the AT group tended to be lower than that of the TCC group ($p= 0.038$, *post hoc* analysis) (Table 5).

4.3.4 Training effects on brain activation

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Figure 3 shows the whole brain activation pattern for the Switch > Non-switch contrast of the three groups at pre-, and post-tests based on the significance criterion of voxel-wise uncorrected $p < 0.0001$ and the cluster size ≥ 34 voxels. Results of the disjunction analysis further delineated the primary activated regions of the Switch > Non-switch contrast across the three groups and two time points (Figure 4). From the disjunction map, the 9 identified functional ROIs were the left IFG, SMA, SMFG1 and SMFG2, and the right SFG, MFG, amygdala, hippocampus, and thalamus (Appendix 3). Table 5 shows that the BOLD magnitude over the 9 ROIs while performing the modified Numerical Stroop tests. There were no group x time interaction effects or group main effects, but a significant time main effect on the BOLD magnitude of the left SMA for the Switch block. For the pooled data of the three groups, from pre- to post-tests, the BOLD magnitude of the left SMA for the Switch block decreased from 7.7 ± 5.4 to 7.0 ± 5.6 [$F(1,53)= 5.0$, p= 0.030].

4.3.5 Training effects on brain volumes

The results of training effects on brain volumes showed significant group x time interaction effects on the left MFG ($p= 0.010$) and the right pallidum ($p= 0.037$) volume (Table 7). The *post hoc* analyses showed that the ST group significantly increased the left MFG volume ($p= 0.014$) and the TCC and ST groups significantly decreased the

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right pallidum volume (both p= 0.004) from pre- to post-tests. There was also a time main effects on the left pallidum volume. For the pooled data of the three groups, from pre- to post-tests, the left pallidum volume decreased from 2084.0 ± 304.5 to 2072.5 ± 296.7 mm^3 [F(1,50)= 5.8,p= 0.020]. There were group main effects on the left IFG (p= 0.040) and the right MFG (p= 0.034) volumes. *Post hoc* analyses revealed that the left IFG volume in ST group tended to be higher than that of the TCC group (9607.9 ± 203.1 verse 8824.7 ± 220.8 mm^3, p= 0.035) and the right MFG volume in the TCC group tended to be higher than that of the AT group (19513.5 ± 332.9 verse 18276.1 ± 318.4 mm^3, p= 0.032) (Table 7).

4.3 Results of correlations

4.3.1 Relationships of changes in CVR indices with changes in task-switching performance, changes in brain activations, and changes in brain volumes

Results of the partial correlation analyses between changes in CVR and changes in task-switching performance, controlling for age, sex, and education, showed only a significant finding, ie., a positive correlation between changes in homocysteine and changes in ER_{Scan_NS} (r= 0.345, p= 0.011), suggesting that across all three groups those who had greater reductions in the homocysteine also had greater reductions in ER_{Scan_NS} after training (Figure 5A). There were no other significant correlations between changes

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in CVR indices and changes in task-switching performances (r= -0.388~0.366, p= 0.086~0.999).

Partial correlation analyses between changes in CVR indices and changes in brain activation, controlling for age, sex, and education, showed positive correlations between the reductions in DBP and decreased BOLD at the right hippocampus for Switch cost (r= 0.438, p= 0.001) (Figure 5B), and at the right amygdala in the Switch condition (r= 0.419, p= 0.002) (Figure 5C) and for Switch cost (r= 0.467, p< 0.001) (Figure 5D). These results suggested that those who had greater reductions in DBP had greater reductions in brain activation in over these two subcortical ROIs for task-switching.

4.3.2 Relationships of changes in CRF with changes in task-switching performances, changes in brain activation, and changes in brain volumes

Partial correlation analyses, controlling for age, sex, and education, showed no significant correlations of the changes in CRF indices and the changes in task-switching performance and the change in brain activations (all p> 0.05). The partial correlation analyses of relationships between changes in CRF indices and changes in brain volumes, controlling for age, sex, education, and eTIV, showed a positive correlation between changes in $\dot{V}O_{2peak}$ and changes in the left IFG volume (r= 0.309, p= 0.026) (Figure 4). This finding suggested that across all three groups those who had greater

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improvement in CRF also had a greater increase in the left IFG volume.

4.1 Results of mediation analysis

4.4.1 Mediating effects of changes in brain activations on relationships between changes in CVR indices and changes in task-switching performances

Many mediation models were tested in this study (Appendix 1). Only two significant mediating effects were found for the changes in brain activation to mediate the relationships between changes in CVR indices and changes in task-switching performances. Although the total effect (c) (β= -0.010, p= 0.788) and direct effect (c') (β= -0.030, p= 0.421) of changes in DBP on changes in ER_{Scan_S}, controlling for age, sex, and education, were not significant, changes in brain activation at the right hippocampus in the Switch condition fully mediated the relationships between changes in DBP and changes in ER_{Scan_S} (ab= 0.020, 95%CI= [0.001, 0.047]). The indirect effect, going in the positive direction, revealed that greater reductions in DBP were associated with greater reductions in brain activation at the right hippocampus in the Switch condition (a= 0.083, p= 0.052), which in turn, were significantly associated with greater reductions in ER_{Scan_S} (b= 0.245, p= 0.049) (Figure 6A).

The total effect (c) (β= 0.256, p= 0.259) and direct effect (c') (β= 0.389, p= 0.088) of changes in homocysteine on changes in ER_{Scan_S}, controlling for age, sex, and

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education, were not significant. Changes in brain activation of the right hippocampus in the Switch condition also fully mediated the relationships between changes in the homocysteine level and changes in ER_{Scan_S} (*ab*= -0.133, 95%CI= [-0.295, -0.015]), after controlling for age, sex, and education. The indirect effect, going in the negative direction, revealed that greater reductions in the homocysteine level were associated with less reduction in brain activation of the right hippocampus in the Switch condition (a= -0.488, *p*= 0.062), and which in turn, was significantly associated with less reduction in ER_{Scan_S} (b= 0.272, *p*= 0.026) (Figure 6B).

4.4.2 Mediating effects of change in brain volume on relationships between change in CRF and change in task-switching performance

The total effect (c) (β= 0.122, *p*= 0.566) and direct effect (c') (β= 0.246, *p*= 0.261) of changes in $\dot{V}O_{2peak}$ on the changes in ER_{Scan_S}, controlling for age, sex, and education, were not significant. The changes in the left IFG volume fully mediated the relationship between changes in $\dot{V}O_{2peak}$ and change in ER_{Scan_S} (*ab*= -0.124, 95%CI= [-0.347, -0.005]). The indirect effect, going in the negative direction, revealed that the greater increases in $\dot{V}O_{2peak}$ were associated with greater increases in the left IFG volume (a= 34.412, *p*= 0.026), which in turn, were associated with greater reductions in ER (b= -0.004, *p*= 0.069) (Figure 6C).

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The total effect (c) (β= 0.117, p= 0.828) and direct effect (c') (β= 0.512, p= 0.347) of changes in $\dot{V}O_{2peak}$ on the changes in IED $Stage_{Completed}$, controlling for age, sex, and education, were not significant. The changes in the left thalamus volume also significantly mediated the relationship between changes in $\dot{V}O_{2peak}$ and changes in IED $Stage_{Completed}$ (ab= -0.396, 95%CI= [-1.029, -0.033]). The indirect effect, going in the negative direction, represented that greater increase in CRF were associated with greater decreases in left thalamus volume (a= -75.390, p= 0.002), and which in turn, was associated with fewer IED $Stage_{Completed}$ (b= 0.005, p= 0.023) (Figure 8).

4.5 Summary of results

The results of this study showed that all three types of exercises could effectively reduce some of CVRs, and improve CRF and task-switching performance in middle-aged and older adults with CVRs. Pooled all the participants together, the changes in CVR were correlated with the change in brain activation; and the change in CRF was correlated with the change in brain volume. The changes in brain activation mediated relationships between changes in CVR and task-switching performance; the changes in brain volume mediated the relationships between changes in CRF and task-switching performance.

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Chapter 5 Discussion

5.1 Training intensity and physical activity level

Although the average exercise intensity was highest for the TCC group, followed by the AT group, and the lowest for the ST group, the physical activity level after training showed the tendency of being higher for the AT and ST groups, compared to the TCC group, the facts that most of the outcome measures in this study only showed main effects may be due to the facts that those who were trained at higher intensity were engaged in less physical activity daily, whereas those who were trained at lower intensity were more physically active daily.

5.2 Training effects on CVR, CRF and physical measures, task-switching performances, brain activation and brain structures

One purpose of this study was to compare the effects of 12-week AT, TCC, and ST exercises on various CVR, CRF, physical, cognitive, and brain outcomes in middle-aged and older adults with CVRs. Overall, the results primarily showed significant time main effects on improving CVR indices of homocysteine and HDL-C, CRF measures of VO_{2peak}, VO_{2peak} in percentage of reference value, and 6MWT, task-switching performances of the IED $stage_{completed}$, and RT and ER on the Modified Numerical Stroop test, and reducing BOLD magnitude over the left SMA in the Switch condition in this population. Significant group x time interaction effects were only found for the

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Sit and Reach Test on flexibility and on brain volume of the left MFG and right pallidum. In particular, the ST group showed significantly improved trunk and leg flexibility, increased left MFG volume, and the TCC and ST groups significantly reduced the right pallidum volume. Taken together, results of this study suggested that for middle-aged and older adults with CVRs, their CVR indices, fitness, cognitive flexibility, and specific brain activation and brain volume could be changes as long as the exercise intensity reached light to moderate.

5.2.1 Similar training effects on CVR, CRF and physical measures across three exercise groups

Results of this study showed that the three types of exercises of 12 weeks were effective on improving CRF and two CVR indices, including homocysteine and HDL-C in middle-aged and older adults with CVRs. These findings supported the beneficial effects of engaging in regular exercises, regardless of the type, on improving CRF and CVR indices in this population.

After 12-week training, the improvements of $\dot{V}O_{2peak}$ in percentage of reference value in the AT, TCC, and ST groups were 5.9%, 3.5%, and 6.4%, respectively. It may because the good compliance for each exercise group, which enhanced the activity levels for each group, and also results in the improvements in other outcome measures

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from physical examinations.

Contrary to our hypothesis, the ST group also improved their CRF with 6.4%. Previous studies showed consistently training effects on improving CRF in middle-aged and older adults for aerobic and TCC training, but controversial results for stretching exercise (Hotting et al., 2012; Kramer et al., 1999; Tworoger et al., 2003; Zheng et al., 2015). The fact that our ST group also improved their CRF might be explained by four possible reasons: (1) Different participant characteristics (age, sex, and numbers of CVRF) and exercise protocol; (2) baseline CRF of the ST group was relatively lower than that of the AT and TCC groups; (3) The change of lifestyle from relatively sedentary to relatively active; (4) The reciprocal associations between improved CVR and CRF.

First, the protocol of stretching exercise and participants in this study may differ from those in studies which showed stretching exercise would not improve CRF (Hotting et al., 2012; Kramer et al., 1999; Tworoger et al., 2003; Zheng et al., 2015). The protocol of the ST in this study emphasized breathing exercises in addition to only performing stretching exercises, which may differ from previous traditional active control stretching exercises, but rather close to yoga. Stretching exercises with slow and deep breaths were supported to increase relaxation feeling (Wongwilairat et al., 2018). Gohel et al. (2021) also found that one-year 5 times per week yoga practice could

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enhance pulmonary functions, flexibility, and CRF in 61 adults who were free from cardiorespiratory illness (aged 29-49 years, 60.7% were females) (Gohel et al., 2021)

Second, people with low CRF or with an inactive sedentary lifestyle may be easier to improve their CRF than those who already have high CRF or live with an active lifestyle (Itoh et al., 2013; Ross et al., 2016; Ross et al., 2015). Some studies supported that ST could increase CRF (Colcombe et al., 2006; Tworoger et al., 2003). Colcombe et al. (2006) found that 6-month stretching training could increase CRF by 5.3% VO_{2peak} in healthy sedentary community-dwelling older adults (aged 60–79 years). Tworoger et al. (2003) also found that a one-year stretching intervention increase 1% VO_{2peak} approximately in postmenopausal sedentary women (aged 50-75 years). Considering the lower baseline CRF of the ST group than that of the AT and TCC groups, it may be easier to improve their CRF for the ST group though the exercise intensity was light.

