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太極拳運動改善中老年人轉換任務功能之療效與神經機制探討：神經認知與神經影像研究

Investigation of Task-switching Effects and the Underlying Neural Mechanisms of Tai Chi Chuan Exercise Training in Middle-aged and Older Adults: Neurocognitive and Neuroimaging Studies

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太極拳運動改善中老年人轉換任務功能之療效與神經機制探討：神經認知與神經影像研究
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本論文係吳孟恬君（D00428003）在國立臺灣大學物理治療學系暨研究所完成之博士學位論文，於民國 108 年 01 月 21 日承下列考試委員審查通過及口試及格，特此證明

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誌謝

腦神經科學是一個迷人且奧秘的研究領域。自民國 100 年入學，知識從零開始學習逐漸增長，非常感謝指導教授—湯佩芳老師，在過程中悉心且耐心地教導，讓我學會如何從問題中找到解答，不僅培養我的研究能力，更能提升個人的職場及生活處事能力。在功能性磁振造影的學習上，感謝吳恩賜老師及周泰立老師對於 MRI 原理、實驗設計及 fMRI 分析的教學；在結構性影像方面，感謝曾文毅醫師及其團隊成員—泳欽學長、譽仁學長、睿紋，無私地提供擴散頻譜影像技術，及協助相關 MRI 掃描及結構性影像分析；在運動訓練方面，感謝張育愷老師給予太極拳運動設計之建議，感謝王玥琚教練及楊高騰教練提供專業的太極拳運動指導，亦感謝永和耕莘醫院、萬華及中正老人服務中心提供訓練場地。本研究論文的資料蒐集方面，感謝高淑芬醫師提供劍橋臨床神經心理測試工具，以及歷年來湯佩芳老師研究室成員—乃綺、建廣、崇韋、培威、珮儀、喬可、小叡，協助收案、評估、及資料整理，感謝研究夥伴們與我一同完成此困難的隨機對照試驗研究。同時感謝系辦秘書雅雯姐、婷婷，這些年的行政作業協助，也感謝亦婷協助我準備口試相關作業，讓我能無後顧之憂，順利地完成論文考試。

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中文摘要

背景：轉換任務能力是指能彈性地轉移注意力，以因應兩種或多重任務需求的能力。轉換任務能力是一種高階執行功能，會隨著年齡增加而下降。中年期是轉換任務能力下降的轉銜期，但具有個別化差異。過去罕有研究探討中年人如何調節大腦功能性活化，以預防或因應此轉換任務能力之下降。太極拳運動訓練已被證實能有效改善老年人之轉換任務表現。然而，太極拳運動訓練如何影響轉換任務相關神經機制仍是未知。本論文之目的有三：(1) 研究一為探討年輕人、中年人、及老年人之轉換任務能力及其相關腦部功能性活化之差異，尤其著重探討中年人之神經機制；(2) 研究二為探討太極拳運動訓練是否能有效改善老年人執行轉換任務時之腦部功能性活化；(3) 研究三為探討太極拳運動訓練是否能增加轉換任務相關之特定白質神經纖維束完整性，或特定白質神經纖維完整性之基準值是否會影響中老年人在太極拳運動訓練後增進轉換任務表現之效益。**方法：**研究一採用修改版的史楚普(Stroop)功能性磁振造影測試，以評估年輕人(n = 30)、中年人(n = 30)、及老年人(n = 30)在執行非轉換任務及轉換任務測試時之腦部功能性活化及行為表現，並探討其腦部活化與行為表現間之關係。研究二使用相同的功能性磁振造影測試及隨機對照試驗設計，隨機分派老年人至太極拳組(n = 16)及控制組(n = 15)，並評估老年人在 12 週太極拳運動介入前、後之腦部功能性活化及轉換任務表現之變化。研究三使用擴散頻譜磁振造影及隨機對照試驗設計，隨機分派中老年人至太極拳組(n = 19)及控制組(n = 19)，探討中老年人在 12 週太極拳運動介入前、後，全腦白質神經纖維束及與轉換任務相關之特定白質神經纖維束的完整性之變化，也探討這些白質神經纖維束完整性之基準值與太極拳促進轉換任務效益之關係。白質神經纖維束完整性以普擴散不等向性分數(generalized fractional anisotropy)表示。在研究二及研究三中，太極拳組受試者接受為期 12 週、每週三次、每次 60 分鐘的楊式 24 式太極拳運動訓練介入，而控制組受試者則未接受任何訓練介入，僅維持其原生活形態，與接受每兩週一次的電話訪問。研究二及研究三除了蒐集影像資料之外，亦會蒐集轉換任務及身體功能之行為表現資料。**結果：**研究一發現雖然三個年齡組之受試者皆有能力依據任務難度需求，調節兩側前額葉-頂葉腦區之功能性活化，但唯有中年人組呈現：在執行轉換任務測試時，左側前額葉活化愈高者，及從非轉換任務至轉換任務測試時，左側前額葉活化增加愈多者，其轉換任務錯誤愈少或反應時間愈短之現象($r = -0.374$ – -0.569, $p \leq 0.05$)。研究二及研究三皆發現太極拳運動訓練有促進轉換任務表現及身體功能之效益。研究二更發現，老年人在接受在 12 週太極拳運動訓練後，在執行轉換任務時，愈有能力提升前額葉活化者，尤其是左側上額迴(left superior frontal gyrus)之活化，其轉換任務錯誤減少得愈多($r = -0.631$, $p = 0.021$)。研究三之結果發現，全腦白質神經纖維束($r = -0.747$, $p = 0.001$)、與前額葉-紋狀體-視丘-前額葉迴路(prefronto-striatal-thalamo-prefrontal loop) ($r = -0.800$, $p < 0.001$)、及前額葉-頂葉/顳葉(prefronto-parietal/occipital) ($r = -0.782$, $p < 0.001$)之白質神經纖維束之基準值愈高者，12 週太極拳運動訓練後之轉換任務錯誤減少得愈多。其中，前額葉-紋狀體-視丘-前額葉迴路白質神經纖維束完整性之基準值為預測 12 週太極拳訓練後之轉換任務進步量之最主要因子($\beta = -0.875$, $R^2 = 0.495$, $p < 0.001$)。**結論：**整體而言，研究一之結果表示調節與轉換任務相關的左側前額葉活化的能力是中年人達成愈佳轉換任務表現之獨特神經機制。因此，建議提供有助於增加此調節能力之訓練，以預防隨年齡增加而來的轉換任務表現下降。研究二之結果建議，太極拳運動訓練是一種有助於提升轉換任務表現的運動型態，因太極拳運動訓練能提升一些老

年人在因應轉換任務測試時，腦部前額葉活化之功能，雖然並非所有老年人皆能呈現此效益。研究三之結果突顯中老年人之前額葉-紋狀體-視丘-前額葉神經纖維束完整性基準值之重要性，較好的神經纖維束完整性有益於中老年人在 12 週太極拳運動訓練後，獲得較佳的轉換任務進步。

關鍵詞：認知彈性、功能性磁振造影、個別化差異、執行功能、身心運動介入、擴散頻譜磁振造影、白質

ABSTRACT

Background: The ability to flexibly shift attention and respond to two or multi-task demands is called task-switching ability. Task-switching ability is a high-level executive function and declines with age. The transition period of task-switching ability declines occurs at midlife, but with individual differences. Little is known about how middle-aged adults modulate brain activation to prevent or handle such declines. Tai Chi Chuan (TCC) exercise training has been shown to improve task-switching performance in older adults. However, how TCC exercise training induces changes in the neural mechanisms of task-switching remains unknown. This dissertation had three purposes: (1) to investigate age differences in non-switch and switch performances and associated functional activations across young, middle-aged, and older adults, with particular focus on the middle-aged in Study One; (2) to investigate whether TCC exercise training has effects on task-switching associated brain functional activations in older adults in Study Two; and (3) to investigate whether TCC exercise training enhances the integrity of specific task-switching associated white matter (WM) tracts and whether the baseline integrity of these tracts influences TCC training-induced task-switching improvement in middle-aged and older adults in Study Three.

Methods: Study One used a modified Stroop task-functional magnetic resonance imaging (fMRI) paradigm to assess the brain functional activations and behaviors during non-switch and switch conditions, and their interrelationships in young (n = 30), middle-aged (n = 30), and older (n = 30) adults. Study Two used the same task-fMRI paradigm and a randomized controlled trial (RCT) design to examine the changes in functional activations and task-switching performances in older adults randomly assigned to a TCC group (n = 16) and a control group (n = 15) before and after a

12-week TCC exercise intervention. Study Three used diffusion spectrum imaging and a RCT design to investigate the changes in general fractional anisotropy (GFA) values, the indices of WM integrity, of the whole brain and specific task-switching associated WM tracts, and the relationships of the baseline GFA values of these WM tracts to task-switching improvement in middle-aged and older adults randomly assigned to a TCC group ($n = 19$) and a control group ($n = 19$) before and after the same 12-week TCC exercise training intervention used in Study Two. In both Studies Two and Three, the TCC group received training in the 24-form Yang-style of TCC exercise three times per week, 60 minutes each time, for 12 weeks. In contrast, the control group did not receive any intervention, but maintained the original lifestyles and received one telephone consultation biweekly. In addition to the imaging data, behavioral task-switching and physical functions were also measured. **Results:** Study One showed that although all three groups showed the ability to modulate the bilateral prefrontoparietal activations according to task demands, only the middle-aged adults showed that greater left prefrontal activations during task-switching or greater increases of these activations from non-switch to switch conditions were associated with less task-switching errors or shorter reaction time ($r = -0.374$ – -0.569, $p \leq 0.05$). Both Study Two and Study Three showed TCC training-induced improvements in task-switching and physical function. Study Two further revealed that after 12 weeks of TCC training, the TCC participants who had the ability to recruit greater prefrontal activation, particularly in the left superior frontal gyrus, during task-switching presented greater reductions of task-switching errors ($r = -0.631$, $p = 0.021$). Study Three provided support for the importance of the baseline integrity of whole brain tracts ($r = -0.747$, $p = 0.001$) and specific task-switching associated WM tracts, the prefronto-striatal-thalamo-prefrontal loop ($r = -0.800$, $p < 0.001$) and the prefronto-parietal/occipital

($r = -0.782$, $p < 0.001$) fiber groups, in predicting error reductions of task-switching performance after 12 weeks of TCC training. In particular, the baseline integrity of the prefronto-striatal-thalamo-prefrontal loop fiber group was the predominant predictor of task-switching improvement after 12 weeks of TCC training ($\beta = -0.875$, $R^2 = 0.495$, $p < 0.001$). **Conclusions:** Altogether, the results of Study One suggest that the ability to scale up task-switching relevant left prefrontal activation is a unique neural mechanism that middle-aged adults could employ to achieve better task-switching performance. Training that could enhance such modulation ability is therefore recommended to prevent age-related declines in task-switching. The findings of Study Two suggest that TCC could serve as one of type of exercise to enhance task-switching ability because this training could provide benefits to some, although not all, older adults to enhance the function of their prefrontal activations during task-switching. The results of Study Three highlight the importance of the baseline integrity of the prefronto-striatal-thalamo-prefrontal loop fiber group in helping middle-aged and older adults achieve more task-switching improvement after 12 weeks of TCC training.

Key words: Cognitive flexibility, fMRI, Individual differences, Executive function, Mind-body exercise intervention, Diffusion spectrum imaging, White matter

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CHAPTER 1

INTRODUCTION

1.1 Background

Age-related declines in task-switching performance

Task-switching ability, a high-level executive function, requires the adaptation of rapid and flexible behavioral responses to environmental task demands (Braver et al., 2003; Diamond, 2013). To investigate cognitive flexibility, researchers typically request research participants to perform two or more different tasks using task-switching experimental paradigms (Kray and Lindenberger, 2000; Reimers and Maylor, 2005). Age-related declines in task-switching ability have been well reported (Cepeda et al., 2001; Kray and Lindenberger, 2000). Older adults perform task-switching with higher error rates and longer reaction times (RTs) compared to young adults, whereas the task-switching accuracy of middle-aged adults is similar to that of young adults, but their RTs fall between those of young and older adults (Kray and Lindenberger, 2000; Reimers and Maylor, 2005). These findings suggest that midlife seems to be a critical transitional period of task-switching declines with aging and imply individual differences in task-switching performance (Kray and Lindenberger, 2000; Reimers and Maylor, 2005). Therefore, investigating task-switching performance in middle-aged adults and the associated brain functional activation might help us understand their efficient or inefficient neural mechanisms during task-switching and shed light on preventing cognitive aging in early midlife senescence.

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Task-switching associated brain functional activations

Research using functional magnetic resonance imaging (fMRI) task-switching paradigms has revealed that people typically recruit greater frontal and parietal functional activations in task-switching trials than in non-switching trials, suggesting a need for greater neural resources for cognitive processing from non-switch to switch conditions, a phenomenon called switch cost (contrast) (Kray and Lindenberger, 2000; Wasylyshyn et a., 2011). In essence, in young adults, the brain regions associated with switch cost include the bilateral, especially the left superior, frontal gyrus (SFG), middle frontal gyrus (MFG), inferior frontal gyrus pars opercularis (IFG_o) and triangularis (IFG_t), superior and inferior parietal lobes, and the frontotemporal junction (Crone et al., 2006; DiGirolamo et al., 2001; Dove et al., 2000; Gold et al., 2010; Hakun et al., 2015; Jimura et al., 2014; Kim et al., 2012; Kimberg et al., 2000; MacDonald et al., 2000; Sakai and Passingham, 2003; Zhu et al., 2014).