Third, 12-week regular supervised exercise training may change their lifestyle from relatively sedentary to relatively active, it may help to improve their CRF (Herdy and Uhlendorf, 2011). Herdy and Uhlendorf (2011) showed that those with active lifestyle would have better CRF. The exercise training protocol in this study asked the participants undertook exercise training three sessions a week, though not significant statistically, it still could notice that the PASE score of the ST group increased from 42.7 ± 26.9 to 53.9 ± 37.5 after exercise training (Table 3).

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Forth, the association between CRF and CVRs may be bidirectional or have interactive effects (Alahmari et al., 2020; Erez et al., 2015; Grundy et al., 2012; Kuziemski et al., 2019). Cross-sectional studies have shown the inverse relationships between CRF and CVR indices in people with or without CVRs (Alahmari et al., 2020; Berry et al., 2011; Wei et al., 1999) Previous evidence supported that CRF as a predictor or a protective role on CVRs (Alahmari et al., 2020; Grundy et al., 2012; Laukkanen et al., 2004). Emerging evidence showed that CVRs may have negative impacts on CRF (Erez et al., 2015; Kuziemski et al., 2019). In this study, results of the partial correlation analyses between changes in CVR indices and changes in CRF, controlling for age and sex, also showed that the reductions in insulin was significantly associated with improvements in 6MWT performance (r= -0.284, p= 0.038). Thus, we speculate that improved CVRs may through other mechanisms (eg. healthier cardiovascular system or better circulation system) to improve CRF. Previous studies supported that ST could improve SBP, DBP, HbA1c (Bisconti et al., 2020; Park, 2015) and muscle flexibility by increasing endothelial function, enhancing arterial remodeling, decreasing arterial stiffness, and promoting vascular function (Bisconti et al., 2020; Medeiros and Lima, 2017). Reduced CVR indices may be beneficial for the cardiovascular system; better flexibility may be advantageous to connective tissues through increased plastic elongation and muscle properties by lengthening the sarcomeres at the ends of muscle

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fibers (Sobrinho et al., 2021; Tran et al., 2001). According to previous studies, increases in CRF may be attributed to better pulmonary and muscular function results from stretching exercise (Gohel et al., 2021; Medeiros and Lima, 2017; Sobrinho et al., 2021; Tran et al., 2001; Udhan et al., 2018).

Our results of training effects on the homocysteine and HDL-C levels were consistent with previous studies. Regular exercises could decrease the homocysteine level (Chien et al., 2013; Palasuwan et al., 2011; Randeva et al., 2002) and increase HDL-C level (Lin et al., 2015; Shakil-Ur-Rehman et al., 2017). Chien et al. (2013) found that 8-weeks yoga exercise could decrease 46.5% homocysteine concentration in healthy young women (Chien et al., 2013). Randeva et al. (2002) found that 6-month brisk walking for 20–60 min for 5 days per week could significantly decreased homocysteine from 10.06 ± 3.22 to 7.36 ± 1.96 μmol/L ($p< 0.05$) and improve CRF in overweight young women (aged 24-37 years, n=21). Palasuwan et al. (2011) also found that 8-week TCC training could decrease homocysteine levels from 11.44 ± 1.88 to 9.51 ± 1.81 μmol/L ($p< 0.05$) in postmenopausal women without CVRs (aged 51-57 years). A meta-analysis on RCT studies showed that regular exercises, any type of exercise intervention lasting for at least 2 weeks (median exercise duration= 12 weeks, maximum= 2 years), could significantly increase HDL-C by 2.32 mg/dL in cognitive normal adults (Lin et al., 2015). Shakil-Ur-Rehman et al. (2017) reported that 25-week

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light-to-moderate intensity supervised aerobic exercise training could significantly increase HDL-C levels in patients with DM (Shakil-Ur-Rehman et al., 2017).

Additionally, contrary to our hypotheses about training effects on CVR indices, our results did not find improvement in GLU-AC and SBP after exercise training. These differences may be associated with the fact that the time the post-tests were performed was at after the Chinese New Year holidays. The fasting blood glucose and results of blood test at post-test may potentially be affected by the diet habit during the holidays. Table 2 shows slight changes in the percentage participants having HTN, DM, or DLP at pre- and post-tests for each group. The percentage of people having HTN in the AT group increased because one participant's resting SBP increased to 144 mmHg and became meeting the criterion of having HTN in this study. The percentage people having of DM in the TCC group decreased because one participant's HbA1c decreased to 6.3% and below the criterion of the DM. There was one participant's HbA1c increased to 6.5% in the ST group and met the criterion of DM.

5.2.2 Training effects on task-switching performances

Similar to the training effects on CRF and CVR indices, regardless of the types of exercises, our results showed that the task-switching performances improved after the 12-week exercise training (Table 5). Although numerous interventional studies have

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demonstrated that AT and TCC exercises can more effectively improve cognitive functions than ST exercises (Kramer et al., 1999; Kramer et al., 2001; Fong et al., 2014;Wu et al., 2018), emerging evidence has shown that yoga, and coordinative exercises, or increased physical activities also can positively influence cognition in older adults (Bosma et al., 2002; Gomes-Osman et al., 2018; Hoy et al., 2021; Kesavayuth et al., 2018; Ludyga et al., 2020). A systematic review on 6 RCTs by Hoy et al. (2021) showed that yoga exercises (duration ranging from 8 to 260 weeks, no intensity level reported) were effective in improving memory and executive funtions in healthy adults aged over 60 years. Though little evidence of ST effects on cognition was found, due to the protocol of stretching in this study similar to yoga and the effects of yoga also was considered similar to stretching exercise (Gothe and McAuley, 2016; Sherman et al., 2011), we speculated that ST also could improve cognitive functions in this population.

The reasons that could explain the enhanced task-switching performances across three exercise groups together in this study may be the improved CRF and the homocysteine and HDL-C levels after training. Better CRF has been shown associated with better cognitive performances in middle-aged and older adults (Brown et al., 2010; Edwards and Loprinzi, 2017; Freudenberger et al., 2016; Weinstein et al., 2012). Therefore, the participants' improvement in their fitness and mobility may have

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contributed to their improved switching performances. Previous studies which showed exercise effects on cognition were mostly conducted in healthy community-dwelling adults and not particularly focused people with CVRs. It had been known that presence of CVRs may affect cognitive performances in middle-aged and older adults (Beeri et al., 2022; Desideri and Bocale, 2021; Qin and Basak, 2020). Participants in all three groups showed reductions of the homocysteine level and increased of the HDL-C levels. Previous studies have shown that lower homocysteine is associated with improvement in memory performance in older women (Bryan et al., 2002) and higher HDL-C is associated with recall and discriminability performance in middle-aged and older women (Bates et al., 2017).

5.2.3 Training effects on brain activation and structures

Training effects on brain activation also did not show differential exercise effects, but the time main effect on decreasing BOLD magnitude at the left SMA in the Switch condition. The SMA, a part of the mPFC, involves selecting and organizing purposeful movements (Crone et al., 2006; Purves, 2017). Previous fMRI studies have shown that performing task-switching primarily requires prefrontal and parietal activation (Aron et al., 2004; Monsell, 2003; Shallice et al., 2008; Wu et al., 2018). Our results showed significant improvements in task-switching performances and decreased brain activation

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at the left SMA after 12-week exercise training. Based on the age-related compensatory activation brain reorganization model (Cabeza et al., 2018), we speculated that the 12-week exercise training may decrease the demand of the compensatory left SMA activation while performing the switching task because of the more effective activation of the prefrontal and parietal regions to fulfill better task-switching performances. That is, decreased brain activation in left SMA may reflect an effective reorganization of the brain network for performing task-switching.

However, our findings were inconsistent with previous studies which showed that exercise type may differentially affect brain function (Chen et al., 2020; Colcombe et al., 2004; Wu et al., 2018). Colcombe et al. (2004) found that older adults who received 24-week aerobic training at moderate-to-vigorous intensity (60–70% heart rate reserve) showed better cognitive performance and significantly greater activation in the right MFG, bilateral SFG, bilateral superior parietal lobules and reduced activation in the bilateral ACC while performing Ericksen Flanker tasks, compared to the stretching and toning group (Colcombe et al., 2004). Wu et al. (2018) also found positive effects of 12-week 24-form Yang style TCC exercises on improving switching function (reduction of switching errors) and increasing brain activation in the task-relevant regions, including the left SFG, the left IFG, the left inferior parietal gyrus, and right MFG in cognitively normal middle-aged and older adults, compared to the passive control group.

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We speculated that the lack of particular changes in brain activation following the AT training may be due to our mild to moderate intensity of the AT training. The studies by Colcombe et al. (2004) and by Voelcker-Rehage et al. (2011) both need greater than moderate intensity (60-70% HRR or 60% $\dot{V}O_{2peak}$) for their AT training. And, the lack of particular changes in brain activation after the TCC training in our study could be due to the poorer training effects of TCC on people who already have CVRs. Indeed, our TCC coach did report that the TCC participants in this study seemed to have greater difficulty with memorizing the 24 forms that were taught to them.

Results of this study showed a significantly increased left MFG volume in the ST group after the 12 weeks of training. The left MFG plays an important role in activating correct behavioral inhibition (Heitzeg et al., 2014) and emotional regulation (Grecucci et al., 2013). Functional connectivity studies have revealed negative functional connectivity between the medial prefrontal cortex and the amygdala, suggesting that activating the medial prefrontal cortex, including the MFG, would inhibit the activation of the amygdala (Roy et al., 2009; Sakaki et al., 2016; Thayer et al., 2009), and therefore prevents primitive emotions from occurring (Phillips et al., 2003; Thayer et al., 2009). That is, the stronger the negative connectivity between the medial prefrontal cortex and amygdala, the better the emotional regulation will be. Evidence has shown that mind-body interventions, such as stretching and yoga exercises, could promote

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positive emotional regulation (Barnes and Orme-Johnson, 2012; Yang et al., 2021). The program of the ST in this study included stretching and breathing exercises, and this were similar to yoga. It was speculated that ST may enhanced the activation of the MFG, which in turn, enlarged the brain volume this region.

The pallidum is involved in the mechanisms of reward and motivation (Smith et al., 2009) and task-switching (Shi et al., 2018). Contrary to our hypotheses, the volume of the pallidum was reduced in the TCC and ST groups after training. Given that our findings that the TCC group did not improve their task-switching performances and balance and muscle strength of the lower extremities to a greater extent than the AT and ST groups, we speculated that the particular benefits of task-switching drills during TCC practice may have not occurred in our TCC participants. It is possible that the training duration may be insufficient for this population to learn the 24 forms well. Lan et al. (2013) reported that 12-week TCC would be sufficient for those with only single CVRs to gain health benefits of TCC training, but 12-month TCC training would be necessary for those with CVDs to gain health benefits (Lan et al., 2013). The duration of training may need to be longer for the TCC training group, since the majority of the TCC group had multiple CVRs. Regarding the reduction of the right pallidum volume of the ST group it may be due to decreased dependence on the reward system after becoming better in emotional regulation (ref)找 yoga, mediation 下降 basal ganglion

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volume.