Comparisons of task-switching associated brain functional activations between young and older adults

Previous fMRI studies have shown that young adults generally recruit functional activations in the left prefrontoparietal regions during task-switching, whereas older adults tend to recruit functional activations in the bilateral prefrontoparietal activation during task-switching (DiGirolamo et al., 2001; Gazes et al., 2012; Kim et al., 2012; Kim et al., 2011; MacDonald et al., 2000; Vallesi et al., 2015; Zhu et al., 2014). This pattern of functional activation in older adults during task-switching shows age-related asymmetry reductions in frontal regions (DiGirolamo et al., 2001; Zhu et al., 2015), in agreement with the “Hemispheric Asymmetry Reduction in Older Adults (HAROLD)” model (Cabeza, 2002). The roles of the left prefrontal regions in task-switching include maintaining the attentional demands of the task (MacDonald et al., 2000), resolving conceptual conflicts (Badre and Wagner, 2006), and classifying stimuli (Philipp et al., 2013), whereas the right prefrontal regions are known to be involved in spatial rules of task-switching (Vallesi et al., 2015), monitoring, and inhibitory control (MacDonald et al., 2000). Young adults might only need left prefrontal activation for processing task demands, resolving conflict, and matching stimulus-response rules while performing task-switching. Older adults, however, might need to recruit additional right frontal activation to deal with all task-switching demands.

When directly comparing the extent or intensity of prefrontal and parietal recruitment during task-switching between young and older adults, the majority of past research has reported that older adults show prefrontoparietal overactivation during both non-switch and switch conditions (DiGirolamo et al., 2001; Zhu et al., 2014; Zhu et al., 2015). These findings reflect increased neural processing costs during task-switching with age, suggesting that older adults may attempt to use a strategy of overactivation to compensate for age-related task-switching declines. However, some researchers have found negative or no relationships of prefrontal overactivation with non-switch and switch performances in older adults (Gazes et al., 2012; Hakun et al., 2015; Zhu et al., 2015). These findings suggest that prefrontal overactivation is an ineffective strategy for older adults while performing task-switching, as it may be an unsuccessful attempted compensatory neural mechanism (Cabeza and Dennis, 2013) or an inefficient neural process (Rypma et al., 2006).

Notably, the ability to modulate brain activation according to changes in task demands from non-switch to switch conditions has shown differences between young and older adults. Compared to young adults, older adults reduce the ability to scale up brain activations to overcome more difficult switch conditions, showing a smaller extent of increases of prefrontoparietal activation from non-switch to switch conditions in older adults (DiGirolamo et al., 2001; Gold et al., 2010). Although older adults may not be efficient in adapting brain activation from non-switch to switch conditions, it remains unknown whether middle-aged adults maintain the adaptive ability of brain functional activation to deal with increasing task demands. Previous memory task-fMRI studies have found that middle-aged adults, whose behavioral performance is similar to that of young adults, have the ability to modulate brain activation from simple to difficult tasks, and that they perform better than older adults do (Cansino et al., 2015; Kennedy et al., 2015). To our knowledge, very few studies have investigated task-switching associated functional activation across the lifespan by including middle-aged adults. It would be interesting to understand how different age groups resemble or differ from each other in neural engagement during task-switching, and in the neural effects on behavior. Therefore, the first study of this dissertation investigated differences in task-switching performance and associated neural mechanisms among young, middle-aged, and older adults by using task-fMRI.

Task-switching performance is associated with integrity of specific white matter tracts in middle-aged and older adults

Diffusion tensor imaging (DTI) measures the diffusion of water molecules in the white matter (WM) tracts and reflects WM properties, such as the orientation and density of fibers, axonal diameter, degree of myelination, and membrane integrity (Beaulieu, 2014; Johansen-Berg and Rushworth, 2009; Le Bihan, 2003). To evaluate WM integrity, four parameters of DTI are typically used, including the mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA) values. The MD value indicates the overall diffusivity of water

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molecules, and the AD and RD values indicate water diffusivity parallel and perpendicular to the primary direction of water diffusion, respectively (Beaulieu, 2014; Concha et al., 2006; Song et al., 2003). Among these parameters, the FA value indicates the degree of diffusion anisotropy of water molecules. The FA value ranges between zero (fully isotropic diffusion) and one (fully anisotropic diffusion). Higher FA and AD values, and lower RD values, represent higher WM integrity. Previous DTI studies have shown that task-switching performance is positively associated with the integrity of specific WM tracts in the prefronto-parietal/occipital regions (Gold et al., 2010; Jolly et al., 2017; Madden et al., 2009) and prefronto-striatal regions (Chiang et al., 2016; Serbruyns et al., 2016; Shang et al., 2013; Ystad et al., 2011). In particular, older adults who have higher FA values in the left superior longitudinal fasciculus (SLF) (Gold et al., 2010), the genu-center of the corpus callosum, and the right splenium-parietal callosal fibers (Madden et al., 2009) perform better in task-switching. Jolly et al. (2017) also found that middle-aged and older adults who had lower RD values, or higher WM integrity, in the left SLF, inferior longitudinal fasciculus (ILF), and inferior fronto-occipital fasciculus (IFOF) exhibited better task-switching performance. Similarly, the importance of the prefronto-striatal-thalamo-prefrontal loop WM tracts in task-switching performance has also been reported. Older adults who have lower magnetization transfer ratios (lower myelin integrity) or lower FA values in the superior corona radiata or prefrontal-striatal tracts perform more poorly on task-switching (Serbruyns et al., 2016; Ystad et al., 2011). Moreover, patients with Parkinson’s disease show task-switching impairments with less dopaminergic medication-related striatal functional responses (Aarts et al., 2014; Cools et al., 2001). In summary, the above literature review shows that three groups of WM tracts are implicated in task-switching performance, namely, brain association fibers connecting

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the prefrontal and parietal/occipital regions, commissural fibers connecting bilateral prefrontal and parietal regions, and projection fibers connecting the prefrontal, striatal, and thalamic regions. It would be worthy to investigate whether exercise training intervention would enhance the WM integrity of the whole brain tracts and the above-mentioned three WM fiber groups, together with cognitive task-switching improvement.

Tai Chi Chuan (TCC) exercise training improves task-switching performance in older adults

Preventing age-related task-switching declines and promoting task-switching performance are critical issues for an aging population. According to the literature, TCC is a mind-body exercise that involves physical activity, motor learning, cognitive training, and social interaction processes. TCC produces benefits on physical function, cognitive performance, and psychological well-being (Chang et al., 2014; Mortimer et al., 2012; Taylor-Piliae et al., 2010; Wang et al., 2010; Wayne et al., 2014). In the domain of cognitive performance, TCC training has been reported to improve task-switching performance (Mortimer et al., 2012; Nguyen and Kruse, 2012; Wayne et al., 2014). Nguyen and Kruse (2012) randomly assigned community-dwelling older adults to a TCC training or a passive control group, and they found that the TCC group, who received six months of training, outperformed the control group on the Trail Making Test-part B (TMT-B). The TMT-B is considered to test both task-switching and working memory components of cognitive function, during which participants switch between two different stimulus categories (letters vs. numbers) (Reitan, 1958; Sanchez-Cubillo et al., 2009). Mortimer et al. (2012) compared changes in task-switching related performance on the TMT-B in older adults who participated in a

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TCC exercise program, walking, or social interaction for 40 weeks, versus a no intervention control group. Their results showed that the TCC group improved on task-switching performance as compared to the control group. In summary, TCC training appears to provide specific benefits on task-switching performance in older adults. We considered that TCC participants require specific drills on task-switching performance while shifting from one posture to the next while practicing TCC routines. These specific TCC training procedures may provide task-switching benefits for middle-aged and older adults; however, the specific changes in brain activation during task-switching after TCC training remain unexplored.

TCC exercise training induces brain functional changes

Most fMRI studies investigating the effects of TCC exercise on brain functional activations use a resting-state fMRI (rs-fMRI) paradigm (Yu et al., 2018). These studies have shown that TCC exercise enhances brain functional connectivity at rest (Li et al., 2014; Yin et al., 2014; Zheng et al., 2015). Using rs-fMRI, Li et al. (2014) found that a 6-week multimodal intervention consisting of TCC, cognitive training, and group counseling improved the brain functional connectivity between the medial frontal cortex and medial temporal lobe in older adults. Critically, at the post-intervention test, the intervention group, who had higher functional connectivity between the medial frontal and temporal lobes, performed better on task-switching (shorter TMT time) (Li et al., 2014). Using a similar 6-week multimodal intervention program and rs-fMRI, Yin et al. (2014) found that the intervention group, but not the control group, increased the amplitude of low frequency fluctuations (ALFF) in the MFG, SFG, and cerebellum. Greater increases of ALFF in the MFG were also correlated with greater task-switching improvements by reducing TMT time in the

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intervention group (Yin et al., 2014). Nevertheless, how TCC exercise alters brain activity during task-switching in older adults remains unclear. Therefore, the second study of this dissertation investigated how TCC exercise training altered brain functional activation during task-switching conditions, and how these changes in functional activation were associated with task-switching performance in older adults, using task-fMRI.

TCC exercise training induces brain structural changes

Volumetric neuroimaging studies have provided evidence supporting that TCC exercise training has benefits on increasing whole brain volume (Mortimer et al., 2012) and gray matter cortical thickness in the frontal, temporal, and occipital regions (Wei et al., 2013). A cross-sectional study revealed that middle-aged adults who had participated in an average of 14 years of TCC exercise had thicker cortices in the right MFG, insula, precentral gyrus, and left superior temporal gyrus, medial occipital-temporal sulcus, and lingual sulcus, compared to age-, gender-, and education-matched middle-aged adults without exercise or meditation experience (Wei et al., 2013). Moreover, a longitudinal intervention study showed that in older adults, whole brain volume increased after a 40-week TCC exercise intervention, compared to the no intervention control group (Mortimer et al., 2012). However, little research has investigated how TCC exercise may influence WM tracts. Other exercise interventions, such as visuo-motor skill training and aerobic exercise training, show effects on increasing the WM integrity of the intraparietal sulcus, frontoparietal association fibers, and frontoparietal commissural fibers of young adults (Scholz et al., 2009; Svatkova et al., 2015). For older adults, although Voss et al. (2013) did not find significant increases in WM integrity after one year of aerobic exercise training, they found that older adults who had greater increases

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in FA values of WM in the prefrontal and temporal regions showed greater improvement in cardiorespiratory fitness. In addition, individual differences in the integrity of specific WM tracts may influence training effects on behavioral performance for older adults. A 10-week memory training intervention showed that the baseline WM integrity of the anterior corpus callosum, left anterior thalamic radiation, and right IFOF was predictive of memory improvements (de Lange et al., 2016). Therefore, it would be worthwhile to investigate whether TCC exercise intervention would enhance WM integrity of the whole brain tracts and the three task-switching associated WM fiber groups, i.e., the association fibers connecting the prefrontal and parietal/occipital regions, the commissural fibers connecting the bilateral prefrontal and parietal regions, and the projection fibers connecting the prefrontal, striatal, and thalamic regions, or whether the baseline WM integrity of the whole brain tracts and these three groups of WM tracts would influence task-switching improvements after TCC training. Therefore, Study Three of this dissertation had two purposes. The first purpose was to investigate whether TCC exercise training would enhance the WM integrity of the whole brain tracts and the three task-switching associated WM fiber groups. The second purpose was to investigate whether the baseline WM integrity of the whole brain tracts and the three task-switching associated WM fiber groups would be predictive of the gains of task-switching performance after TCC exercise training in middle-aged and older adults.

In summary, Study One of this dissertation was a cross-sectional study in which 30 young adults, 30 middle-aged adults, and 30 older adults were recruited to investigate age differences in prefrontoparietal activation and the activation–behavior relationships under a modified Stroop fMRI paradigm across the lifespan. Studies Two and Three of this dissertation were longitudinal intervention studies that extracted data

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from a registered single-blind stratified randomized controlled trial (RCT) (ClinicalTrials.gov ID number: NCT02270320), in which the effects of a 12-week TCC intervention on task-switching performance and associated brain functional activations and WM integrity in community-dwelling sedentary middle-aged and older adults were investigated.

In the original RCT (Figure 1.1), we screened 211 participants and determined each participant's eligibility according to the inclusion and exclusion criteria described in detail in the Methods sections of Study Two and Study Three. We originally excluded 160 participants and included 51 participants aged between 50 and 85 years old (Figure 1.1). They were randomly assigned to the TCC group (n = 26) and control group (CON) (n = 25) according to age stratification. However, to prevent potential confounding effects from age heterogeneity on the outcomes of interest in the respective studies and in consideration of the availability of valid imaging data, we used behavioral and fMRI imaging data from participants aged between 60 and 69 years old in Study Two (n = 31; TCC group, n = 16; CON group, n = 15) and behavioral and diffusion imaging data from participants aged between 55 and 69 years old in Study Three (n = 38; TCC group, n = 19; CON group, n = 19). After the 12-week intervention, no participants in the TCC group dropped out, whereas four participants in the CON group dropped out due to bone fracture (n = 1) and refusal to complete post-tests (n = 3).

In both Study Two and Study Three, we used the Intra–Extra Dimensional Set Shift (IED) test of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Ltd., Bottisham, Cambridge, UK) to target the testing on task-switching ability. In Study Two, using task-fMRI, we measured neural responses in a modified numerical Stroop task-switching paradigm adapted from Huang et al. (2012). In Study Three, using diffusion spectrum imaging (DSI), we measured the generalized

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fractional anisotropy (GFA) values of three groups of WM tracts that were known to be associated with task-switching, before and after the 12-week intervention. All behavioral and imaging data were analyzed using the intention-to-treat (ITT) analyses in Study Two and Study Three.

1.2 Purposes

The purposes of this dissertation were to investigate task-switching performance and the underlying neural mechanisms across the lifespan, and also the task-switching related brain functional and structural alterations in community-dwelling sedentary middle-aged and older adults without cognitive impairment after a 12-week TCC exercise intervention.

Study One.

To investigate the age differences in task-switching performance and associated neural mechanisms using task-fMRI among cognitively intact young, middle-aged, and older adults.

Study Two.

(1) To investigate task-switching behavioral benefits and associated functional activation changes after a 12-week TCC exercise training intervention in cognitively intact older adults.

(2) To investigate whether the changes of functional activation in these older participants would be correlated with changes of task-switching performance after a 12-week TCC exercise training intervention.

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Study Three.

1. (1) To investigate whether a 12-week TCC exercise training intervention would enhance the WM integrity of the whole brain tracts and the three groups of task-switching associated WM tracts, including the association fibers connecting the prefrontal and parietal/occipital regions, the commissural fibers connecting bilateral prefrontal and parietal regions, and the projection fibers connecting the prefrontal, striatal, and thalamic regions, in cognitively intact middle-aged and older adults.
2. (2) To investigate whether the baseline WM integrity of the above-mentioned whole brain tracts and the three groups of task-switching associated WM tracts would influence task-switching improvement after a 12-week TCC exercise training intervention for these middle-aged and older adults.

1.3 Hypotheses

Study One.

1. (1) Middle-aged adults would perform better on task-switching performance than the older adults, but more poorly than the young adults.
2. (2) Similar to the older adults, middle-aged adults would show greater bilateral prefrontoparietal activation than the young adults during task-switching, and their greater prefrontoparietal activation would be correlated with poorer task-switching performance.

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Study Two.

(1) Only the TCC group would improve on task-switching performance and increase task-switching associated prefrontal functional activation during task-switching fMRI after a 12-week TCC exercise training intervention.

(2) In the TCC group, the task-switching improvement would be positively correlated with the increases in prefrontal activation during task-switching from pre- to post-intervention.

Study Three.

(1) In middle-aged and older adults, the WM integrity of the whole brain tracts and the three task-switching associated WM fiber groups would not increase after a 12-week TCC exercise training intervention.

(2) Middle-aged and older adults who had higher baseline WM integrity of the whole brain tracts and the three task-switching associated WM fiber groups would show greater improvements in task-switching after a 12-week TCC exercise training intervention.

1.4 Relevance

Task-switching is a crucial executive function and shows age-related declines, starting in middle age. However, the neural mechanisms underpinning this decline in the middle-aged remain unknown. TCC exercise training has shown benefits on improving task-switching ability, increasing brain cortical thickness, and enhancing resting-state connectivity in older adults. However, the effects of TCC exercise training on functional neural responses during task-switching tasks and the integrity of specific

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WM tracts remain unclear. The three studies in this dissertation will help us bridge the knowledge gaps and facilitate the understanding of the neural mechanisms of the aging processes involving task-switching across the lifespan and the structural and functional neural mechanisms of the effects of TCC exercise on task-switching improvements. The findings of these studies may shed light on designing or determining future exercise interventions aimed to prevent age-related task-switching declines or promote cognitive functions in middle-aged and older adults.

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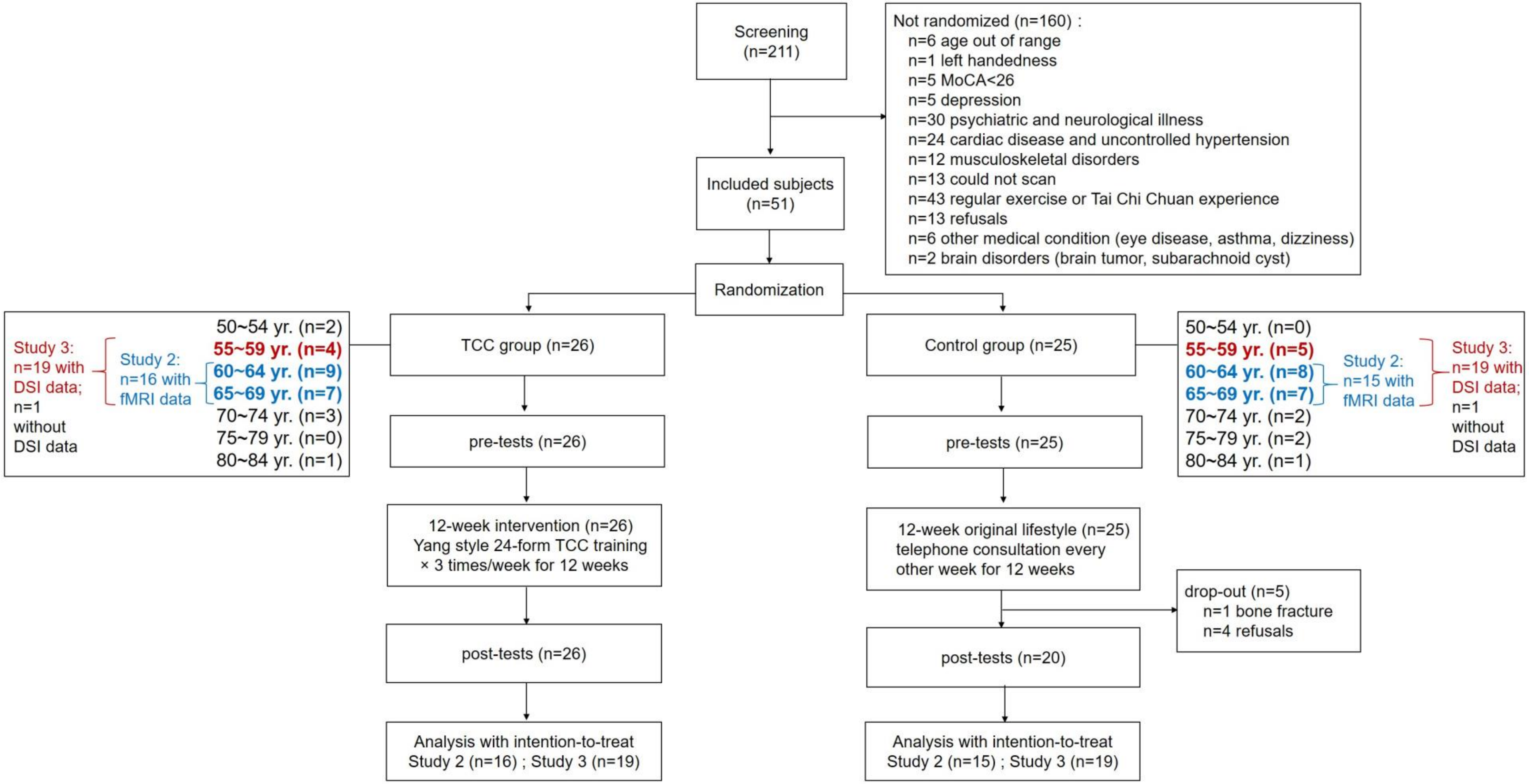

Figure 1.1 Consort chart of the randomized controlled trial (ClinicalTrials.gov ID number: NCT02270320)

CHAPTER 2

Ability to Modulate the Left, but not the Right, Prefrontal Cortex Activity Helps Middle-aged Adults to Achieve Better Task-switching Performance

中年人調節左側，而非右側，前額葉活化之能力有助其達到較佳之轉換任務表現

中文摘要

背景：轉換任務能力在中年期開始下降，但具有個別化差異。有些中年人下降得比同輩慢。本研究探討是否中年人呈現較佳的轉換任務表現時會採用特定的腦部功能性活化，並與年輕人及老年人做比較。**方法：**本研究使用修改版的史楚普(Stroop)功能性磁振造影測試，比較認知正常之年輕人、中年人、及老年人，在執行非轉換任務及轉換任務測試時，腦部功能性活化強度及認知行為表現。**結果：**與年輕人相比，老年人及中年人分別在非轉換任務及轉換任務下會徵召較高的右側前額葉-頂葉腦區之功能性活化。然而，此右側前額葉-頂葉腦區的活化與行為表現無關。此外，中年人呈現獨特的活化與行為之關係。中年人組內，有能力在執行轉換任務時，增加較高的左側前額葉活化者，或能從非轉換任務至轉換任務測試時，左側前額葉功能性活化調節較高者，有較佳的轉換任務表現。**結論：**本研究突顯出，在面臨困難的轉換任務時，調節與轉換任務相關之左側前額葉活化是中年人能採用之一種有效的關鍵性神經機制，以預防隨年齡增長而造成的轉換任務表現下降。

關鍵詞：認知老化、認知彈性、功能性磁振造影、個別差異、中年

English Abstract

Background: Declines in task-switching ability start at midlife, but with individual differences. Some middle-aged decline slower than their cohorts. This study explored whether there are specific brain activations that are associated with better task-switching performance in the middle-aged, compared to in the young and older adults. **Methods:** Using a modified Stroop fMRI paradigm, we assessed brain functional activations of young (YA), middle-aged (MA), and older (OA) cognitively normal adults while performing non-switch and switch tasks, and measured behavioral performances. **Results:** Compared to the YA, the MA and OA presented right prefrontoparietal over-recruitment during the non-switch and switch tasks, respectively; however, their right prefrontoparietal activity did not correlate with behaviors. Uniquely found in the MA, those who showed greater left prefrontal activation during the switch tasks or those who showed greater increases of the left prefrontal activation from the non-switch to switch tasks had better switch performance. **Conclusions:** These findings underscore that modulating task-relevant left prefrontal activation in difficult switch conditions is a crucial effective neural mechanism to prevent age-related task-switching declines in the middle-aged.

Key words: Cognitive aging, Cognitive flexibility, fMRI, Individual differences, Midlife

2.1 Introduction

Task-switching, also called cognitive flexibility, mental flexibility, or set shifting, is one of the core components of executive function (Diamond, 2013). To perform task-switching, one has to be able to rapidly and flexibly adapting behaviors to meet shifting task demands (Braver et al., 2003; Monsell, 2003). The neural activity engaged during task-switching subserves various cognitive processes, including maintenance of task goals, evaluation of contexts and stimuli features, matching contexts to the relevant task goals, inhibition of irrelevant information, and initiation and execution of appropriate behavioral responses to fulfill the task goals under the contexts (Sakai, 2008).

Task-switching performance declines with age (Cepeda et al., 2001; Kray and Lindenberger, 2000). Past research has shown that, relative to young adults, older adults are slower and less accurate in task-switching performance, whereas the middle-aged fall between young and older adults in their task-switching performance, with increasing individual differences with age (Kray and Lindenberger, 2000; Reimers and Maylor, 2005). Thus, midlife is a pivotal period of age-related changes of this central cognitive ability, with some middle-aged perform similarly well to young adults whereas others resemble older adults. However, research investigating task-switching associated neural mechanisms has rarely incorporated the middle-aged, which prohibits comprehensive understanding of individual differences in the changes of these neural mechanisms during this critical period, as well as across the lifespan.

Switching tasks typically evoke higher neural activity over bilateral frontal and parietal regions compared to non-switching tasks, reflecting greater neural resource costs involved. Studies on young and older adults showed that the brain areas specifically implicated in task-switching, i.e., the areas related to switch cost, including the bilateral superior frontal gyri (SFG), middle frontal gyri (MFG), inferior frontal gyri pars opercularis and triangularis (IFG_o and IFG_t), inferior frontal junctions, medial frontal gyri, superior parietal lobules (SPL), and inferior parietal lobules (IPL) (DiGirolamo et al., 2001; Dove et al., 2000; Gazes et al, 2012; Gold et al., 2010; Kim et al., 2012; Kimberg et al., 2000; MacDonald et al., 2000; Sakai, 2008). Moreover, past research revealed that the core regions that young adults commonly recruited across various types of switching tasks were the left, but not the right, prefrontoparietal areas (Badre and Wagner, 2006; Kim et al., 2012; Kim et al., 2011; Philipp et al., 2013; Vallesi et al., 2015). This may be because the left prefrontal regions are heavily involved in maintaining and representing the attentional task demands (MacDonald et al., 2000), resolving conceptual conflict (Badre and Wagner, 2006), and classifying stimuli (Philipp et al., 2013); and the left parietal regions are involved in adapting response modalities (Philipp et al., 2013), resolving response conflict (Badre and Wagner, 2006), and representing task sets (Kim et al., 2011). Relatively speakly, the right prefrontal cortex is involved specifically in spatial rules of task-switching (Vallesi et al., 2015) and the right anterior cingulate cortex is involved in monitoring and inhibitory control (MacDonald et al., 2000).

Much evidence in older aduts has suggested that as people age, there are three major changes in task-switching related brain activations. First, there is a reduction of the left-dominant frontoparietal activation pattern during task-switching (Gold et al., 2010; Nashiro et al., 2018; Zhu et al., 2014), a phenomenon supporting the hemispheric asymmetry reduction in older adults, the HAROLD model of cognitive aging (Cabeza, 2002). Older adults tend to over-recruit the right frontoparietal areas compared to young adults (Gold et al., 2010; Nashiro et al., 2018; Zhu et al., 2014). Second, older adults present greater brain recruitment in both the non-switch and switch conditions compared to young adults (DiGirolamo et al., 2001; Zhu et al., 2014; Zhu et al., 2015), suggesting that older adults may over-recruit these regions as a neural strategy to overcome the declines of brain functions. However, research also shows that the prefrontal activation intensity in older adults is either associated with poorer non-switch and switch performances, or has no relationships with these performances (Gazes et al., 2012; Hakun et al., 2015; Nashiro et al., 2018; Zhu et al., 2015), implying that age-related prefrontal over-recruitment may be an unsuccessful attempted compensatory neural mechanism (Cabeza and Dennis, 2013) or inefficient neural processing (Rypma et al., 2005; Rypma et al., 2006), and therefore has no effects to offset age-related declines in task-switching ability.Third, older adults show a smaller extent of prefrontoparietal activation increases from the non-switch to switch condition compared to young adults (DiGirolamo et al., 2001; Gold et al., 2010), perhaps due to the difficulty of older adults to modulate brain activation intensity according to different levels of task demands. Since older adults already recruit a great extent of prefrontoparietal activation in the simple non-switch condition, there might be left only a small room of brain activation for them to scale up to the level needed to effectively perform the difficult switching tasks. However, the above-mentioned age related changes are all based on comparisons between young and older adults, it remains unknown whether middle-age adults would have similar HAROLD phenomenon, greater ineffective brain activations in both non-switch and switch conditions, and difficulty to modulate brain activation intensity according to task difficulty level, as found in older adults.