5.3 Correlations of changes in CVR indices and CRF with changes on task-switching performances and the brain

5.3.1 Changes in CVR indices were associated with changes in task-switching performance and subcortical activation

Our findings showed that people with greater reductions in the homocysteine level presented greater improvements in task-switching performances, ie., greater reduction in the ER of the Non-switch trials during fMRI scan. Cross-sectional studies have shown the higher homocysteine levels are associated with poorer cognitive function in nondemented older adults (aged 60-90 years) (Budge et al., 2002; Prins et al., 2002). A meta-analysis study on 48 cross-sectional studies, revealed inverse relationships between greater homocysteine levels and poorer cognitive performance in middle-aged and older adults (Setien-Suero et al., 2016). Though interventional studies have supported that regular exercises could help decrease the homocysteine level (Chien et al., 2013; Palasuwan et al., 2011; Randeva et al., 2002), no research has investigated the relationships between changes in the homocysteine level and changes in cognitive performance after exercise training. Thus, to our best knowledge, our study was the first RCT to support that reduced homocysteine level after exercises was associated with task-switching performance improvements in middle-aged and older adults with CVRs.

Although previous studies have demonstrated that presence of CVRs has negative

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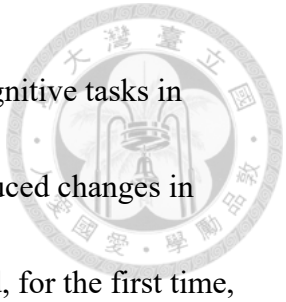

impacts on brain structures and brain activation while performing cognitive tasks in middle-aged and older adults, the relationships between exercise-induced changes in CVRs and changes in the brain remain unknown. This study explored, for the first time, the relationships of exercise-induced changes in CVRs and the brain. The results showed that the exercise-induced reductions in DBP were significantly positive correlated with reductions in brain activation at the right amygdala and hippocampus after the 12-week training. There were no significant relationships between changes in CVRs and changes in brain volumes found. Having CVRs could affect the conditions of cardiovascular systems and disturbed cerebral hemodynamics indirectly. Presence or poor-controlled CVRs may lead to endothelial dysfunction of cerebral vessels, neuronal dysfunction, neurotransmitter changes, increase oxidative stress and inflammation, and brain hypoperfusion (de la Torre, 2012; Flicker, 2010; Peri-Okonny et al., 2015). In this study, brain activation was measured by using the BOLD signals. The BOLD signal is known to reflect the neurovascular coupling — i.e., the neuronal activity required while performing cognitive tasks influences the hemodynamic responses of cerebral blood flow, cerebral blood volume, and cerebral blood oxygen consumption of the surrounding vasculature (D'Esposito et al., 2003). Changes in blood pressure have been found to be associated with the detection of BOLD signals in fMRI studies (Gianaros et al., 2008; Hendriks-Balk et al., 2022; Wang et al., 2006). An animal study revealed that

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blood pressure increases resulting in an enhanced cerebral activation and the blood pressure decreases produced corresponding decreases in BOLD intensity (Wang et al., 2006). Gianaros et al. (2008) reported those with greater stressor-evoked mean arterial pressure reactivity exhibited greater amygdala activation. Hendriks-Balk et al. (2022) found the BOLD signal intensity responses to cold pressor test were greater in those without HTN compared to those with HTN. Therefore, we speculate that exercise-induced improvement of DBP may have influenced the cardiovascular function and indirectly influenced the brain activation.

In this study changes in CVRs did not show any significant correlations with changes in brain structure. We speculated that changes in brain volumes task a longer period of time and reflect a more static change of the brain, whereas changes in BOLD reflect more dynamic hemodynamics that are more likely to be influenced by CVRs.

5.3.2 Change in CRF was correlated with change in brain volume

There were no significant associations between changes in CRF indices and changes in task-switching performances in this study. Espana-Irla et al. (2021) found that this association was age-specific, and mainly occurred in older adults, not in younger middle-aged subgroup (aged 40– 54 years). We speculated that the small range of improvement in CRF (3.5%~6.4%) due to the low to moderate intensity of exercise

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may make it difficult to find these associations. However, our study did reveal a significant association between improvements in $\dot{V}O_{2peak}$ and increases in the volume of the left IFG. Previous studies have demonstrated that regular exercises and better CRF have positive impacts on brain structures (Colcombe et al., 2003; Gordon et al., 2008; Jonasson et al., 2016). However, the relationships between exercise-induced changes in CRF and changes in brain structure in middle-aged and older adults with CVRs remain unknown. Our results were consistent with the hypotheses and previous studies performed on the general older population (Erickson et al., 2011; Nagamatsu et al., 2016).

The IFG is supplied by the distal cortical branches of the middle cerebral artery. We speculated that greater improvement in CRF may better improve the blood supply to three distal branches and enhance the synaptogenesis, angiogenesis and neurogenesis over the IFG (Cotman et al., 2007; Stillman et al., 2016)

5.4 Change in brain structures and activation mediated the relationships of changes in CVR and CRF with changes in task-switching performances, respectively

There were four significant mediation models found in this study. Among them, two of them supported the hypotheses, the other two refuted the hypotheses. Those supported the hypotheses are discussed first.

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One of the significant mediation model showed a positive indirect effect of changes in DBP on changes in ER_{Scan_S} via the changes in the BOLD magnitude of the right hippocampus in the Switch condition. That is, exercise-induced reduction in DBP indirectly lower the ER_{Scan_S} through lowering the BOLD magnitude of the right hippocampus in the Switch condition. Lowering the BOLD magnitude of the hippocampus, as an effective mediator between reductions in DBP and reductions in task-switching error. Therefore, reductions of the BOLD of the right hippocampus during task-switching indicated a successful functional reorganization while performing the switching task in middle-aged and older adults with CVRs after training (Cabeza et al., 2018). It was speculated that lowering the dependency on the brain activation at the right hippocampus could indirectly promote the brain efficiency while performing switching task in people with CVRs.

The hippocampus, located in the deep part of the medial temporal lobe, is part of the limbic system (Bettio et al., 2017). The roles of the right hippocampus in cognitive functions include conjunctive (Rudy and O'Reilly, 2001), relational (Giovanello et al., 2004; Holdstock et al., 2010), spatial learning (Konishi et al., 2017), recollective, and associative forms of memory (Brown and Aggleton, 2001). Thus, the hippocampus plays a crucial role in learning and memory consolidation (Konishi et al., 2017). Review articles and neuroimaging studies have revealed that brain regions correlated with task-

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switching usually are located in the medial and lateral regions of the prefrontal cortices while performing switching task (Aron et al., 2004; Hakun et al., 2015; Liakakis et al., 2011; Shallice et al., 2008), and sometime in the parietal lobes, cerebellum, and some subcortical regions (Monsell, 2003). In the beginning of the study task, our participants may need to use the hippocampus to learning and memorize the rules of the task-switching modified Numerical Stroop test, after they became more used to the rules, they may no longer need so much of the activation of the right hippocampal activation to perform the tasks.

As mentioned in the section 5.2.2, BOLD magnitude, reflecting the neurovascular coupling, may be affected by the cerebral hemodynamic responses (D'Esposito et al., 2003; Wang et al., 2006). Reduction of DBP may affect the cerebral hemodynamic responses and the brain perfusion (de la Torre, 2012). The hippocampal vascular supply may affect the cognition (Perosa et al., 2020). Therefore, we suspect that improving the conditions of CVRs may improve the cardiovascular function and indirectly improve the cognitive function through the mediation of the reductions of unnecessary brain activation.

When it comes to the interrelationships among changes in CVRs, in brain, and in cognition after exercises, previous studies only used changes in brain structures as the mediators (Luo et al., 2019; Moran et al., 2019; Wang et al., 2017) or used brain

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perfusion to build up these complex associations. There was little evidence using brain activation as the mediators. This is the first study using brain activation while performing switching tasks as the mediators to discuss the interrelationships among changes in CVRs, brain activation, and task-switching performance after exercise training.

The CRF-related mediation model which correspond to our hypotheses was that the increased left IFG gray matter volume could fully mediated the relationships of the enhanced $\dot{V}O_{2peak}$ and the improved task-switching performance. Patient-lesion studies and neuroimaging studies have revealed that the left IFG is critical for post-retrieval selection for resolving proactive interference during task switching (Badre and Wagner, 2007; Zhang et al., 2004) and response inhibition (Swick et al., 2008). A meta-analysis on 485 functional imaging studies on healthy adults showed that the left IFG is involved in working memory (Brodmann area 44), language processing (semantic, phonological processing, Brodmann area 45/46) and empathy (Brodmann area 47). Chung et al. (2017) found that healthy older adults (N=39, aged 65–92 years) with lower gray matter volume in the left ventrolateral prefrontal cortex not only made irrational economic decisions more frequently but also made more severe economic errors in decision making. This finding pointed out that the left vlPFC is also crucial for appropriate decision-making and suggested that changes in gray matter volume may affect cognitive

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performance (Chung et al., 2017).

Our findings were consistent with findings of previous studies which showed that brain volume of the frontal regions were mediators between CRF and cognitive function in middle-aged and older adults (Hayes et al., 2013; Weinstein et al., 2012). Greater volumes of the right IFG were mediated the relationships between better CRF and better Stroop performance; and greater dlPFC volumes mediated the associations between better CRF and better spatial working memory performance (indirect effect= 0.114, 95% CI= [0.007, 0.343] for the right dlPFC; indirect effect= 0.116, 95% CI= [0.010, 0.307] for the left dlPFC) (Weinstein, A. M. et al., 2012). However, these studies were only cross-sectional studies.

In healthy older adults, Erickson et al. (2011) also found that the correlations between greater improvement in CRF after aerobic exercise were associated with greater increases in the volume of hippocampus, and greater increase in hippocampus volume were associated with greater improvements in memory performance. However, they did not perform the mediation analysis to reveal the complex interrelationships among changes in CRF, in brain volume, and in cognition. Furthermore, most studies investigated the issues of CRF-related mediation between brain structure and cognitive performance in healthy adults, few studies have examined in middle-aged and older adults with CVRs. Thus, this study is the first one that reported changes in the left IFG

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volume after exercise training mediated the relationship between improvements in CRF and improvements in task-switching performance.

We also found two significant indirect-only mediation models that were refuting our hypotheses: (1) changes in brain activation of the right hippocampus in the Switch condition mediated the relationships between changes in the homocysteine level and changes in ER_{Scan_S} (ab= -0.133, 95%CI= [-0.2953, -0.0148]), (2) changes in the brain volume of the left thalamus mediated the relationship between changes in $\dot{V}O_{2peak}$ and change in numbers of IED $Stage_{completed}$ (ab= -0.396, 95%CI= [-1.0288, -0.0325]).

The directions of these two indirect effects went in the negative direction which were primarily due to the negative β between the relationships of changes in homocysteine and changes in the BOLD of the right hippocampus in the Switch condition and the negative β between the changes in $\dot{V}O_{2peak}$ and changes in the volume of the left thalamus. These two mediation models contradicted to our expectations. According to Zhao et al. (2011), these significant but unexplainable mediators are yet be taken into more complex models, such as Structural equation modeling, to figure out the complex relationship among independent variables, dependent variables and mediators.

5.5 Strengths and limitations of this study

There were three strengths of this study. First, this is the first study using the

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exercise-induced change in CVRs to investigate protective effects of exercise on task-switching performance and brain activation. Second, this is the first study using mediation analysis to investigate the complex interrelationships among exercise-induced changes in CVRs, CRF, the brain, and task-switching performances. Third, this is the first study that differential neural mechanisms through which the relationships between changes in CVRs and changes in CRF with changes in cognitive functions after exercise training can be effectively altered.