Therefore, using functional magnetic resonance imaging (fMRI) and a task-switching paradigm, we compared non-switch and switch task performances and

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the relevant prefrontoparietal activation associated with the two tasks across young (YA), middle-aged (MA), and older adults (OA), and investigated the relationships between prefrontoparietal activation and task-switching performance in each group. We hypothesized that similar to the OA group, the MA group would show the HAROLD phenomenon and greater prefrontoparietal activations than the YA group during task-switching, but unlike the OA group, this greater prefrontoparietal activation in the MA would be associated with better task-switching performance. In addition, we hypothesized that the MA group preserve the ability to effectively modulate task-switching associated brain activation from the non-switch to switch condition, and those who have better modulation ability would achieve better task-switching performance. To clearly characterize and compare the brain activation patterns during non-switch and switch conditions across the three groups, we applied both whole-brain and region-of-interest (ROI) approaches.

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2.2 Methods

Participants

Ninety cognitively normal adults, 30 young adults (YA), 30 middle-aged adults (MA), and 30 older adults (OA), participated in this study. The participants were all native speakers of Mandarin Chinese and signed informed consent forms approved by the Institutional Review Board. Inclusion criteria were education ≥ 6 years, Montreal Cognitive Assessment (MoCA) score ≥ 26 (Nasreddine et al., 2005), Geriatric Depression Scale 15-item Short-form (GDS-15) score < 8 (Nyunt et al., 2009), right-handedness (Oldfield, 1971), and no disability (Lawton and Brody, 1969). Exclusion criteria were psychiatric and neurological illness, brain tumor, severe or uncontrolled cardiovascular diseases, and any MRI contraindications. Color Trails Test parts 1 and 2 (CTT-1 and CTT-2) (D'Elia et al., 1996) performances were also acquired to assess attention and switching abilities, respectively.

Task-switching paradigm

We conducted a hybrid block/event-related fMRI experiment using a task-switching paradigm modified from a numerical Stroop study (Huang et al., 2012). The paradigm included two runs of fMRI scans, with each scan consisting of a physical size (16 trials, 84 seconds) block, a numerical magnitude (16 trials, 84 seconds) block, and a task-switching (32 trials, 166 seconds) block (Figure 2.1). Each trial lasted for 2 seconds and the inter-trial interval was varied between 2, 4, and 6 seconds. In each trial, participants saw two single-digit numbers of different font sizes (55 vs. 73) and different numerical magnitudes (differing by 3, 4, or 5) presented side by side. In the physical size block, cued by green text, participants judged which digit was physically larger than the other. In the numerical magnitude block, cued by red text, participants judged which digit was numerically greater than the other. In the task-switching block, physical size and numerical magnitude trials were pseudo-randomly ordered; participants switched between these two tasks and made decisions based on the color cued text. The order of the physical size and numerical magnitude blocks in the two runs was counterbalanced across participants in each group; the task-switching block was always the last block in each run for each participant. To facilitate baseline brain response estimation, 20 seconds of rest fixation preceded all blocks and followed the task-switching block of each run. Stimuli were generated and presented using E-prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA). Participants were instructed to respond as quickly and accurately as possible by pressing the left or right button of the response box using the index or middle finger of the dominant hand, respectively. The reaction time (RT) and error rate of each response was recorded via a custom-written MATLAB script. Error rate (percent of incorrectly answered trials) and mean RT (of all correctly answered trials) of the non-switch condition (all trials of 2 physical size and 2 numerical magnitude blocks) and the switch condition (all trials of 2 switch blocks), as well as switch costs of error rate and RT (= values in switch condition - values in non-switch condition), were calculated to represent behavioral measures during the fMRI experiment. All participants underwent two short practice sessions and reached ≥ 80 % accuracy before entering the scanner. To understand group differences on behavioral measures, we performed a 3 (group) × 2 (condition) two-way repeated measures (RM) ANCOVA on error rate and RT, and a one-way ANCOVA on switch cost of error rate and RT, both controlling for education. The significance level was set at $\alpha = 0.05$, with Bonferroni corrections for post hoc analyses.

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Imaging data acquisition

Brain imaging data were acquired using a 3-Tesla Trio MRI scanner system with a 32-channel head coil (Siemens, Erlangen, Germany). Three types of brain images were 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 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 210 volumes and co-planar 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 = $3 \times 3 \times 4$ mm^3.

fMRI data processing

All preprocessing and statistical analysis of brain imaging data were conducted using Statistical Parametric Mapping (SPM 12) software. The EPI images were then corrected for slice acquisition time with sinc interpolation and spatially realigned to the first image of each run to correct for head motion using 6-parameter rigid body transformation. All image data met the criteria of head motion < 3 mm in translation and < 3 degrees in rotation. The EPI images of the first volume in the first run were co-registered with the T2 image and then used to coregister and overlay functional images to T1-weighted images. The coregistered images from each participant were segmented into the grey matter, white matter, and cerebrospinal fluid, and normalized using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra

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(Ashburner, 2007). A study-specific template (SST) was generated from all participants' segmented images. The flow fields containing the deformation parameters from native space to SST space were used to normalize the EPI volumes to Montreal Neurological Institute (MNI) space. The normalized EPI images were then spatially smoothed with an 8-mm full-width half-maximum isotropic Gaussian kernel.

For statistical analysis, we applied a first-level general linear model with three condition regressors for non-switch physical size, non-switch numerical magnitude, and task-switching trials, respectively. Only correct response trials were included, while error trials were modeled using a dummy regressor. Furthermore, condition and dummy regressors were the trial onset vectors convolved with the canonical hemodynamic response function. Six motion parameters were included as covariates. Contrasts were then performed for the non-switch condition (by combining non-switch physical size and non-switch numerical magnitude regression coefficients) and the switch condition, relative to rest fixation. Subsequently, the individual contrast maps were fed into a second-level whole-brain random effects analysis of the non-switch (relative to rest fixation) and switch conditions (relative to rest fixation) and the switch cost contrast (switch – non-switch) for each group. The threshold was set at family-wise error (FWE) correction of $p < 0.001$ and $k \geq 50$ voxels.

Group analyses

To compare the group differences of functional activation, we used two approaches. First, we chose to use the ROI approach with the stricter disjunction analysis method (Smith et al., 2013; Wu et al., 2018) to reduce the multiple comparisons between group contrasts in fMRI data processing, and to fairly consider all brain functional activation sensitive to switch > non-switch contrast across groups. The disjunction map was

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created from the switch > non-switch contrast across groups, and the threshold was set as voxel-wise $p < 0.001$ with FWE correction and at least of clusters $k \geq 50$ voxels. From the disjunction map, we delineated functional ROIs in the lateral prefrontoparietal regions with 5mm-radius spheres surrounding peak activation coordinates. Mean BOLD response estimates for the non-switch and switch conditions (relative to rest fixation) were then extracted from each participant's first-level contrasts from each functional ROI using the Marsbar toolbox (Brett et al., 2002). The BOLD response estimates of these ROIs were compared across groups and conditions by using a 3 (group) by 2 (condition: non-switch / switch) mixed model RM ANCOVA, with education as a covariate. Bonferroni corrections were performed for post-hoc analyses. Second, we used the whole-brain analyses to compare the MA > YA, OA > YA, and MA > OA group contrasts, and those reverse group contrasts, to obtain the whole-brain view of the group differences. The threshold was set at voxel-wise $p < 0.0001$ (uncorrected) and at least of clusters $k \geq 50$ voxels.

Correlation analysis

Partial correlation analyses were used to analyze the relationships of brain activation with switch and non-switch performances. Specifically, the correlations of the BOLD response estimates over the identified functional ROIs with the RT and error rate of behavioral performances were performed for the non-switch and switch conditions and for each group, controlling for age and education. We also correlated the BOLD response estimates of switch > non-switch contrast with behavioral performance of the switch condition, controlling for age and education, to realize whether the modulation of brain activation was related to switch behavioral measures. The significance level was set at $\alpha = 0.05$.

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2.3 Results

Demographics and neuropsychological performances

The three groups were similar in gender distribution, GDS-15, body mass index, and MoCA (all $p > 0.05$), but years of education was greater in the YA group ($F_{2,87} = 12.17$, $p < 0.001$) than in the MA ($p = 0.001$) and OA groups ($p < 0.001$) (Table 2.1). The YA group had better CTT-1 and CTT-2 performances than the MA and OA groups (all $p < 0.001$); and the MA group had better CTT-1 ($p = 0.001$) and CTT-2 ($p < 0.001$) performances than the OA group (Table 2.1).

Group differences in behavioral performances during fMRI non-switch and switch tasks

For error rates, there was a group × condition interaction effect ($F_{2,86} = 3.36$, $p = 0.040$) (Figure 2.2A). The error rate was larger in the OA group than in the MA and YA groups in the non-switch and switch conditions (all $p < 0.008$). The YA and OA groups, but not the MA group, showed greater error rates in the switch condition than in the non-switch condition (both $p < 0.017$). There was also a significant group main effect ($F_{2,86} = 10.87$, $p < 0.001$), with the error rate being greater in the OA group ($p < 0.017$), and a condition main effect ($F_{1,86} = 9.06$, $p = 0.003$), with the error rate being greater in the switch condition.

For RTs, there was no group × condition interaction effect ($F_{2,86} = 2.71$, $p = 0.072$) (Figure 2.2B). We found a significant group main effect ($F_{2,86} = 33.6$, $p < 0.001$), with the OA group presenting the longest RTs, followed by the MA group, and then the YA group (both $p < 0.017$). There was also a condition main effect ($F_{1,86} = 21.35$, $p < 0.001$). The RT of the switch condition was longer than that of the non-switch condition ($p <$

0.001).

Group differences in functional brain responses during fMRI non-switch and switch tasks

Results of the ROI approach using the disjunction map showed ten ROIs in the lateral prefrontoparietal regions for the switch > non-switch contrast (Figure 2.3A and Table 2.2). No regions showed significantly greater activation in the non-switch than in the switch condition at the set threshold. The RM ANCOVA analysis of BOLD response estimates over the ten ROIs revealed significant group × condition interactions in five ROIs, group main effects in four ROIs, and condition main effects in six ROIs (Table S2.1). Post hoc analyses of interaction effects revealed that during the non-switch tasks, functional activation in the right SFG ($p < 0.001$) and right IFG$_o$ ($p = 0.002$) was greater in the OA group than in the YA group, whereas the MA and YA groups did not differ in these regions (Figure 2.3B and Table S2.1). During the switch task, the MA group had greater functional activation in the right IFG$_o$ ($p = 0.008$), angular gyrus (AG) ($p = 0.001$), and IPL ($p < 0.001$) compared to the YA, and in the right IPL compared to the OA ($p = 0.006$) (Figure 2.3B and Table S2.1). Post hoc analyses of group main effects revealed that the MA group showed greater functional activation in the right IFG$_o$ ($p = 0.010$) and IPL ($p = 0.001$) compared to the YA group, and the OA group showed greater functional activation in the right SFG ($p = 0.002$) and IFG$_o$ ($p = 0.004$) compared to the YA group. The condition main effects revealed that functional activation was greater during the switch condition than during the non-switch condition in the bilateral MFG and IFG$_o$, and the right IPL and AG across the three groups (Table S2.1).

Results of the whole-brain group analyses revealed that during the non-switch tasks, the OA group recruited greater activation in bilateral prefrontoparietal regions, showing the highest T-value and largest clusters in the right SPL (T value = 6.20, cluster size = 1320 voxels), as compared to the YA group; whereas the MA group only showed a small increase of functional activation in the right AG (T-value = 4.43, cluster size = 96 voxels), as compared to the YA group (Table 2.3 and Figure S2.1). Moreover, in comparison with the MA group, the OA group recruited greater functional activation in the left SPL (T-value = 4.40, cluster size = 71 voxels) during the non-switch task. While performing the switch tasks, the MA group predominantly increased functional activation in the right prefrontoparietal regions (cluster size = 1673 voxels), but showed a small increase in the left SPL (T-value = 4.79, cluster size = 90 voxels), as compared to the YA group; whereas the OA group recruited greater functional activation in the right IFG$_o$ and SPL, but recruited less functional activation in the left rolandic operculum compared to the YA group (Table 2.3 and Figure S2.2). There were no differences in activation during the switch condition between the MA and OA groups. For the switch > non-switch contrast, the MA group recruited greater functional activation in the left superiomedial frontal gyrus, right middle orbital frontal gyrus and IPL compared to the YA group, and recruited greater functional activation in the left supramarginal gyrus and right superiomedial frontal gyrus compared to the OA group (Table 2.3 and Figure S2.3).

Taken together, the results from the ROI approach and the whole brain analysis both revealed that as compared to the YA group, the OA group predominantly over-recruited the right prefrontoparietal activation regions during the non-switch tasks, whereas the MA group predominantly over-recruited the right prefrontoparietal activation during the switch tasks. Age differences in functional activation were predominantly in the right prefrontoparietal regions during both the non-switch and switch tasks. In addition, all three age groups were able to scale up their prefrontoparietal activations from non-switch to switch tasks with the MA showing the greatest modulation of brain activity.

Correlations between BOLD response estimates and behavioral performance

While performing the non-switch tasks, the MA individuals who recruited less functional activation in the left MFG and IFG$_t$ had lower error rates ($r = 0.417$, $p = 0.027$) and shorter RTs ($r = 0.465$, $p = 0.013$), respectively (Figure 2.4A). While performing the switch tasks, the MA individuals who recruited greater functional activation in the left MFG and IFG$_o$ had lower error rates ($r = -0.400$, $p = 0.035$) and shorter RTs ($r = -0.374$, $p = 0.050$), respectively (Figure 2.4B). Moreover, the MA individuals who showed a greater increase in functional activation in the left MFG ($r = -0.380$, $p = 0.046$) and left IFG$_t$ ($r = -0.569$, $p = 0.002$) from the non-switch to the switch condition presented a lower error rate in switch performance (Figure 2.4C). No significant associations were found between BOLD response estimates and error rates and RTs for the non-switch and switch conditions in the YA and OA groups (Table S2.2 and S2.3).

2.4 Discussion

In this research, we compared non-switch and switch performances and the associated brain BOLD response estimates across young, middle-aged, and older adults, and evaluated the relationships between BOLD response estimates and behavioral performances in each age group, with a particular interest on the MA group. There were three most important findings. First, we found that compared with the YA group, the OA group showed the right prefrontoparietal over-recruitment pattern during the non-switch tasks, whereas the MA group revealed such right prefrontoparietal over-recruitment pattern during the switch tasks. And, these right prefrontoparietal activations were not related to non-switch and switch performances in the OA and MA groups, respectively. Second, we found that all three groups could increase the prefrontoparietal activation from the non-switch to switch condition with the MA showing the greatest increases. Third, only in the MA did we find that the ability to modulate brain activation in the left prefrontal regions according to task difficulty was related to their task-switching performance.

Behaviorally, in both the non-switch and switch conditions, the error rates of the MA group were similar to those of the YA group and smaller than those of the OA group, and the RTs of the MA group fell between those of the YA and OA groups. Similar trends were found for the switch costs in error rate and RT. These findings indicated that while dealing with the task-switching paradigm, the MA group preserved the ability to accurately perform the tasks, but their responses were slower than those of the YA group. These findings are consistent with previous studies on task-switching across the life span and may suggest that middle-age is an important transitional stage of slowing down of task-switching performance. Kray and Lindenberger (2000) found

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that similarly to older adults, the middle-aged presented a greater switch cost in RT than did young adults. Reimers and Maylor (2005) found a linear decline in task-switching RT, but a relatively stable error rate, from young (18 years old) to late middle-age or early older age (66 years old). Similarly, Huff et al. (2015) found that the middle-aged had a switch cost in RT falling between those of young and older adults but an error rate similar to that of young adults in both non-switch and switch trials. The above findings, in combination with our findings, strongly suggest that age-related declines in task-switching performance in midlife may mainly be manifested by a slower speed of performance rather than a higher error rate. It may be that the MA group tends to adopt the speed-accuracy tradeoff strategy while performing task-switching (Starns and Ratcliff, 2010).

The results from both disjunction analysis and whole brain analysis showed that the OA group early over-recruited the ***right*** prefrontoparietal activation during the non-switch condition, as compared to the YA group, whereas the MA group presented overactivation in the ***right*** prefrontoparietal regions during the switch condition, as compared to the YA group. These findings are similar to those of previous studies in older adults showing that age-related over-recruitment of brain activation for task-switching mainly occurs in the ***right*** prefrontoparietal regions (Gold et al., 2010; Nashiro et al., 2018; Zhu et al., 2014). Our findings further suggest that compared to the YA group, the MA group already present the HAROLD phenomenon, but primarily during the more difficult switch tasks. In contract, the the OA group presents the HAROLD phenomenon even in the easier non-switch tasks.

Furthermore, the functional activations in these right prefrontoparietal regions were not related to the switch RT and accuracy in the OA and MA groups, suggesting

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that the over-recruitment in these regions was not effective in compensating for age-related decline in behaviors. Previous studies in older adults showed that the over-recruitment in the right frontoparietal lobes was related to poorer behavioral performance (Gazes et al., 2012; Nashiro et al., 2018; Zhu et al., 2014; Zhu et al., 2015). Zhu et al. (2015) showed that greater increases of the right prefrontal activation were not only associated with poorer task-switching performance, and also associated with lower white matter integrity of the genu and body parts of corpus callosum and right radiata in older adults. It suggests that the older adults may attempt to compensate for the white matter degeneration with increasing greater prefrontal activation, but this strategy turned out to be ineffective. Similarly, our findings that the right prefrontoparietal over-recruitment pattern in the MA and OA groups failed to lead to better behavioral performance also indicate an attempted but unsuccessful compensation (Cabeza and Dennis, 2013) or inefficiency of brain activation (Nashiro et al., 2018; Rypma et al., 2005; Rypma et al., 2006). Therefore, unsuccessful compensatory brain activation could occur as early as in the middle-aged.

Our ROI approach showed a significant condition main effect on BOLD response estimates－greater functional activation over bilateral MFG and IFG$_o$, and right IPL and AG for the switch condition compared to the non-switch condition regardless of age groups. The whole-brain analysis showed that the MA increased their brain activation from the non-switch to switch conditions to a greater extent compared to the other two groups. These findings suggest that all three groups had ability to modulate functional activation in prefrontoparietal regions from non-switch to switch task with the MA showing the greatest modulation. Previous studies also support for the modulation ability in young and older adults (Derrfuss et al., 2005; DiGirolamo et al., 2001; Dove et al., 2000; Kim et al., 2012; Kimberg et al., 2000), but our study further suggested that the MA not only preserved the modulation ability, but also showed the greatest modulation from the non-switch to switch condition. Similar findings have been reported in studies using semantic judgement or source memory retrieval task in the middle-aged (Cansino et al., 2015; Kennedy et al., 2015). These studies showed that middle-aged preserved the ability to modulate neural resources comparably to young adults, and better than the older adults. In addition, although we found that similar to the YA and MA groups, the OA was able to increase their activation from the non-switch to the switch conditions, we found that their activation in the non-switch tasks was greater than that of the YA in the non-switch task already, whereas their activation in the switch tasks was not greater than that of the YA or MA. These findings suggest a decline in the ability of OA to modulate their brain activation according to task difficulty. Indeed, previous studies using other cognitive tasks revealed significant reductions in the modulation of frontal activation during context memory task (Ankudowich et al., 2016) and working memory task (Toepper et al., 2014; Hakun and Johnson, 2017) in older adults.

Another important finding of our study was that we found significant correlations between non-switch and switch behavioral performances and the left prefrontal activity in the MA group. Such brain activation-behavioral correlation was unique to the MA group and was not found in the YA and OA groups. In the non-switch condition, the MA individuals with better performance recruited less functional activation in the ***left MFG and IFG***$_t$; in contrast, in the switch condition, the MA individuals with better performance recruited greater functional activation in the ***left MFG and IFG***$_o$. These findings highlight the importance of recruiting and modulating the left prefrontal activations as needed for performing task-switching for the MA group. The MA individuals who could implement a neural efficiency strategy by minimizing left prefrontal activity in the non-switch condition could achieve better non-switch performance, and that those who could scale up left prefrontal activity in the task-demanding switch condition could achieve better switch performance. Furthermore, the MA individuals who showed greater increases in the ***left MFG*** activation from the non-switch to switch conditions had lower error rates of switch performance, indicating that those MA individuals who could better modulate left prefrontal activation according to task demands, presented better switch ability. Therefore, our study further revealed that MA individuals who are more flexible in adjusting the left prefrontal activation according to different task-switching demands could more successfully handle the switch tasks. These findings also suggest that there is a wide range of individual differences on task-switching of the middle-aged. We speculate that this variability may be closely related to their individual differences in brain anatomical structures, which in turn, influence their brain activation intensity and patterns (Bunce et al. 2010; Ferreira et al., 2017; Gunstad et al., 2006). For instance, Ferreira et al. (2017) reported that middle-aged adults who showed a greater reduction of cortical thickness in the parietal-temporal-occipital association cortices, or a larger increase of white matter mean diffusivity in the cingulum and inferior frontal occipital fasciculus, had a greater reduction of global cognitive ability. Bunce et al. (2010) showed that middle-aged adults with greater white matter hyperintensities in the frontal and temporal lobes had poorer performance on choice reaction time tasks and face recognition tasks, respectively. Similarly, Adolfsdottir et al. (2014) found that in a mixed group of middle-aged and older adults, those with lower gray matter volume in the middle frontal gyrus had poorer abilities of switching and inhibition. Future research is warranted to investigate whether the ability to modulate the left prefrontal activation according to different levels of task-switching difficulty is related to changes in brain structures in the middle-aged.

2.5 Conclusion

In conclusion, our key and novel findings are that middle-aged adults are at the cusp of age-related influences on brain activation associated with task-switching, and that individuals who are better at modulating neural processing in the relevant left prefrontal areas can better circumvent age-related declines and switch between tasks. Older adults present poorer task-switching performance, and they lack ability to efficiently use prefrontoparietal activation to compensate for task-switching performance declines and their ability to modulate the brain activation was also poorer than the YA and MA. These findings may shed light on ways to promote healthy cognitive aging in the middle-aged. Future studies may test whether interventions that offer a wide range of task difficulties could help promote the ability of middle-age adults to modulate brain activation according to task demands, and in turn, delay cognitive aging. Future studies are also needed to investigate how alterations in brain structures might be related to the ability to modulate the left prefrontal activation during task-switching in the middle-aged.

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Table 2.1 Demographics and neuropsychological test performances of the three groups

	YA (n = 30)			MA (n = 30)			OA (n = 30)			p
	Mean	±	SD	Mean	±	SD	Mean	±	SD	
Age (yr.)	24.9	±	3.5	59.2	±	3.4 [a]	70.8	±	4.1 [a, b]	< 0.001*
Age Range (yr.)	20	–	32	52	–	64	65	–	80	
Sex (Male : Female) [c]	10	:	20	7	:	23	9	:	21	0.685
Education (yr.)	16.5	±	1.1	14.1	±	2.4 [a]	13.7	±	3.2 [a]	< 0.001*
GDS-15 (score)	2.1	±	2.3	1.2	±	1.3	1.4	±	1.8	0.191
BMI ($\mathrm{kg/m^2}$)	22.5	±	2.3	23.4	±	2.6	22.3	±	2.7	0.189
MoCA (score)	28.6	±	1.2	28.4	±	1.3	28.0	±	1.2	0.146
CTT-1 (sec)	28.0	±	7.9	41.7	±	12.4 [a]	58.6	±	20.3 [a, b]	< 0.001*
CTT-2 (sec)	54.6	±	10.0	82.2	±	20.5 [a]	110.1	±	29.3 [a, b]	< 0.001*

* significant group differences at $p < 0.05$ using one-way ANOVA. [a] significantly different from the YA group in post hoc analysis at $p < 0.017$. [b] significantly different from the MA group in post hoc analysis at $p < 0.017$. [c] Chi-square analysis. Abbreviations: BMI, Body Mass Index; CTT-1, Color Trail Test-part 1; CTT-2, Color Trail Test-part 2; GDS-15, Geriatric Depression Scale 15-item Short-form; MA, middle-aged adults; MoCA, Montreal Cognitive Assessment; OA, older adults; SD, standard deviation; YA, young adults.

Table 2.2 Peak coordinates of significant activation clusters from the disjunction map of the Switch > Non-switch contrast across groups with threshold set at voxel-wise $p < 0.001$ with FWE correction, $k \geq 50$ voxels

No.	Brain regions (Automated Anatomical Labeling)	x	y	z	T
1	L MFG$_1$	-26	12	57	8.47
2	L MFG$_2$	-50	26	33	8.10
3	L IFG$_t$	-42	20	24	7.80
4	L IFG$_o$	-50	14	35	8.34
5	L IPG	-45	-50	45	7.94
6	R SFG	29	2	54	8.02
7	R MFG	51	36	23	7.13
8	R IFG$_o$	51	20	29	7.93
9	R IPG	51	-45	51	7.04
10	R AG	47	-59	53	7.20

Abbreviations: AG, angular gyrus; IFG$_o$, inferior frontal gyrus pars opercularis; IFG$_t$, inferior frontal gyrus pars triangularis; IPG, inferior parietal gyrus; L, left; MFG, middle frontal gyrus; R, right; SFG, superior frontal gyrus.

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Table 2.3 Peak Montreal Neurological Institute (MNI) coordinates and activation details in the prefrontoparietal regions that showed significant group differences for the Non-switch and Switch activation relative to baseline, and for the Switch > Non-switch contrast from the whole-brain analysis

Non-Switch > Rest	x	y	z	T	voxels	Switch > Rest	x	y	z	T	voxels	Switch > Non-switch	x	y	z	T	voxels
MA > YA																	
R AG	29	-62	45	4.43	96	L SPL	-27	-59	63	4.79	90	L SMFG	-2	57	11	4.55	53
						R SFG	27	-12	66	4.98	194	R MOFG	38	57	-8	4.72	53
						R MFG	45	20	36	5.18	313	R IPL	54	-47	50	4.44	138
						R MOFG	36	56	-9	4.39	67						
						R IFG$_t$	53	26	23	4.71	189						
						R Ant Cingulum	12	35	24	4.42	65						
						R SPL	24	-62	65	4.86	116						
						R IPL	53	-45	50	5.04	479						
						R AG	42	-68	41	5.14	250						
OA > YA																	
L MFG	-39	11	35	4.51	186	R IFG$_o$	35	14	35	4.61	81	No suprathreshold voxels					
L SPL	-33	-44	57	4.46	101	R SPL	26	-63	65	5.65	216						
L IPL	-27	-59	45	4.57	70	L RO	-39	-18	12	**-4.85**	53						
R SFG	23	20	45	4.47	50												
R SPL	32	-45	48	6.20	1320												
MA > OA																	
L SPL	-23	-53	75	**-4.40**	71	No suprathreshold voxels						L SMG	-65	-44	30	4.67	331
												R SMFG	5	63	26	5.21	106

Whole-brain analysis with threshold set at voxel-wise $p < 0.0001$ (uncorrected), $k \geq 50$ voxels. Positive t-values indicate the group comparison results being MA > YA, OA > YA, or MA > OA in activation intensity; and negative t-values indicate the group comparison results being MA < YA, OA < YA, or MA < OA in activation intensity. Abbreviations: AG, angular gyrus; Ant, anterior; IFG$_{o}$, inferior frontal gyrus pars opercularis; IFG$_{t}$, inferior frontal gyrus pars triangularis; IPL, inferior parietal lobule; L, left; MA, middle-aged adults; MFG, middle frontal gyrus; MOFG, middle orbital frontal gyrus; OA, older adults; R, right; RO, rolandic operculum; SFG, superior frontal gyrus; SMFG, superiomedial frontal gyrus; SMG, supramarginal gyrus; SPL, superior parietal lobule; YA, young adults.