There were five limitations of this study. First, the completer (per-protocol) analysis instead of the intention-to-treat analysis were used due to the 20% drop out rate (Armijo-Olivo et al., 2009). Intention-to-treat analysis is a strategy used to analyze every participant who is randomized at the beginning of an RCT (Gupta, 2011) in order to keep the randomization of the study sample. Using the completer analysis may decrease the total sample size and may lead to potential selection bias because completers could not represent the entire target sample, and may not reflect the training effects in a real life situation (Montori and Guyatt, 2001). However, we have reported that the demographics of the completer were very similar with those of the original sample. Therefore, we expected that our results still could reflect the results of the original sample. Second, there were baseline differences in the number of CVRF and resting SBP among the three groups, which may affect the training results despite of

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using statistical procedures to control for baseline difference. Third, the time point for post-tests was close to the Lunar New Year holidays. The more sedentary lifestyle and unhealthy diet condition during these holidays may have negative impacts on CVRs, and may have cancelled out some of the beneficial effects of the 12-week exercise training. Fourth, it was difficult to control some covariates (eg., diet and habits). Fifth, this study only used simple mediation models, more complex models are needed to clarify the interrelationships among changes in CVRs, CRF, the brain, and task-switching performances in the future studies.

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Chapter 6 Conclusions

Our results supported that light to moderate intensity exercises could effectively improve physical and cognitive health in middle-aged and older adults with CVRs regardless of the types of exercise. Our results also provided different brain mechanisms (BOLD or volume) mediated the relationships between changes in CVRs and changes in CRF with changes in task-switching performances in middle-aged and older adults with CVRs. In summary, this study shed light on the underlying neural mechanisms that mediated exercise-induced cognitive effects and highlighted that the negative impacts from CVRs on cognitive performances are reversible through regular exercises in this population.

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Figure

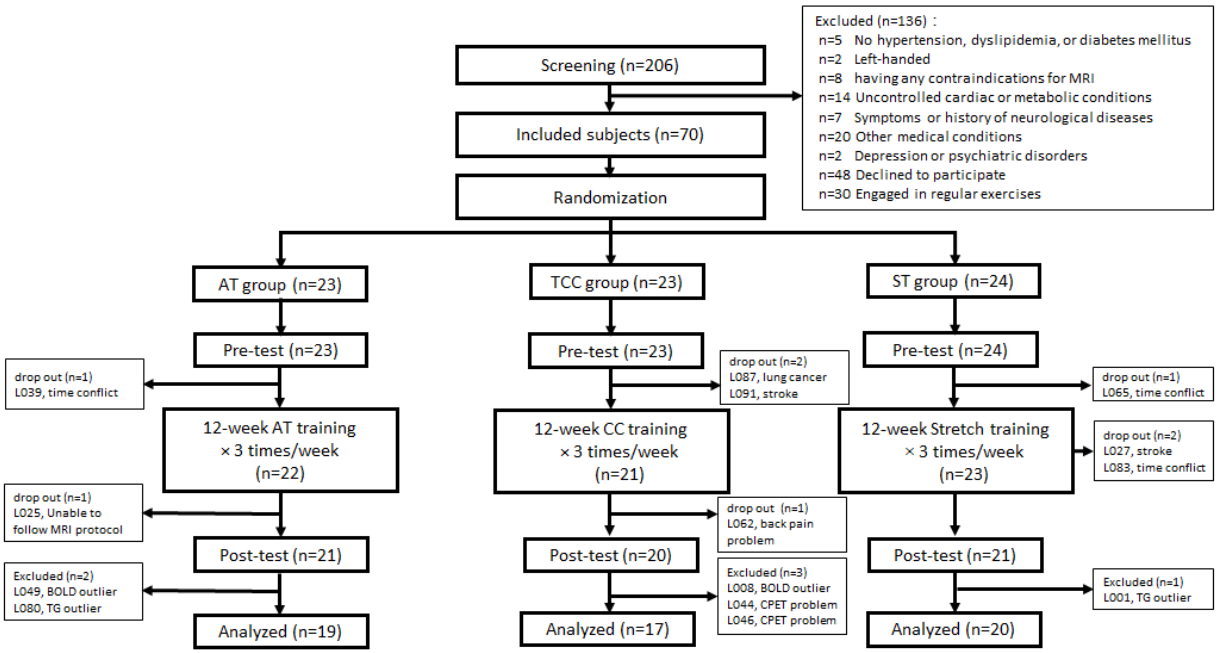

Figure 1. Consort chart of the entire randomized controlled clinical trial.

Abbreviations: AT= Aerobic training group; TCC= Tai Chi Chuan group; ST= Stretching training group.

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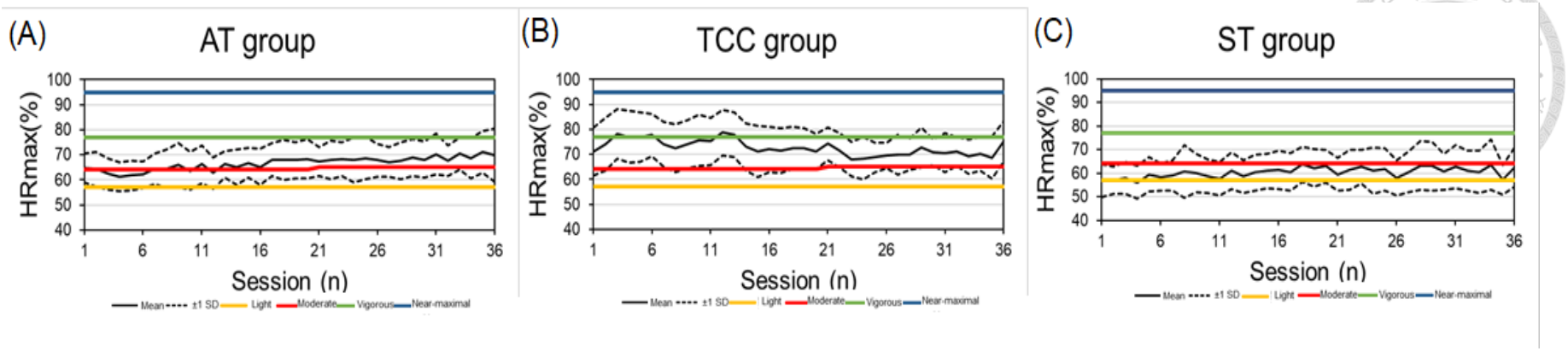

Figure 2. Training intensity across 36 exercise sessions for the AT, TCC, and ST groups.

(A)-(C) Training intensity expressed in percentage of HRmax for the AT, TCC, and ST groups, respectively, across the 36 sessions. Each thick black line indicates the mean intensity of the entire group; each dashed black line indicates 1 standard deviation above or below the mean intensity of the entire group. The yellow line indicates the cutoff criterion of light exercise intensity (57% HRmax), the red line indicates the cutoff criterion of moderate exercise intensity (64% HRmax), the green line indicates the cutoff criterion of vigorous exercise intensity (77% HRmax), and the blue line indicates the cutoff criterion of near-maximal exercise intensity (96% HRmax) according to the ASCM Guidelines. Abbreviations: ACSM= American College of Sports Medicine; AT= Aerobic training group; HRmax= Maximum heart rate; ST= Stretching training group; TCC= Tai Chi Chuan group.

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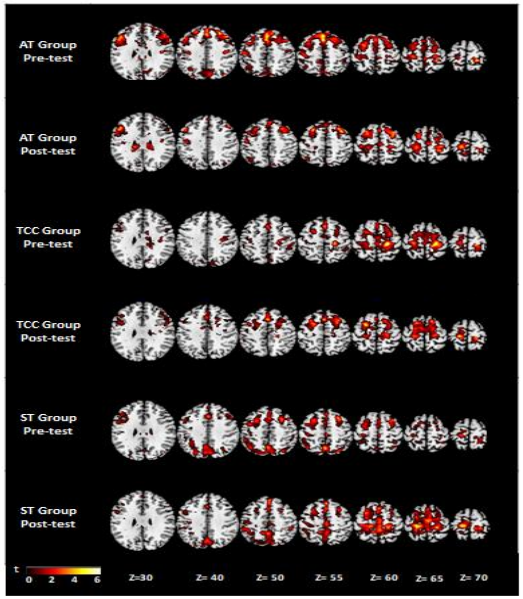

Figure 3. Brain activation patterns for the Switch > Non-switch contrast of the AT, TCC, and ST groups at Pre-, and Post-tests

Brain activation patterns for the Switch > Non-switch contrast of the AT, TCC, and ST groups at Pre-, and Post-tests based on the significance criterion of voxel-wise uncorrected $p < 0.0001$ and the cluster size of at least 34. The locations of Z from the MNI coordinate were presented. The range of t value was presented as color bar. Abbreviations: AT= Aerobic training group; TCC= Tai Chi Chuan group; ST= Stretching training group.

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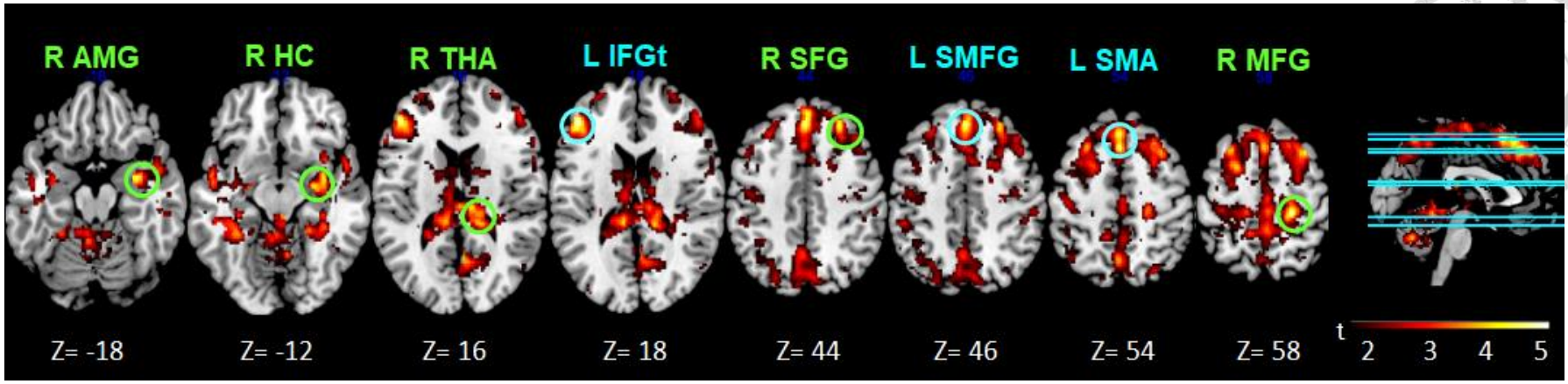

Figure 4. Disjunction map.

Disjunction map of the Switch > Non-switch contrast across three groups and two time points showing the right ROIs for brain activation analysis.The locations of Z from the MNI coordinate were presented. The range of t value was presented as color bar. The locations of the functional ROIs from right hemisphere are indicated using green colored circles; those from left hemisphere are indicated using brilliant blue circles. Abbreviations: AMG= Amygdala; HC= Hippocampus; IFGt= Triangularis of inferior frontal gyrus; L= Left; MFG= Medial frontal gyrus; R= Right; SFG= Superior frontal gyrus; SMA= Supplementary motor area; SMFG= Superior medial frontal gyrus.