Table S2.1 Results of RM ANCOVA analysis on BOLD estimates for switch cost contrast within the 10 functional ROIs for the YA, MA, and OA groups in the non-switch and switch conditions

No.	Functional ROIs	Condition	YA Mean ± SD	MA Mean ± SD	OA Mean ± SD	Group × Condition (*p*-value)	Group (*p*-value)	Condition (*p*-value)
1	L MFG$_1$	Non-Switch	-0.95 ± 3.66	-0.56 ± 2.68	1.36 ± 2.38	0.054	0.175	0.150
		Switch	3.39 ± 4.10	4.37 ± 3.44	4.16 ± 2.51			
2	L MFG$_2$	Non-Switch	0.40 ± 3.86	0.09 ± 3.76	1.35 ± 4.01	0.150	0.940	0.019*
		Switch	5.24 ± 5.38	7.21 ± 4.98	6.14 ± 3.73			
3	L IFG$_t$	Non-Switch	1.15 ± 2.95	1.92 ± 2.12	2.89 ± 2.69	0.541	0.136	0.300
		Switch	5.29 ± 3.48	5.39 ± 2.75	5.82 ± 3.19			
4	L IFG$_o$	Non-Switch	2.56 ± 3.39	2.80 ± 4.12	4.40 ± 3.52	0.068	0.784	0.026*
		Switch	8.14 ± 4.43	10.02 ± 5.89	8.73 ± 4.66			
5	L IPG	Non-Switch	2.76 ± 2.98	2.78 ± 3.00	3.98 ± 2.95	0.004*	0.527	0.501
		Switch	5.40 ± 3.71 ^{c}	7.55 ± 4.82 ^{c}	5.76 ± 3.23 ^{c}			
6	R SFG	Non-Switch	1.96 ± 3.04	3.33 ± 2.09	4.88 ± 2.48 ^{a}	0.009*	0.022*	0.063
		Switch	5.24 ± 2.84 ^{c}	7.16 ± 2.62 ^{c}	6.67 ± 2.91 ^{c}			

No.	Functional ROIs	Condition	YA Mean ± SD	MA Mean ± SD	OA Mean ± SD	Group × Condition (p-value)	Group (p-value)	Condition (p-value)
7	R MFG	Non-Switch	-0.01 ± 4.14	0.83 ± 3.96	1.73 ± 4.14	0.088	0.063	0.022[*]
		Switch	3.03 ± 3.98	6.52 ± 4.36	5.65 ± 4.45			
8	R IFG$_o$	Non-Switch	-1.27 ± 4.20	0.77 ± 3.87	2.56 ± 4.38 [a]	0.037[*]	0.012[*]	0.002[*]
		Switch	3.64 ± 4.41 [c]	7.42 ± 4.91 [c]	6.16 ± 4.82 [c]			
9	R IPG	Non-Switch	1.95 ± 3.86	3.65 ± 3.91	3.72 ± 3.93	0.001[*]	0.009[*]	0.018[*]
		Switch	3.72 ± 4.63	9.50 ± 5.61 [a, c]	5.21 ± 5.23 [b]			
10	R AG	Non-Switch	0.76 ± 5.30	1.71 ± 6.98	2.18 ± 4.27	0.005[*]	0.048[*]	0.003[*]
		Switch	3.79 ± 6.51 [c]	10.13 ± 7.28 [a, c]	5.41 ± 5.69 [c]			

[*] denotes significant group difference at $p < 0.05$ assessed using two-way RM ANCOVA, controlling for education. [a] denotes significant difference relative to the YA group in post hoc pairwise comparisons with Bonferroni correction at $p < 0.008$. [b] denotes significant difference relative to the MA group in post hoc pairwise comparisons with Bonferroni correction at $p < 0.008$. [c] denotes significant difference between the non-switch and switch conditions in post hoc analysis at $p < 0.017$. Abbreviations: AG, angular gyrus; IFG$_o$, inferior frontal gyrus pars opercularis; IFG$_t$, inferior frontal gyrus pars triangularis; IPG, inferior parietal gyrus; L, left; MA, middle-aged adults; MFG, middle frontal

gyrus; No., the number of region of interest from the disjunction map; OA, older adults; R, right; SD, standard deviation; SFG, superior frontal gyrus; YA, young adults.

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Table S2.2 Partial correlations (*r*-value) between lateral prefrontal and parietal ROIs and behavioral performance by age group

Age group	L MFG$_1$	L MFG$_2$	L IFG$_t$	L IFG$_o$	L IPG	R SFG	R MFG	R IFG$_o$	R IPG	R AG
YA										
RT$_{\text{non-switch}}$	0.050	0.091	0.265	0.086	-0.176	0.289	0.049	0.086	-0.056	-0.091
RT$_{\text{switch}}$	-0.115	-0.069	0.059	0.092	-0.323	0.140	-0.284	-0.093	-0.258	-0.152
Error$_{\text{non-switch}}$	-0.067	0.090	-0.060	0.059	0.028	-0.170	0.088	0.281	0.030	0.097
Error$_{\text{switch}}$	0.150	-0.067	0.129	0.073	-0.288	-0.097	-0.120	-0.249	-0.198	-0.260
MA										
RT$_{\text{non-switch}}$	0.270	0.320	**0.465***	-0.086	0.149	0.097	0.135	0.323	-0.013	0.027
RT$_{\text{switch}}$	0.056	-0.210	0.226	**-0.374**†	0.013	-0.203	-0.291	-0.041	-0.114	0.066
Error$_{\text{non-switch}}$	0.206	**0.417***	0.188	0.242	-0.058	0.151	0.192	0.266	0.155	0.176
Error$_{\text{switch}}$	0.287	**-0.400***	-0.231	-0.034	-0.145	0.178	-0.196	-0.212	-0.061	0.012
OA										
RT$_{\text{non-switch}}$	-0.031	0.106	0.091	-0.173	-0.184	-0.064	-0.002	0.189	-0.005	0.033
RT$_{\text{switch}}$	-0.017	-0.127	0.027	-0.034	-0.054	0.141	-0.236	-0.112	0.127	0.164
Error$_{\text{non-switch}}$	-0.123	0.078	0.231	0.199	-0.164	0.060	-0.011	0.105	0.041	-0.092
Error$_{\text{switch}}$	-0.039	-0.065	0.139	0.047	-0.292	0.056	-0.135	-0.066	-0.019	-0.190

Partial correlations, controlling for age and education in each group. $^*p < 0.05$; $^\dagger p = 0.05$. Abbreviations: AG, angular gyrus; Error, error rate; IFG$_o$, inferior frontal gyrus pars opercularis; IFG$_t$, inferior frontal gyrus pars triangularis; IPG, inferior parietal gyrus; L, left; MA, middle-aged adults; MFG, middle frontal gyrus; OA, older adults; R, right; RT, reaction time; SFG, superior frontal gyrus; YA, young adults.

Table S2.3 Partial correlations (*r*-value) between the modulation of functional activation from non-switch to switch condition in lateral prefrontal and parietal ROIs and behavioral performance in the switch condition by age group

Age group	**L MFG$_1$**	**L MFG$_2$**	**L IFG$_t$**	**L IFG$_o$**	**L IPG**	**R SFG**	**R MFG**	**R IFG$_o$**	**R IPG**	**R AG**
YA										
Error$_{switch}$	0.067	-0.086	0.301	-0.060	-0.135	-0.022	0.058	-0.187	-0.217	-0.161
RT$_{switch}$	-0.137	-0.053	-0.007	0.099	-0.094	-0.033	-0.116	-0.029	-0.113	0.056
MA										
Error$_{switch}$	-0.121	**-0.380***	**-0.569***	-0.254	-0.265	-0.008	-0.181	-0.234	-0.251	-0.259
RT$_{switch}$	-0.024	-0.108	-0.079	-0.240	-0.027	-0.144	-0.209	-0.165	-0.061	0.128
OA										
Error$_{switch}$	-0.169	-0.303	-0.035	-0.169	-0.311	0.056	-0.287	-0.117	0.100	-0.184
RT$_{switch}$	-0.238	-0.307	0.036	-0.157	0.081	-0.043	-0.293	-0.212	0.271	0.039

Partial correlations, controlling for age and education in each group. $^*p < 0.05$. Abbreviations: AG, angular gyrus; Error, error rate; IFG$_o$, inferior frontal gyrus pars opercularis; IFG$_t$, inferior frontal gyrus pars triangularis; IPG, inferior parietal gyrus; L, left; MA, middle-aged adults; MFG, middle frontal gyrus; OA, older adults; R, right; RT, reaction time; SFG, superior frontal gyrus; YA, young adults.

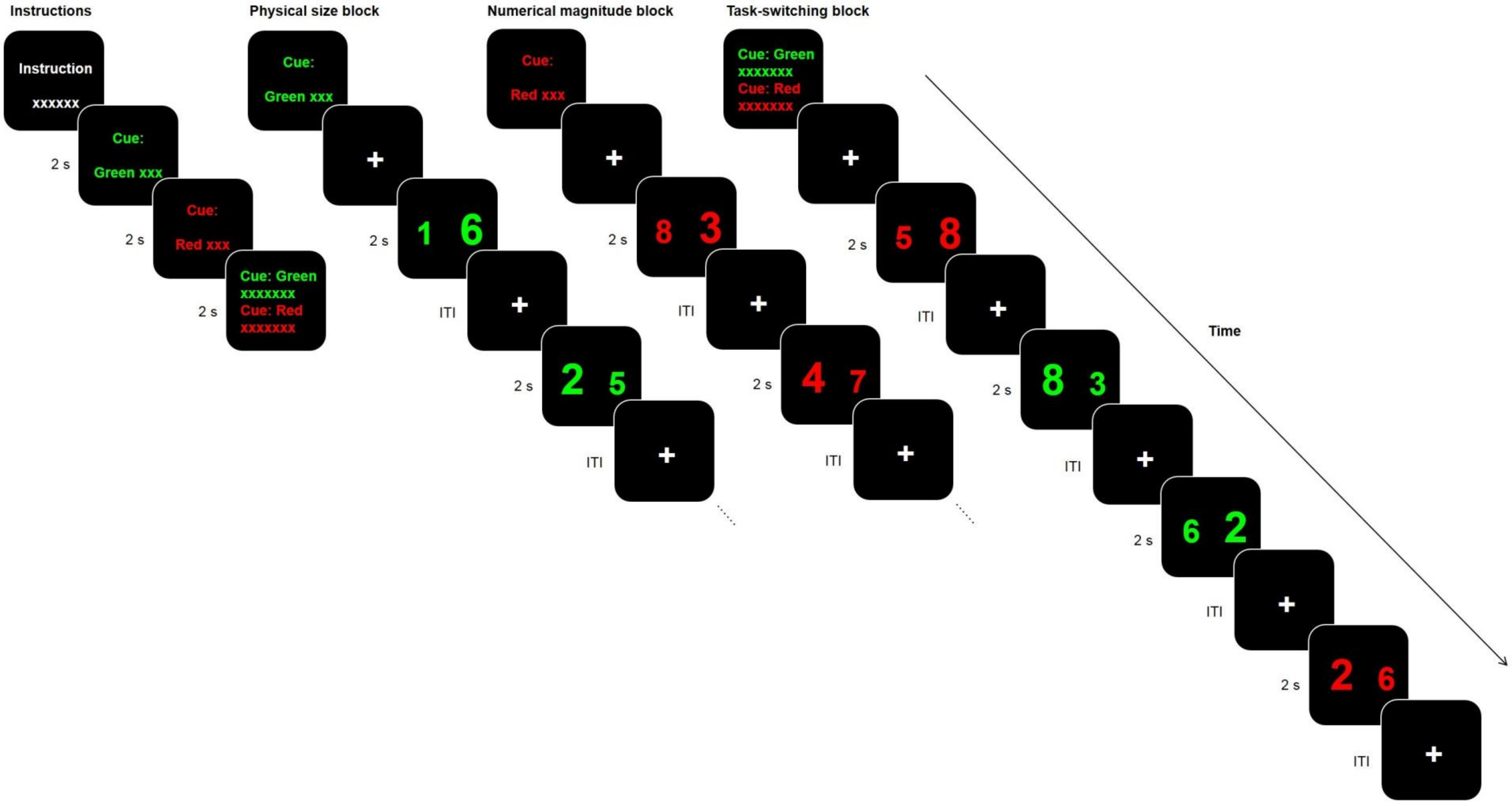

Figure 2.1 Task-switching functional MRI paradigm

Abbreviation: ITI, inter-trial interval.

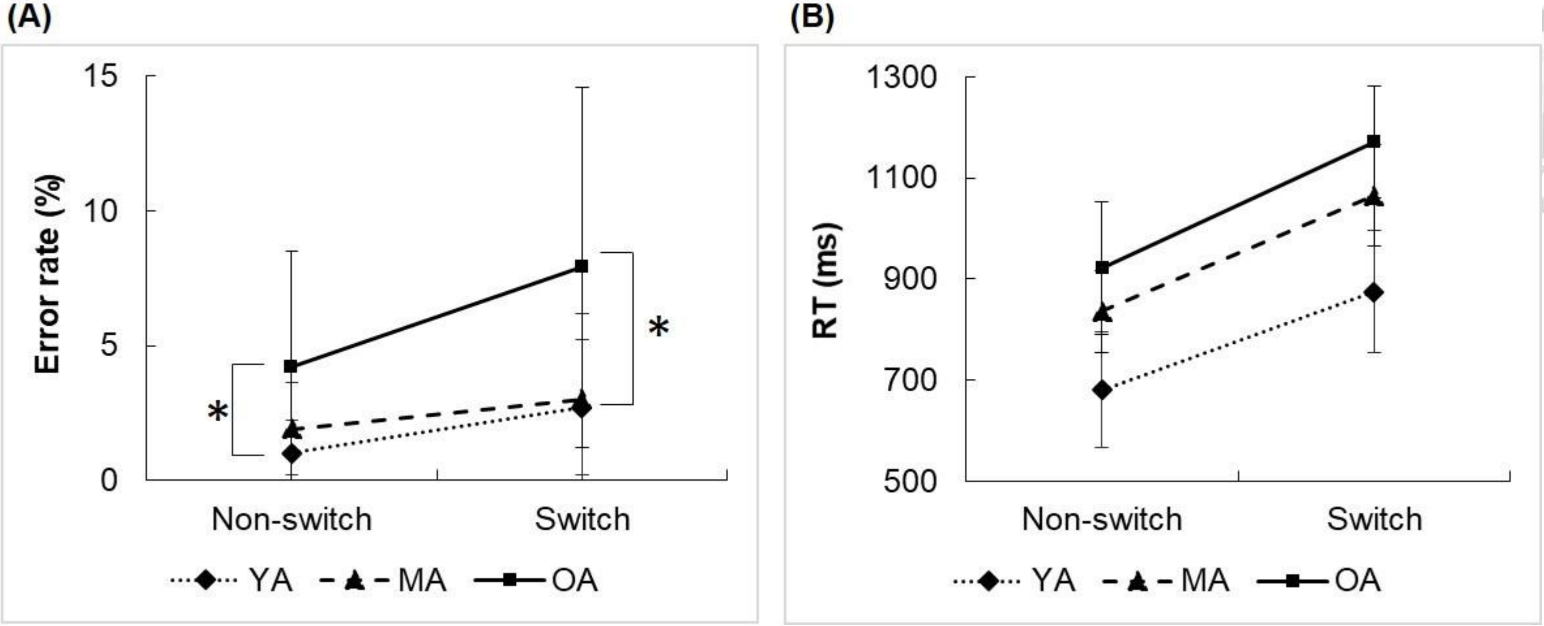

Figure 2.2 Behavioral error rates and reaction times (RTs) of the non-switch and switch conditions for the YA, MA, and OA groups

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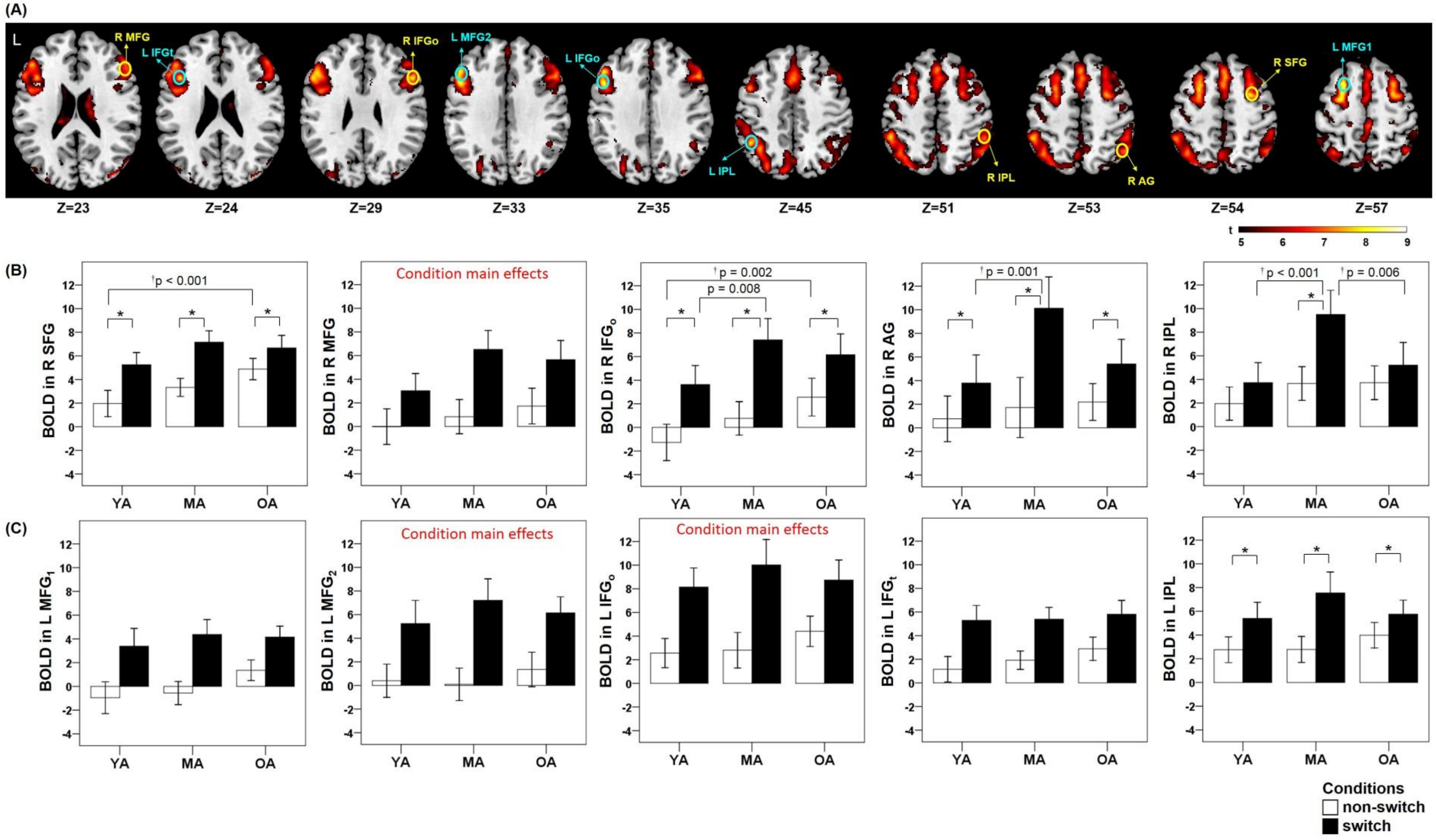
(A)
L
R MFG
L IFGt
R IFGo
L MFG2
L IFGo
L IPL
R IPL
R AG
R SFG
L MFG1
Z=23
Z=24
Z=29
Z=33
Z=35
Z=45
Z=51
Z=53
Z=54
Z=57
t
5
6
7
8
9
(B)
BOLD in R SFG
†p < 0.001
*
BOLD in R MFG
Condition main effects
BOLD in R IFGo
†p = 0.002
p = 0.008
BOLD in R AG
†p = 0.001
BOLD in R IPL
†p < 0.001
†p = 0.006
12
10
8
6
4
2
0
-2
-4
YA
MA
OA
(C)
BOLD in L MFG1
BOLD in L MFG2
Condition main effects
BOLD in L IFGo
Condition main effects
BOLD in L IFGt
BOLD in L IPL
Conditions
☐ non-switch
■ switch

Figure 2.3 (A) Whole brain disjunction map of the switch cost contrast across the YA, MA, and OA groups, with the threshold set at $p <$ 0.001 (FWE correction). (B) BOLD response estimates in the prefrontoparietal regions during the non-switch and switch conditions. Bars are means and standard errors. Abbreviations: AG, angular gyrus; IFG_{o}, inferior frontal gyrus pars opercularis; IFG_{t}, inferior frontal gyrus pars triangularis; IPL, inferior parietal lobule; L, left; MA, middle-aged group; MFG, middle frontal gyrus; OA, older group; R, right; SFG, superior frontal gyrus; YA, young group.

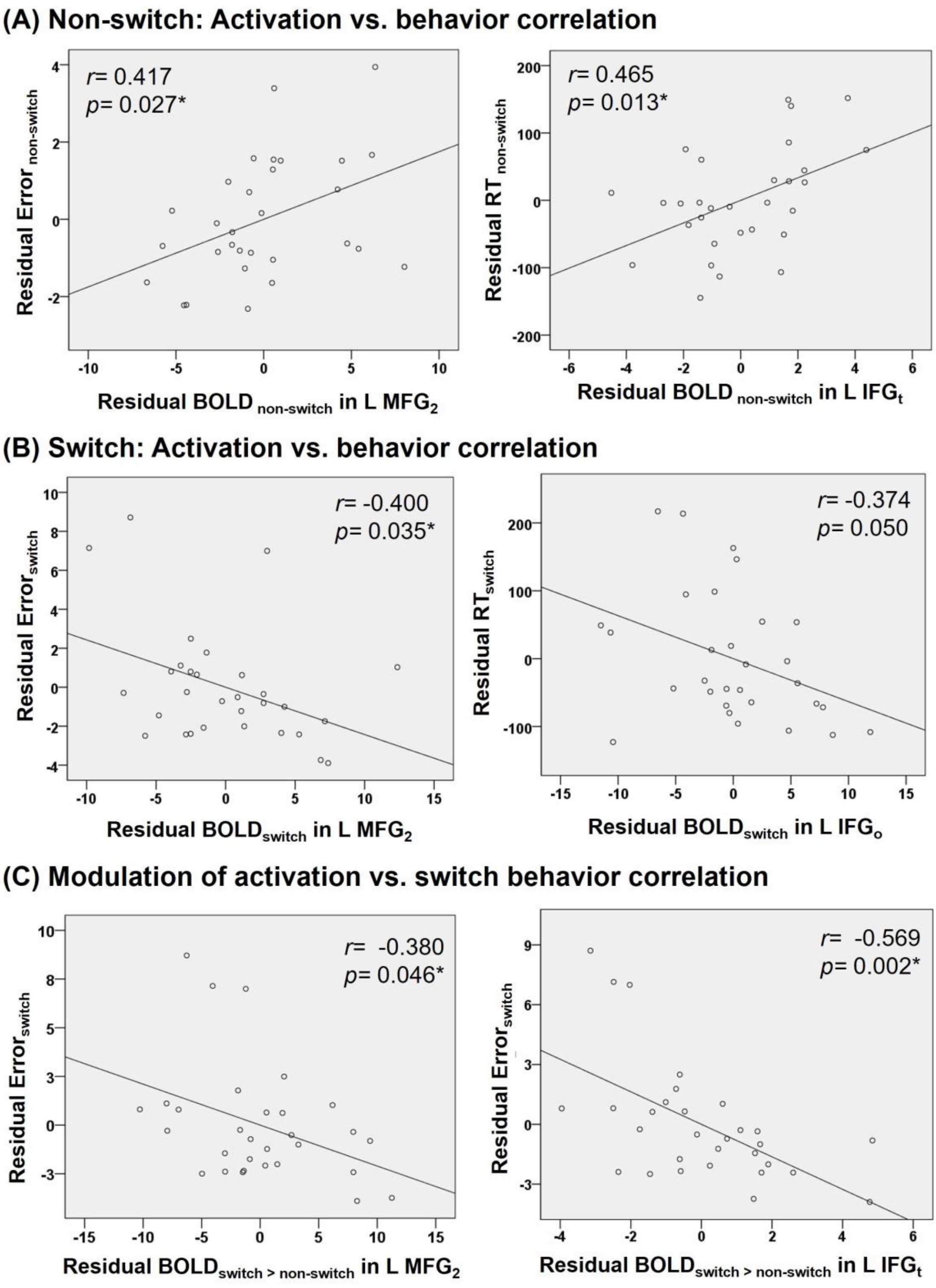

Figure 2.4 (A) Partial correlation plots of the BOLD response estimates against behavioral performance in the non-switch task for the MA group. (B) Partial correlation plots of the BOLD response estimates against behavioral performance in the switch task for the MA group. (C) Partial correlation plot of the changes of

BOLD response estimates from non-switch to switch condition against error rates in the switch task for the MA group.

Abbreviations: IFG_o, inferior frontal gyrus pars opercularis; IFG_t, inferior frontal gyrus pars triangularis; L, left; MFG, middle frontal gyrus.