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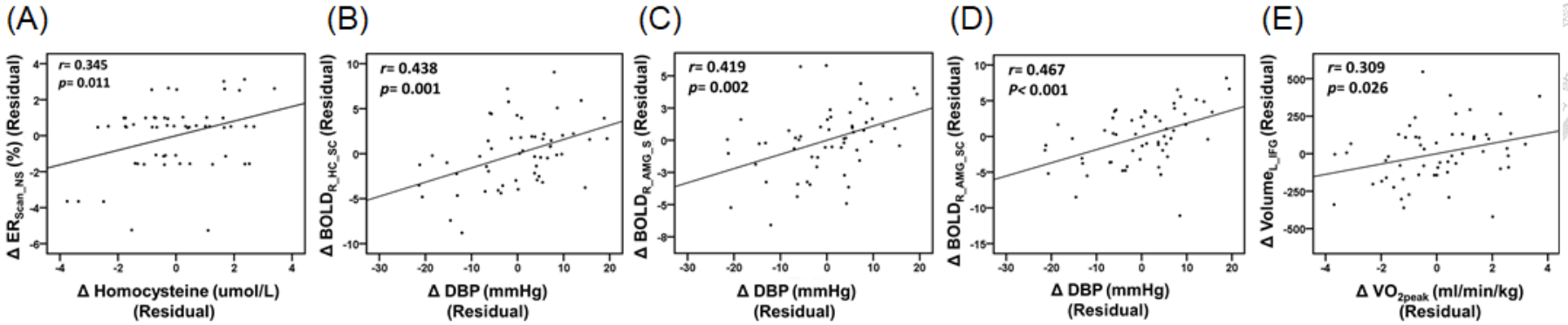

Figure 5. Partial correlation plots

Partial correlation plots of changes in CVRs or CRF versus changes in task-switching performance or changes in the brain after training for pooled subjects across the three groups. Covariates were age, sex, and education for (A)-(D), and plus the estimated total intracranial volume for (E). (A) Δ homocysteine were correlated with Δ ER_{Scan_NS} ; (B) Δ DBP were correlated with Δ $BOLD_{R\_HC\_SC}$; (C) Δ DBP were correlated with Δ $BOLD_{R\_AMG\_S}$; (D) Δ DBP were correlated with Δ $BOLD_{R\_AMG\_SC}$. (E) Δ VO_{2peak} were correlated with Δ $Volume_{L\_IFG}$. Change (Δ) = Data value from Post-test – data value from Pre-test. Abbreviations: AMG= Amygdala; BOLD: Blood oxygen level dependent; $BOLD_{R\_AMG\_S}$ = Brain activation at the right amygdala in the Switch condition of the Modified Numerical Stroop test; $BOLD_{R\_AMG\_SC}$ = Brain activation at the right amygdala for Switch cost; $BOLD_{R\_HC\_SC}$= Brain activation at the right hippocampus for Switch Cost; CRF= Cardiorespiratory fitness; CVRs= Cardiovascular risks; DBP= diastolic blood pressure; ER_{Scan_NS}=Error rate in the Non-switch condition while performing the Modified Numerical Stroop test during the fMRI scans; HC= Hippocampus; IFG= inferior frontal gyrus; NS= Non-switch condition of the Modified Numerical Stroop test; S= Switch condition of the Modified Numerical Stroop test; SC= Switch cost; $Volume_{L\_IFG}$= Brain volume at the left inferior frontal gyrus.

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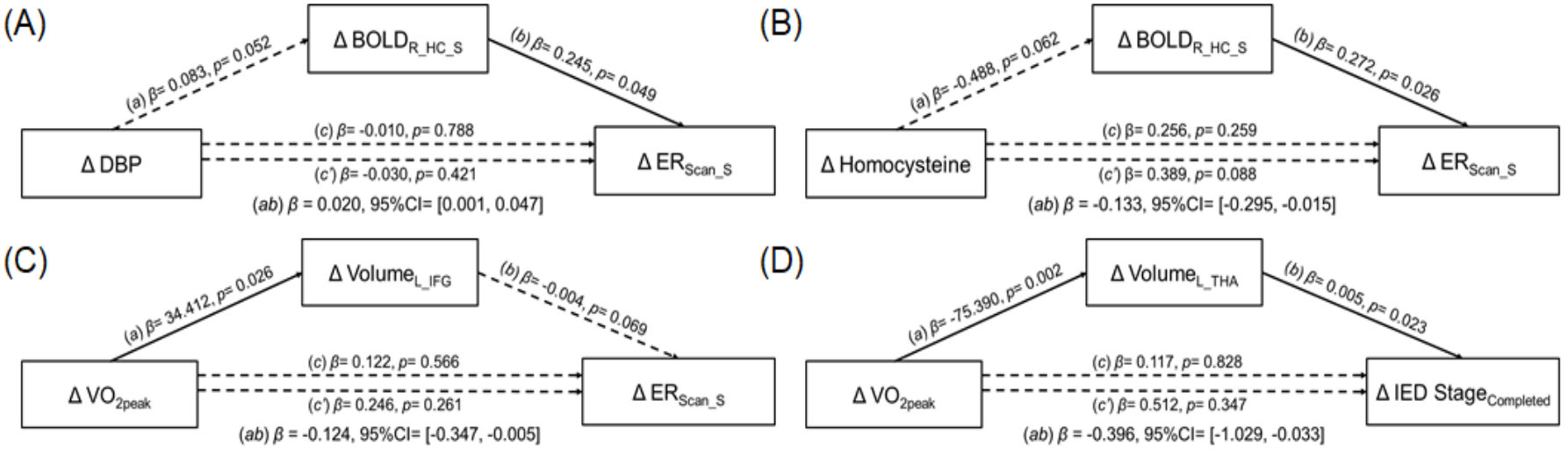

Figure 6. Mediation models

Exercise-induced changes in brain volumes or brain activations mediated the relationships between changes in CVRs or CRF and changes in task-switching performances after training for pooled subjects across the three groups. Covariates were age, sex, and education for (A)-(B), and plus the estimated total intracranial volume for (C)-(D). (A) Mediation model for the relationship between Δ DBP and Δ ERScan_S through the indirect effect of Δ BOLDR_HC_S; (B) Mediation model for the relationship between Δ Homocysteine and Δ ERScan_S through the indirect effect of Δ BOLDR_HC_S; (C) Mediation model for the relationship between Δ VO2peak and Δ IED StageCompleted through the indirect effect of Δ VolumeL_THA; (D) Mediation model for the relationship between Δ VO2peak and Δ ERScan_S through the indirect effect of Δ VolumeL_IFG. The 95% confidence intervals did not include zero, indicating significant indirect effect. Coefficients for all paths are unstandardized. Path (c) means the total effect of independent on dependent variable. Path (c') means the direct effect of independent on dependent variable through a mediator. Path (a) means the effect of independent on the mediator variable. Path (b) means the effect of the mediator on dependent variable. The multiplication of the paths a and b (ab) means the indirect effect of independent on dependent variable through a mediator. Change (Δ) = Data value from Post-test – data value from Pre-test. Solid

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line means significant. Dashed line means non-significant. Abbreviations: BOLD: Blood oxygen level dependent; BOLDR_HC_SC= Brain activation at the right hippocampus for Switch cost; CI= Confidence interval; CRF= Cardiorespiratory fitness; CVRs= Cardiovascular risks; DBP= diastolic blood pressure; ERScan_NS= Error rate in the Non-switch condition while performing the Modified Numerical Stroop test during the fMRI scans; HC= Hippocampus; S= Switch condition of the Modified Numerical Stroop test; VO2peak= Peak oxygen uptake; VolumeL_IFG= Brain volume at the left inferior frontal gyrus.

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Tables

Table 1. Demographics and clinical characteristics of the AT, TCC, and ST groups at Pre-tests

Item	AT (N= 19)	TCC (N= 17)	ST (N= 20)	*p*
Age (year)	63.2 ± 8.1	63.7 ± 8.2	65.8 ± 5.8	0.513
Middle-aged: older (%)	52.6 : 47.4	47.1 : 52.9	40.0 : 60.0	0.730
Sex (Male)	9 (47.4%)	4 (23.5%)	6 (30.0%)	0.288
Education (year)	15.3 ± 2.5	15.4 ± 2.7	15.0 ± 3.0	0.875
MoCA (score)	28.5 ± 1.9	28.8 ± 1.3	28.1 ± 1.7	0.424
Height (cm)	162.0 ± 7.1	160.4 ± 7.2	159.6 ± 8.2	0.612
Weight (kg)	68.1 ± 14.3	62.9 ± 10.2	66.6 ± 12.0	0.439
BMI (kg/m^2)	25.9 ± 4.8	24.4 ± 2.9	26.0 ± 3.7	0.373
WC (cm) (Male/Female)	91.5 ± 10.4 / 85.9 ± 10.5	88.8 ± 9.7 / 84.2 ± 8.5	93.3 ± 5.1 / 89.9 ± 11.7	0.233
CVRF (1:2:3:4)[†]	0.0 : 52.6 : 26.3 : 21.1	41.2 : 41.2 : 17.6 : 0.0[a]	35.0 : 45.0 : 10.0 : 10.0	0.047[*]
HTN (%)	89.5	64.7	55.5	0.056
DM (%)	42.1	29.4	35.0	0.727
DLP (%)	89.5	76.5	85.0	0.562
Smoking (%)	10.5	5.9	10.0	0.869
HTN Medication (%)	78.9	64.7	50.0	0.169
DM Medication (%)	26.3	23.5	30.0	0.905
DLP Medication (%)	42.1	42.1	55.0	0.631

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Resting HR (bpm)	67.2 ± 8.1	73.9 ± 7.6	73.8 ± 7.5	0.013*
Resting SBP (mmHg)†	134.1 ± 15.0	118.9 ± 15.5[a]	127.4 ± 15.4	0.016*
Resting DBP (mmHg)	75.0 ± 9.4	67.9 ± 10.1	72.5 ± 10.1	0.104

Data are presented as mean ± standard deviation or percentage. Abbreviations: AT= Aerobic training group; BMI= Body mass index; CVRF= Number of cardiovascular risk factors; DBP= Diastolic blood pressure; DLP= Dyslipidemia; DM= Diabetes mellitus; HR= Heart rate; HTN= Hypertension; MoCA= Montreal cognitive assessment; PASE= Physical Activity Scale for Elderly; SBP= Systolic blood pressure; ST= Stretching training group; TCC= Tai Chi Chuan group; WC= Waist circumference.

* $p < 0.05$: showing a significant group difference in the one-way ANOVA procedure or chi-square test.

[a] $p < 0.0167$: showing a significant difference from the AT group in *post hoc* analysis ($p = 0.008$ between AT and TCC groups for CVRF and $p = 0.013$ between AT and TCC groups for resting SBP).

† The p value with the tendency to be significant in *post hoc* analysis— $p = 0.029$ between the AT and ST groups for CVRF; $p = 0.034$ between the AT and TCC groups and $p = 0.030$ between AT and ST groups for resting HR.

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Table 2. Exercise adherence and exercise intensity of the AT, TCC, and ST groups over different periods of the 12-week training

Item	AT (N= 19)	TCC (N= 17)	ST (N= 20)	*p*
Adherence	0.99 ± 0.01	0.98 ± 0.04	0.94 ± 0.12	0.073
Exercise intensity				
HRmax (%)				
Average across 12 weeks	66.5 ± 5.6	72.8 ± 5.7[a]	60.0 ± 6.5[a,b]	< 0.001[*]
Week 1-2	62.8 ± 4.7	75.9 ± 8.9[a]	57.7 ± 5.9[b]	< 0.001[*]
Week 3-4	64.6 ± 6.4	75.1 ± 8.0[a]	59.6 ± 6.6[b]	< 0.001[*]
Week 5-12	68.0 ± 6.0	71.2 ± 5.5	60.7 ± 6.9[a,b]	< 0.001[*]

Data are presented as mean ± standard deviation. Abbreviations: TCC= Tai Chi Chuan group; AT= Aerobic training group; ST= Stretching training group; HRmax= Maximum heart rate.

[*] $p < 0.05$: showing a significant difference in the one-way ANOVA procedure.

[a] $p < 0.0167$: showing a significant difference from the AT group in *post hoc* analysis.

[b] $p < 0.0167$: showing a significant difference from the TCC group in *post hoc* analysis.

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Table 3. Blood pressure and blood test results of the AT, TCC, and ST groups at Pre- and Post-tests

Item	AT (N= 19)		TCC (N= 17)		ST (N= 20)		Group x Time	Time	Group
	Pre-test	Post-test	Pre-test	Post-test	Pre-test	Post-test			
SBP (mmHg)[§]	135.2 ± 18.5	133.1 ± 14.8	116.4 ± 16.5	125.6 ± 12.0	128.5 ± 18.5	129.3 ± 17.6	0.957	< 0.001*	0.957
DBP (mmHg)	75.3 ± 12.2	73.1 ± 8.6	66.9 ± 11.3	70.3 ± 10.6	72.8 ± 11.7	71.0 ± 9.7	0.224	0.889	0.210
Homocysteine (μmol/L)	11.5 ± 3.0	11.3 ± 2.9	10.7 ± 2.3	9.8 ± 2.1	11.5 ± 3.4	11.0 ± 3.1	0.510	< 0.001*	0.538
TCHO (mg/dL)	204.3 ± 38.9	197.4 ± 39.5	193.5 ± 34.7	200.9 ± 34.5	196.4 ± 40.2	206.3 ± 42.9	0.177	0.390	0.932
TG (mg/dL)	97.5 ± 47.6	97.0 ± 47.8	118.0 ± 57.9	105.8 ± 47.7	112.2 ± 62.8	88.9 ± 30.1	0.301	0.053	0.593
HDL-C (mg/dL)	58.3 ± 15.2	59.8 ± 16.5	53.3 ± 12.4	57.7 ± 13.0	52.2 ± 12.3	56.9 ± 15.7	0.156	< 0.001*	0.585
LDL-C (mg/dL)	121.4 ± 33.6	114.5 ± 33.1	113.7 ± 31.6	117.4 ± 29.9	116.9 ± 34.0	127.1 ± 37.0	0.556	0.181	0.804
HbA1c (%)	6.2 ± 0.4	6.2 ± 0.5	6.1 ± 0.7	6.0 ± 0.6	6.2 ± 0.6	6.2 ± 0.7	0.898	0.706	0.736
GLU-AC (mg/dL)	109.9 ± 20.9	113.2 ± 30.8	104.1 ± 16.8	110.6 ± 24.4	105.3 ± 13.8	111.3 ± 17.3	0.723	0.005*	0.803
Insulin (μU/mL)	11.3 ± 6.2	12.4 ± 9.7	12.7 ± 6.2	12.3 ± 5.3	12.5 ± 7.0	13.1 ± 7.4	0.745	0.603	0.898
HTN (%)	89.5	94.7	64.7	64.7	55.5	55.5	-	0.836	-
DM (%)	42.1	42.1	29.4	23.5	35.0	40.0	-	1.000	-
DLP (%)	89.5	89.5	76.5	82.4	85.0	80.0	-	1.000	-

Data are presented as mean ± standard deviation or percentage. Abbreviations: AT= Aerobic training group; DBP= Diastolic blood pressure; DLP= Dyslipidemia; DM= Diabetes mellitus; HbA1c= Glycated hemoglobin; HDL-C= High density lipoprotein cholesterol; HTN= Hypertension; SBP= Systolic blood pressure; ST= Stretching training group; TCC= Tai Chi Chuan group; TCHO= Total cholesterol; TG= Triglyceride; LDL-C= Low density lipoprotein cholesterol; GLU-AC= Fasting plasma glucose.

* $p < 0.05$: showing a significant difference in the RM ANOVA procedure or chi-square test.

§. Controlling for the baseline difference ($p = 0.016$).

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Table 4. Cardiopulmonary Exercise Testing and physical examination results of the AT, TCC, and ST groups at Pre- and Post-tests

Item	AT (N= 19)		TCC (N= 17)		ST (N= 20)		Group x Time	Time	Group
	Pre-test	Post-test	Pre-test	Post-test	Pre-test	Post-test			
Cardiopulmonary Exercise Testing									
$Workload_{peak}$ (Watt)[§]	92.1 ± 31.0	101.1 ± 36.3	73.9 ± 24.3	81.8 ± 28.4	71.8 ± 23.7	79.1 ± 21.6	0.934	0.163	0.934
RER_{peak}	1.21 ± 0.07	1.21 ± 0.09	1.19 ± 0.08	1.23 ± 0.06	1.19 ± 0.10	1.2 ± 0.1	0.124	0.024*	0.191
$\dot{V}O_{2AT}$ (ml/min/kg)	11.8 ± 1.6	13.2 ± 2.1	11.4 ± 2.1	12.0 ± 1.6	11.2 ± 2.1	11.5 ± 2.2	0.108	< 0.001*	0.158
$\dot{V}O_{2peak}$ (ml/min/kg)	19.0 ± 3.6	20.4 ± 3.9	17.8 ± 4.0	18.5 ± 3.5	16.9 ± 2.8	18.2 ± 2.7	0.543	< 0.001*	0.132
$\dot{V}O_{2peak}$ in percentage of reference value (%)	80.1 ± 14.0	86.0 ± 15.2	77.2 ± 14.7	80.7 ± 12.2	73.7 ± 10.0	80.1 ± 11.1	0.507	< 0.001*	0.296
Muscle strength and Endurance									
UE grip strength (kg)	26.9 ± 11.1	27.5 ± 10.3	23.2 ± 6.6	24.1 ± 6.0	22.8 ± 7.2	24.2 ± 7.4	0.670	0.015*	0.306
LE strength (kg)	28.2 ± 10.4	27.7 ± 8.2	23.2 ± 5.1	22.4 ± 4.2	23.6 ± 5.6	24.6 ± 5.8	0.449	0.902	0.057
6MWT (m)	541.6 ± 51.9	572.6 ± 53.0	530.4 ± 54.7	552.0 ± 59.0	510.9 ± 75.1	536.1 ± 54.6	0.768	< 0.001*	0.175
Flexibility									
Scratch test (cm)	-0.3 ± 10.6	-1.4 ± 11.3	1.0 ± 10.9	-1.1 ± 14.7	-1.6 ± 8.3	-0.8 ± 7.1	0.143	0.202	0.944
Sit and reach test (cm)	-1.2 ± 11.7	2.1 ± 12.6	1.1 ± 8.4	-0.8 ± 8.0	-3.6 ± 13.0	4.9 ± 12.0[a]	0.001*	0.003*	0.990

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Balance									
One-leg standing (s)	24.6 ± 8.3	26.9 ± 5.9	27.5 ± 5.7	29.0 ± 4.0	26.7 ± 7.3	27.4 ± 6.4	0.424	0.006*	0.477
Mobility									
FSST (s)	7.7 ± 1.3	7.2 ± 1.3	7.6 ± 1.1	7.2 ± 1.1	8.0 ± 1.5	7.6 ± 1.3	0.987	0.013*	0.536
TUG (s)	9.2 ± 1.3	8.4 ± 1.4	8.8 ± 1.5	8.7 ± 0.9	9.5 ± 1.5	8.3 ± 1.0	0.056	< 0.001*	0.849
FTSST (s)	8.5 ± 2.2	7.4 ± 1.4	8.3 ± 1.8	8.2 ± 1.7	8.7 ± 2.0	7.9 ± 1.7	0.299	0.005*	0.737
Physical activity level									
PASE (score)	52.4 ± 30.0	55.2 ± 30.7	35.5 ± 29.6	41.4 ± 21.5	42.7 ± 26.9	53.9 ± 37.5	0.712	0.130	0.193

Data are presented as mean ± standard deviation. Abbreviations: AT= Aerobic training group; FSST= Four Square Step test; FTSST= Five Times Sit to Stand test; LE= Lower extremity; PASE= Physical Activity Scale for Elderly; RER= Respiratory exchange ratio; 6MWT= Six-Minute Walk Test; ST= Stretching group; TCC= Tai Chi Chuan group; TUG= Timed Up and Go test; UE= Upper extremity; $\dot{V}O_{2AT}$= Oxygen uptake at anaerobic threshold; $\dot{V}O_{2peak}$= Peak oxygen uptake.

* $p < 0.05$: showing a significant difference in the RM ANOVA procedure.

a. $p < 0.0167$: Showing a significant difference between Pre- and Post-tests for the same group in *post hoc* analysis.

§. Controlling for the significant baseline difference ($p = 0.043$).

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Table 5. Task-switching performances on the CTT, IED, and Modified Numerical Stroop tests of the AT, TCC, and ST groups at Pre- and Post-tests

Item	AT (N= 19)		TCC (N= 17)		ST (N= 20)		Group x Time	Time	Group
	Pre-test	Post-test	Pre-test	Post-test	Pre-test	Post-test			
CTT									
CTT1 (s)	50.3 ± 14.7	48.0 ± 18.3	45.7 ± 16.5	53.3 ± 17.7	47.2 ± 10.9	50.3 ± 14.3	0.183	0.197	0.985
CTT2 (s)	98.6 ± 29.7	97.5 ± 33.1	102.8 ± 31.0	107.3 ± 29.0	105.9 ± 32.6	103.5 ± 29.4	0.545	0.917	0.711
CTT2 − CTT1 (s)	48.3 ± 19.9	49.5 ± 25.4	57.1 ± 25.7	54.0 ± 28.5	58.8 ± 36.6	52.2 ± 24.9	0.715	0.478	0.589
IED									
$Stage_{Completed}$ (n)	8.2 ± 0.9	9.9 ± 4.3	8.5 ± 0.9	12.7 ± 8.2	8.2 ± 1.3	11.4 ± 7.3	0.567	0.002*	0.400
$Trial_{Total}$ (n)	93.3 ± 22.1	83.1 ± 14.9	80.2 ± 14.8	86.7 ± 22.8	99.8 ± 27.7	90.4 ± 20.0	0.073	0.478	0.123
$ERROR_{Total}$ (n)	26.3 ± 13.6	20.0 ± 11.7	16.8 ± 8.9	21.4 ± 12.7	27.4 ± 14.7	25.2 ± 12.3	0.103	0.206	0.109
Modified Numerical Stroop test									
$ER_{Practice\ NS}$ (%)	5.5 ± 5.1	3.2 ± 3.2	4.6 ± 4.1	4.6 ± 4.4	8.4 ± 5.3	5.0 ± 3.6	0.173	0.012*	0.066
$ER_{Practice\ S}$ (%)	10.4 ± 8.2	6.4 ± 5.3	13.7 ± 9.4	10.8 ± 6.3	14.7 ± 8.5	9.9 ± 6.3	0.772	0.001*	0.104
$ER_{Practice\ SC}$ (%)	4.9 ± 8.5	3.3 ± 5.8	9.1 ± 9.1	6.2 ± 6.4	6.3 ± 8.7	4.9 ± 7.0	0.112	0.325	0.120
$ER_{Scan\ NS}$ (%)	1.4 ± 2.1	0.7 ± 1.4	1.3 ± 1.5	0.5 ± 1.8	1.5 ± 2.3	1.0 ± 1.4	0.756	0.011*	0.762
$ER_{Scan\ S}$ (%)	3.6 ± 3.1	2.5 ± 1.9	2.3 ± 2.4	2.1 ± 1.6	4.9 ± 3.6	3.1 ± 2.6	0.215	0.004*	0.067
$ER_{Scan\ SC}$ (%)	2.2 ± 2.5	1.8 ± 2.7	1.0 ± 2.7	1.6 ± 1.7	3.4 ± 3.3	2.1 ± 2.7	0.106	0.314	0.138

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$RT_{Scan\ NS}$ (ms)	842.2 ± 131.5	820.2 ± 97.9	843.5 ± 95.4	834.4 ± 101.4	845.7 ± 83.0	859.6 ± 99.9	0.324	0.568	0.777
$RT_{Scan\ S}$ (ms)	1017.6 ± 97.5	981.5 ± 110.9	1080.0 ± 102.1	1043.5 ± 102.2	1073.1 ± 105.8	1021.2 ± 104.7	0.733	< 0.001*	0.141
$RT_{Scan\ SC}$ (ms)	175.4 ± 74.6	161.4 ± 42.9	236.6 ± 62.2	209.1 ± 65.8	227.6 ± 109.8	161.6 ± 78.7	0.147	0.003*	0.043*

Data are presented as means ± standard deviations. Abbreviations: AT= Aerobic training group; CTT= Color Trail Making test; ER= Error rate; IED= Intra-Extra Dimensional Set Shift test from the Cambridge Neuropsychological Test Automated Battery; NS= Non-switch condition of the Modified Numerical Stroop test; Practice= Practice trials of the Modified Numerical Stroop test conducted prior to the fMRI scans; RT= Reaction time; S= Switch condition of the Modified Numerical Stroop test; SC= Switch cost; Scan= Scan Trials of the Modified Numerical Stroop test conducted during the fMRI scans; ST= Stretching training group; TCC= Tai Chi Chuan group.

*$p < 0.05$: showing a significant difference in the RM ANOVA procedure.

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Table 6. BOLD magnitude over the selected ROIs during performance of the Modified Numerical Stroop test in the AT, TCC, and ST groups at Pre-, and Post-tests

ROI	AT (N= 19)		TCC (N= 17)		ST (N= 20)		Group x Time	Time	Group
	Pre-test	Post-test	Pre-test	Post-test	Pre-test	Post-test			
Non-switch condition									
L $IFGt_{NS}$	1.0 ± 5.7	1.9 ± 6.4	4.6 ± 5.7	2.8 ± 6.2	4.4 ± 5.6	3.3 ± 5.9	0.693	0.262	0.310
L SMA_{NS}	2.2 ± 4.3	2.2 ± 6.7	0.7 ± 5.5	0.3 ± 4.9	1.2 ± 3.8	-0.3 ± 6.0	0.783	0.723	0.430
L $SMFG1_{NS}$	-5.8 ± 3.8	-5.5 ± 5.1	-6.2 ± 6.7	-6.2 ± 6.5	-6.4 ± 4.0	-7.1 ± 7.1	0.949	0.803	0.572
L $SMFG2_{NS}$	-3.1 ± 4.7	-3.0 ± 5.9	-4.1 ± 5.7	-5.8 ± 5.9	-4.5 ± 5.4	-6.2 ± 8.0	0.787	0.895	0.311
R AMG_{NS}	-0.9 ± 2.6	-1.0 ± 2.2	-1.4 ± 3.2	-1.1 ± 3.8	-0.8 ± 2.3	-0.6 ± 2.5	0.669	0.911	0.741
R HC_{NS}	0.0 ± 2.0	-0.4 ± 2.0	-0.9 ± 2.5	-0.5 ± 2.9	0.0 ± 2.1	-0.6 ± 2.1	0.473	0.466	0.525
R SFG_{NS}	-6.8 ± 3.9	-5.0 ± 5.2	-3.6 ± 3.3	-4.1 ± 5.7	-5.3 ± 5.4	-4.7 ± 4.6	0.649	0.421	0.157
R MFG_{NS}	1.1 ± 4.0	0.1 ± 5.6	2.0 ± 6.4	0.6 ± 5.7	0.5 ± 4.6	0.9 ± 4.2	0.599	0.179	0.773
R THA_{NS}	-0.9 ± 3.2	-2.3 ± 3.9	0.0 ± 2.9	0.0 ± 3.9	-0.2 ± 3.2	-0.7 ± 2.9	0.427	0.861	0.156
Switch condition									
L $IFGt_{S}$	9.8 ± 6.5	9.6 ± 7.1	10.2 ± 9.0	10.3 ± 6.3	11.4 ± 9.6	10.3 ± 6.9	0.820	0.448	0.952
L SMA_{S}	8.3 ± 4.9	7.7 ± 5.4	8.2 ± 6.3	8.4 ± 6.3	6.6 ± 5.1	5.8 ± 4.8	0.724	0.030*	0.394
L $SMFG1_{S}$	0.6 ± 4.4	0.4 ± 4.7	-0.9 ± 5.9	-0.5 ± 5.0	-1.0 ± 4.6	-2.0 ± 5.6	0.639	0.965	0.405
L $SMFG2_{S}$	3.5 ± 5.7	3.0 ± 4.6	1.6 ± 5.5	1.3 ± 5.2	1.5 ± 5.7	0.5 ± 6.4	0.933	0.718	0.357
R AMG_{S}	0.7 ± 1.9	0.7 ± 2.6	1.4 ± 1.8	2.2 ± 3.1	1.2 ± 2.6	1.0 ± 1.7	0.418	0.439	0.174

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R HC_S	0.8 ± 1.3	0.3 ± 2.5	0.9 ± 1.8	2.7 ± 2.9	1.7 ± 3.5	1.5 ± 1.9	0.077	0.228	0.191
R SFG_S	-1.1 ± 5.2	-1.3 ± 5.0	-0.8 ± 4.7	-1.1 ± 4.6	-1.0 ± 5.2	-1.5 ± 5.7	0.982	0.240	0.920
R MFG_S	5.7 ± 5.8	7.4 ± 7.3	6.7 ± 6.7	8.4 ± 5.8	7.3 ± 7.3	6.1 ± 5.1	0.220	0.859	0.895
R THA_S	2.2 ± 3.7	2.4 ± 3.2	1.9 ± 2.9	2.0 ± 4.4	2.1 ± 2.7	1.7 ± 2.3	0.773	0.872	0.958
Switch cost									
L $IFGt_{SC}$	8.7 ± 6.5	7.7 ± 8.0	5.7 ± 6.6	7.6 ± 5.3	7.0 ± 7.1	7.0 ± 7,8	0.726	0.076	0.663
L SMA_{SC}	6.1 ± 3.9	4.8 ± 6.1	7.5 ± 5.6	8.1 ± 5.9	5.4 ± 6.1	6.1 ± 6.9	0.816	0.100	0.257
L $SMFG1_{SC}$	6.4 ± 4.6	5.9 ± 5.0	5.3 ± 6.0	5.7 ± 6.5	5.5 ± 5.6	5.1 ± 7.2	0.787	0.736	0.989
L $SMFG2_{SC}$	6.7 ± 6.2	6.0 ± 5.4	5.7 ± 5.6	7.1 ± 6.1	6.0 ± 6.7	6.7 ± 7.6	0.787	0.736	0.989
R AMG_{SC}	1.6 ± 2.3	1.7 ± 2.6	2.9 ± 2.5	3.3 ± 4.7	2.1 ± 3.4	1.6 ± 2.2	0.692	0.675	0.072
R HC_{SC}	0.8 ± 2.2	0.7 ± 2.0	1.8 ± 2.6	3.2 ± 4.2	1.7 ± 4.0	2.0 ± 1.9	0.589	0.635	0.068
R SFG_{SC}	5.7 ± 6.2	3.7 ± 4.3	2.8 ± 5.1	2.9 ± 5.2	4.3 ± 4.2	3.1 ± 4.5	0.656	0.794	0.440
R MFG_{SC}	4.6 ± 5.5	7.2 ± 8.6	4.7 ± 5.6	7.9 ± 6.8	6.9 ± 7.1	5.2 ± 6.2	0.094	0.309	0.916
R THA_{SC}	3.1 ± 4.0	4.7 ± 2.4	1.9 ± 2.8	2.0 ± 5.3	2.3 ± 3.7	2.4 ± 3.0	0.429	0.794	0.137

Data are presented as mean ± standard deviation. Abbreviations: AT= Aerobic training group; AMG= Amygdala; BOLD= Blood oxygen level dependent; HC= Hippocampus; L= Left; R= Right; IFGt= Triangularis of inferior frontal gyrus; MFG= Middle frontal gyrus; NS= Non-switch condition of the Modified Numerical Stroop test; ROI= Region of interest; S= Switch condition of the Modified Numerical Stroop test; SC= Switch cost; SFG= Superior frontal gyrus; SMA= Supplementary motor area; SMFG= Superior medial frontal gyrus; ST= Stretching group; TCC= Tai Chi Chuan group; THA= thalamus.

* $p< 0.05$: showing a significant difference in the RM ANCOVA, controlling for age, sex, and education.

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Table 7. Volumetric measures of selected brain regions of the AT, TCC, and ST groups at the Pre- and Post-tests

Brain region (cm^3)	AT (N= 19)		TCC (N= 17)		ST (N= 20)		Group x Time	Time	Group
	Pre-test	Post-test	Pre-test	Post-test	Pre-test	Post-test			
eTIV	1478.73 ± 126.80	1478.92 ± 127.37	1411.83 ± 118.49	1416.99 ± 122.74	1450.50 ± 146.97	1454.26 ± 147.21	0.720	0.946	0.720
GM_{Total}	589.29±39.84	588.67±40.32	573.02±32.17	575.09±46.85	575.09±46.85	578.03±47.23	0.149	0.587	0.859
GM_{Sub}§	54.52±3.68	54.47±3.93	53.06±3.43	53.43±3.73	51.54±3.07	51.76±3.14	0.368	0.100	0.368
$GM_{Cerebral}$	433.64±30.18	433.14±30.23	421.69±26.43	420.89±20.34	428.25±26.43	430.26±42.45	0.179	0.195	0.526
$WM_{Cerebral}$	442.42±47.04	423.91±33.41	423.91±33.41	424.55±33.93	422.27±42.51	421.20±43.46	0.589	0.303	0.497
L SFG	20.02±2.12	19.98±2.13	19.24±1.72	19.23±1.74	19.86±2.44	19.83±2.39	0.994	0.272	0.711
L MFG	19.13±1.81	18.94±1.57	18.54±1.58	18.64±1.71	19.14±2.27	19.33±2.39[a]	0.010*	0.183	0.252
L dlPFC	39.16±3.54	38.91±3.35	37.78±2.78	37.88±2.90	39.00±4.48	39.16±4.55	0.061	0.088	0.367
L IFG†	9.44±1.25	9.44±1.16	8.62±0.90	8.61±0.90	9.50±1.52	9.60±1.49	0.179	0.355	0.040*
L OFG	11.91±0.99	11.87±1.07	11.68±1.03	11.85±1.07	11.77±1.24	11.90±1.33	0.106	0.588	0.458
L HC	3.71±0.36	3.71±0.36	3.78±0.30	3.77±0.28	3.65±0.37	3.60±0.30	0.739	0.764	0.196
L ACC	4.05±0.71	4.03±0.70	3.56±0.66	3.62±0.62	3.90±0.83	3.95±0.80	0.290	0.148	0.460
L THA	6.97±0.69	6.93±0.74	6.81±0.85	6.98±0.88	6.59±0.47	6.55±0.55	0.336	0.781	0.140
L Caudate	3.22±0.35	3.27±0.35	3.13±0.39	3.18±0.41	3.06±0.35	3.02±0.30	0.328	0.275	0.143
L Putamen	4.58±0.46	4.54±0.48	4.30±0.44	4.31±0.39	4.29±0.45	4.30±0.47	0.616	0.915	0.547
L Pallidum	2.14±0.30	2.13±0.27	2.08±0.37	2.07±0.36	2.04±0.25	2.02±0.27	0.854	0.020*	0.473
L AMG	1.53±0.23	1.53±0.22	1.50±0.18	1.51±0.16	1.44±0.23	1.44±0.21	0.909	0.380	0.604

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R SFG	18.90±2.01	18.78±2.06	18.17±1.71	18.32±1.81	18.65±3.09	18.66±2.94	0.692	0.826	0.755
R MFG†	18.81±2.18	18.72±2.09	18.99±1.67	19.19±1.65	18.88±2.50	19.04±2.05	0.714	0.952	0.034*
R dlPFC	37.71±3.63	37.50±3.55	37.16±3.20	37.51±3.31	37.53±5.28	37.70±5.03	0.701	0.885	0.194
R IFG	9.85±0.85	9.83±0.87	9.37±1.19	9.63±1.34	9.75±1.51	9.76±1.44	0.326	0.747	0.843
R OFG	12.29±1.25	12.17±1.06	11.69±0.81	11.83±0.98	11.88±1.40	12.15±1.46	0.135	0.875	0.991
R HC	4.04±0.42	4.04±0.39	4.06±0.28	4.10±0.29	3.83±0.36	3.89±0.36	0.343	0.293	0.065
R ACC§†	3.87±0.71	3.87±0.01	3.21±0.48	3.24±0.52	3.84±0.69	3.83±0.74	0.918	0.403	0.918
R THA	7.17±0.68	7.14±0.72	6.84±0.66	7.00±0.80	6.82±0.62	6.90±0.57	0.155	0.308	0.822
R Caudate	3.29±0.30	3.27±0.31	3.16±0.40	3.19±0.42	3.10±0.39	3.11±0.36	0.597	0.089	0.231
R Putamen	4.63±0.43	4.26±0.46	4.42±0.37	4.40±0.40	4.26±0.48	4.32±0.43	0.202	0.567	0.227
R Pallidum	2.02±0.23	2.02±0.23	2.04±0.34	1.92±0.33[a]	1.93±0.22	1.84±0.20[a]	0.037*	0.735	0.223
R AMG	1.68±0.19	1.68±0.21	1.61±0.15	1.59±0.14	1.57±0.22	1.59±0.24	0.293	0.972	0.730

Data are presented as means ± standard deviations. Abbreviations: ACC= Anterior cingulate gyrus; AMG= Amygdala; AT= Aerobic training group; dlPFC= Dorsolateral prefrontal cortex; eTIV= Estimated total intracranial volume; GM= Gray matter; HC= Hippocampus; IFG= Inferior frontal gyrus; L= Left; MFG= Middle frontal gyrus; OFG= Orbitofrontal gyrus; R= Right; SFG= Superior frontal gyrus; Sub= Subcortical; ST= Stretching training group; TCC= Tai Chi Chuan group; THA= Thalamus; WM= White matter.

* $p < 0.05$: showing a significant difference in the RM ANCOVA procedure, controlling for age, sex, education, and eTIV.

a. $p < 0.0167$: Showing a significant difference between Pre- and Post-tests for the same group in *post hoc* analysis.

§. Controlling for significant baseline group difference ($p = 0.012$ for GM_{Sub} and $p = 0.023$ for R ACC).

† The p value with the tendency to be significant in *post hoc* analysis— $p = 0.042$ between the AT and TCC groups and $p = 0.018$ between the TCC and ST groups for R ACC; $p = 0.035$ between the TCC and ST groups for L IFG; $p = 0.032$ between the AT and TCC groups for R MFG.

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Appendix

Appendix 1. List of independent variables, dependent variables, and mediators for all mediation analysis procedures performed in this study.

Change in brain activation or volume as the mediator (N=56)						
Independent variable (Δ X)		Mediator (Δ M)		Dependent variable (Δ Y)		Covariate
CVR (9)	SBP	BOLD (27)	L $IFGt_{NS}$	Cogntion (13)	IED $stage_{completed}$	age, sex, edu
	DBP		L SMA_{NS}		IED $error_{total}$	
	Homocysteine		L $SMFG1_{NS}$		IED $trial_{total}$	
	HDL-C		L $SMFG2_{NS}$		CTT2-CTT1	
	LDL-C		R $AMG_{N\ S}$		$ER_{practice\_NS}$	
	TCHO		R HC_{NS}		$ER_{practice\_S}$	
	TG		R SFG_{NS}		$ER_{practice\_SC}$	
	HbA1c		R MFG_{NS}		ER_{scan_NS}	
CRF (3)	VO_{2peak}		R THA_{NS}		ER_{scan_S}	
	VO_{2peak} in percentage		L $IFGt_{S}$		ER_{scan_SC}	
	6MWT		L SMA_{S}		RT_{scan_NS}	
			L $SMFG1_{S}$		RT_{scan_S}	
			L $SMFG2_{S}$		RT_{scan_SC}	
			R AMG_{S}			
			R HC_{S}			
			R SFG_{S}			
			R MFG_{S}			
			R THA_{S}			
			L $IFGt_{SC}$			
			L SMA_{SC}			
			L $SMFG1_{SC}$			
			L $SMFG2_{SC}$			
			R AMG_{SC}			
			R HC_{SC}			
			R SFG_{SC}			
			R MFG_{SC}			
			R THA_{SC}			
		Brain volume (29)	L SFG			age, sex, edu, eTIV
			L MFG			
			L dlPFC			
			L IFG			
			L OFG			
			L ACC			
			R SFG			
			R MFG			
			R dlPFC			
			R IFG			
			R OFG			
			R ACC			
			L THA			
			L caudate			
			L putamen			
			L Pallidum			
			L HC			
			L AMG			
			R THA			
			R caudate			
			R putamen			
			R Pallidum			
			R HC			
			R AMG			
			$GM_{Subcortical}$			
			GM_{Total}			
			GM_{Cortex}			
			$WM_{Cerebral}$			

Abbreviations: ACC= Anterior cingulate gyrus; AMG= Amygdala; BOLD= Blood oxygen level dependent; DBP= Diastolic blood pressure; dlPFC= Dorsolateral prefrontal cortex; ER= Error rate; eTIV= Estimated total intracranial volume; HDL-C=

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High density lipoprotein cholesterol; HC= Hippocampus; HbA1c= Glycated hemoglobin; IED= Intra-Extra Dimensional Set Shift test from the Cambridge Neuropsychological Test Automated Battery; IFG= Inferior frontal gyrus; IFGt= Triangularis of inferior frontal gyrus; L= Left; LDL-C= Low density lipoprotein cholesterol; MFG= Middle frontal gyrus; NS= Non-switch condition of the Modified Numerical Stroop test; OFG= Orbitofrontal gyrus; Outside= Outside-scanner means performance during the Practice= Practice trials of the Modified Numerical Stroop test conducted prior to the fMRI scans; R= Right; RT= Reaction time; S= Switch condition of the Modified Numerical Stroop test; S= Switch condition of the Modified Numerical Stroop test; SBP= Systolic blood pressure; SC= Switch cost; Scan= Scan Trials of the Modified Numerical Stroop test conducted during the fMRI scans; SFG= Superior frontal gyrus; SMA= Supplementary motor area; SMFG= Superior medial frontal gyrus; 6MWT= Six-minute Walk test; TCHO= Total cholesterol; THA= thalamus; TG= Triglyceride; $\dot{V}O_{2peak}$= Peak oxygen uptake; $\dot{V}O_{2peak}$ in percentage= $\dot{V}O_{2peak}$ in percentage of reference value.

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Appendix 2. Demographics and clinical characteristics of the original AT, TCC, and ST groups before removing outliers and data from participants who dropped out (N= 70)

Item	AT (N= 23)	TCC (N= 23)	ST (N= 24)	*p*
Age (year)	64.4 ± 8.0	64.2 ± 7.5	65.3 ± 6.4	0.852
Middle-aged: older (%)	43.5 : 56.5	43.5 : 56.5	37.5 : 62.5	0.890
Sex (Male)	43.5%	30.4%	29.2%	0.524
Education (year)	15.4 ± 2.3	15.5 ± 2.4	14.5 ± 4.2	0.484
MoCA (score)	28.5 ± 1.8	28.6 ± 1.6	27.0 ± 6.0	0.270
Height (cm)	161.3 ± 7.2	160.9 ± 8.1	152.4 ± 33.4	0.249
Weight (kg)	66.5 ± 13.8	63.1 ± 11.4	63.4 ± 17.4	0.684
BMI (kg/m^2)	25.5 ± 4.6	24.4 ± 3.1	25.5 ± 6.3	0.687
WC (cm) (Male/Female)	90.6 ± 10.3 / 85.3 ± 9.7	87.6 ± 10.3 / 82.9 ± 8.6	93.8 ± 4.8 / 89.1 ± 10.8	0.747
CVRF (1:2:3:4)	21.7 : 56.5 : 8.7 : 13.0	52.2 : 21.7 : 26.1 : 0.0[a]	45.8 : 25.0 : 29.2 : 0.0[a]	0.010*
HTN (%)†	91.3	60.9[a]	62.5	0.036*
DM (%)	39.1	30.4	37.5	0.807
DLP (%)	87.0	78.3	83.3	0.734
Smoking (%)	8.7	4.3	8.3	0.816
HTN Medication (%)	82.6	60.9	58.3	0.153
DM Medication (%)	21.7	21.7	33.3	0.574
DLP Medication (%)	47.8	43.5	58.3	0.577
Resting HR (bpm)†	65.4 ± 8.1	73.0 ± 9.3	73.0 ± 10.9	0.011*
Resting SBP (mmHg)	137.8 ± 18.4	119.5 ± 18.7[a]	129.5 ± 17.3	0.004*

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Resting DBP (mmHg)	76.1 ± 11.4	68.7 ± 11.8	73.1 ± 10.9	0.095

Data are presented as means ± standard deviations or percentages. Abbreviations: AT= Aerobic training group; BMI= Body mass index; CVRF= Number of cardiovascular risk factors; DBP= Diastolic blood pressure; DLP= Dyslipidemia; DM= Diabetes mellitus; HR= Heart rate; HTN= Hypertension; MoCA= Montreal cognitive assessment; PASE= Physical Activity Scale for Elderly; SBP= Systolic blood pressure; ST= Stretching training group; TCC= Tai Chi Chuan group; WC= Waist circumference.

[*] $p < 0.05$: showing a significant group difference in the one-way ANOVA procedure or chi-square test.

[a.] $p < 0.0167$: showing a significant difference from the AT group in *post hoc* analysis. ($p = 0.010$ between AT and TCC groups and $p = 0.014$ between AT and ST groups for CVRF; $p = 0.016$ between AT and TCC groups for HTN; $p = 0.003$ between AT and TCC groups for resting SBP).

[†] The p value with the tendency to be significant in *post hoc* analysis— $p = 0.020$ between AT and ST groups for HTN; $p = 0.029$ between the AT and TCC groups and $p = 0.025$ between AT and ST groups for resting HR.

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Appendix 3. Montreal Neurological Institute coordinates of the voxels showing peak activations on the eight regions of interest selected from the disjunction map of the Switch > Non-switch contrast of BOLD across three groups across pre- and post-tests based on the threshold of voxel-wise uncorrected $p < 0.0001$ and cluster size ≥ 34 voxels.

Location	BA	No. of voxels	T	x	y	z
L IFGt	46	99	4.98	-46	38	18
L SMA		216	4.83	0	18	54
L SMFG1			4.81	0	36	46
L SMFG2			4.62	0	30	52
R AMG		81	4.63	32	-2	-18
R HC			4.36	28	-10	-12
R SFG	8	35	4.5	26	36	44
R MFG	6	36	4.41	32	16	58
R THA		45	4.27	10	-24	16

Abbreviations: AMG= Amygdala; BA= Brodmann area; HC= Hippocampus; L= Left; R= Right; IFGt= Triangularis of inferior frontal gyrus; MFG= Middle frontal gyrus; SFG= Superior frontal gyrus; SMA= Supplementary motor area; SMFG= Superior medial frontal gyrus; THA= Thalamus.

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