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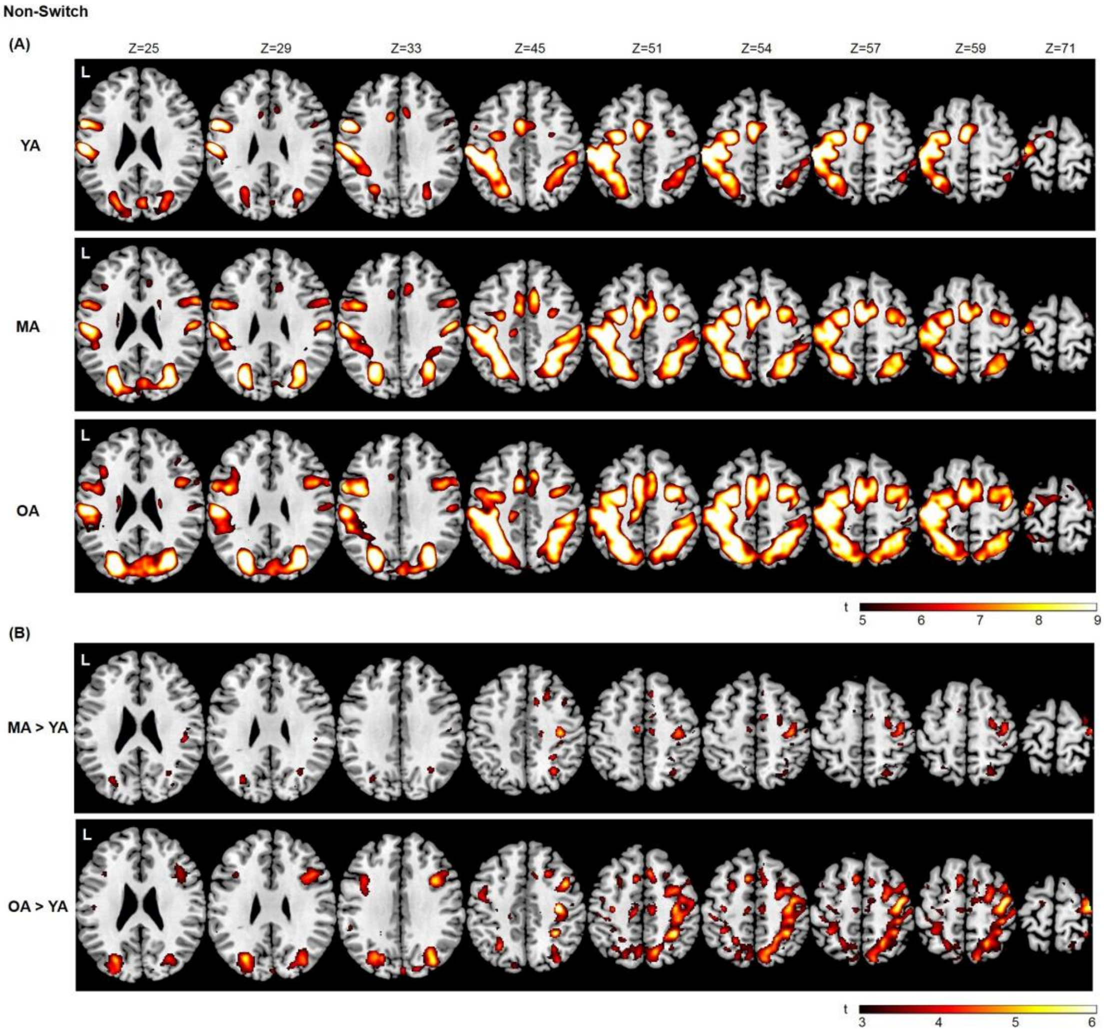

Figure S2.1 (A) Whole brain maps of the non-switch condition for the YA, MA, and OA groups. (B) Whole brain maps of the non-switch condition at the MA > YA and OA > YA group contrasts.

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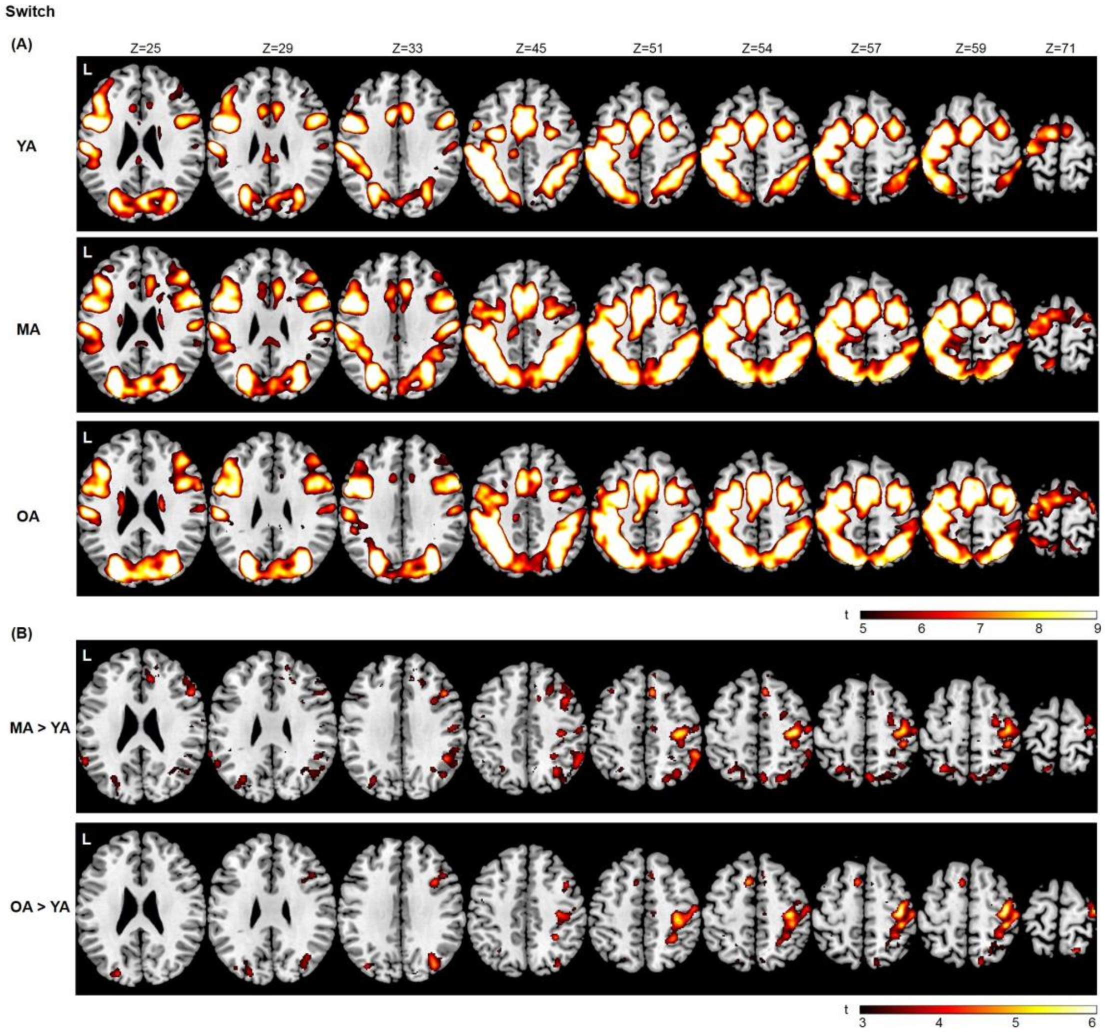

Figure S2.2 (A) Whole brain maps of the switch condition for the YA, MA, and OA groups. (B) Whole brain maps of the switch condition at the MA > YA and OA > YA group contrasts.

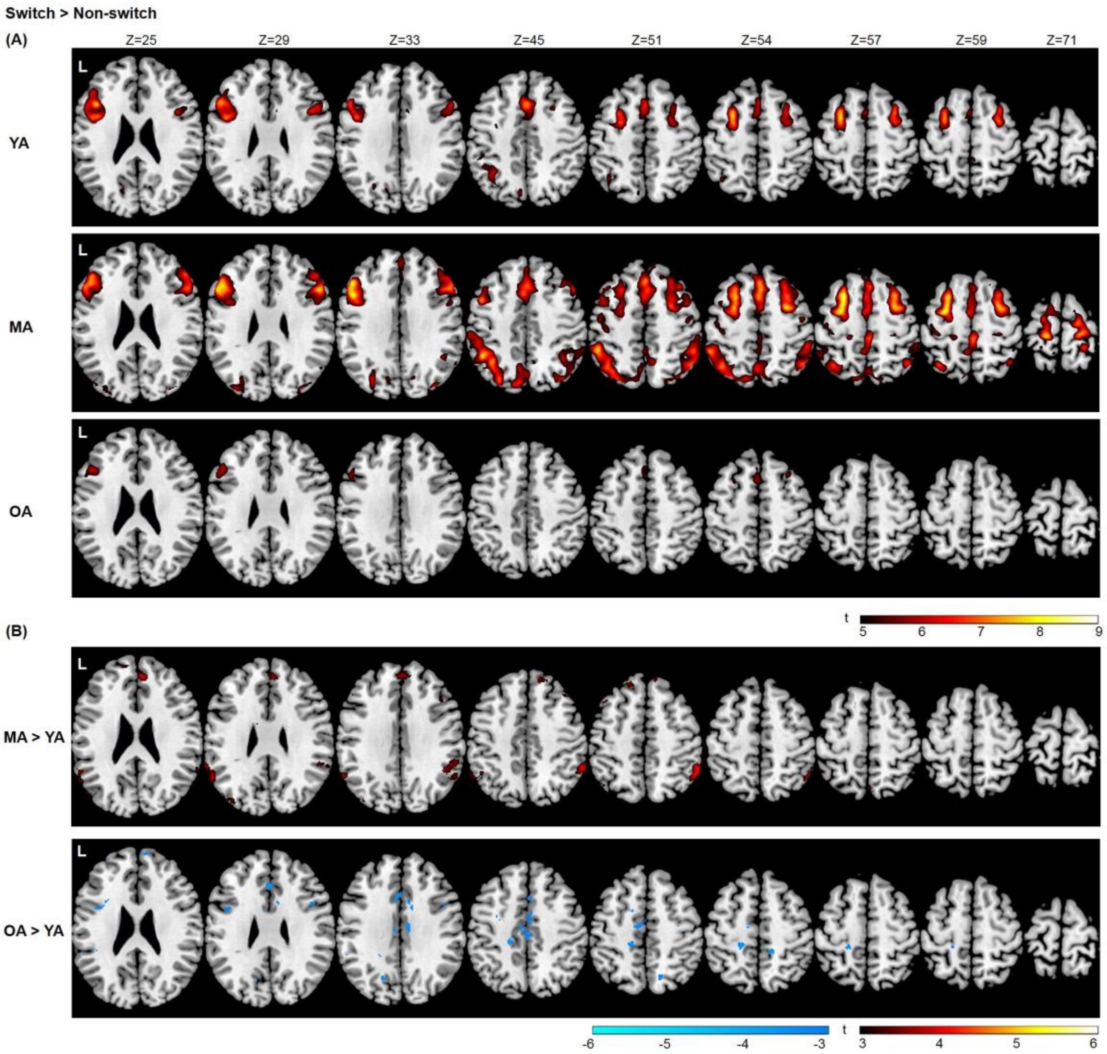

Figure S2.3 (A) Whole brain maps of the switch > non-switch contrast for the YA, MA, and OA groups. (B) Whole-brain maps of the switch > non-switch contrast at the MA > YA and OA > YA group contrasts.

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CHAPTER 3

Task-switching Performance Improvements after Tai Chi Chuan Training Are Associated with Greater Prefrontal Activation in Older Adults

太極拳運動訓練促進老年人轉換任務表現與提升前額葉活化相關

The study presented in this chapter was published in a peer-reviewed journal.

Wu, M. T., Tang, P. F., Goh, J. O. S., Chou, T. L., Chang, Y. K., Hsu, Y. C., Chen, Y. J., Chen, N. C., Tseng, W. Y., Gau, S. S., Chiu, M. J., & Lan, C. (2018). Task-switching performance improvements after Tai Chi Chuan training are associated with greater prefrontal activation in older adults. Front Aging Neurosci, 10(280). doi:10.3389/fnagi.2018.00280

中文摘要

背景：過去文獻指出太極拳運動訓練能有效改善老年人轉換任務能力。然而，仍缺乏文獻探討太極拳運動訓練促進轉換任務表現之神經機制。**方法：**本研究使用功能性磁振造影與數字史楚普(numerical Stroop)研究設計，探討老年人在太極拳介入前、後，執行轉換任務測試時，大腦前額葉功能性活化及轉換功能表現之變化，與兩者變化量間之關係。認知功能正常之老年人被隨機分派至太極拳組及控制組。太極拳組接受為期 12 週、每週 3 次、每次 60 分鐘之楊式 24 式太極拳運動訓練，而控制組在 12 週期間僅接受每兩週一次的電話訪問，不進行任何訓練且不改變其原有生活型態。所有實驗參與者皆須於介入前、後完成身體功能、轉換任務功能、及腦部功能性磁振造影掃描之評估。**結果：**共有 26 位參與者完成全程實驗，分別為太極拳組 16 人、控制組 10 人。結果發現兩組於行為表現及腦部功能性活化上，均呈現顯著的組別與時間之交互作用。太極拳組在訓練後能有效提升身體功能及降低轉換任務錯誤數，且參與太極拳運動訓練之老年人，在執行轉換任務時，左側前額葉活化愈高者，亦能有較佳的轉換任務表現之進步量；控制組未見此變化。**結論：**太極拳運動訓練有潛力提升一些老年人，雖非所有老年人，其執行轉換任務測試時前額葉腦區活化之效能。

關鍵詞：老化、認知功能、執行功能、功能性神經影像、太極拳、運動介入

English Abstract

Background: Studies have shown that Tai Chi Chuan (TCC) training has benefits on task-switching ability. However, the neural correlates underlying the effects of TCC training on task-switching ability remain unclear. **Methods:** Using task-related functional magnetic resonance imaging (fMRI) with a numerical Stroop paradigm, we investigated changes of prefrontal brain activation and behavioral performance during task-switching before and after TCC training and examined the relationships between changes in brain activation and task-switching behavioral performance. Cognitively normal older adults were randomly assigned to either the TCC or control (CON) group. Over a 12-week period, the TCC group received three 60-min sessions of Yang-style TCC training weekly, whereas the CON group only received one telephone consultation biweekly and did not alter their life style. All participants underwent assessments of physical functions and neuropsychological functions of task-switching, and fMRI scans, before and after the intervention. **Results:** Twenty-six (TCC, N=16; CON, N=10) participants completed the entire experimental procedure. We found significant group by time interaction effects on behavioral and brain activation measures. Specifically, the TCC group showed improved physical function, decreased errors on task-switching performance, and increased left superior frontal activation for Switch > Non-switch contrast from pre- to post-intervention, that were not seen in the CON group. Intriguingly, TCC participants with greater prefrontal activation increases in the switch condition from pre- to post-intervention presented greater reductions in task-switching errors. **Conclusions:** These findings suggest that TCC training could potentially provide benefits to some, although not all, older adults to enhance the function of their prefrontal activations during task-switching.

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Key words: Aging, Cognition, Executive function, Functional neuroimaging, Tai Chi Chuan, Exercise intervention

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3.1 Introduction

Task-switching allows a person to rapidly and flexibly adapt behaviors to respond to multi-task rules and demands (Braver et al., 2003) such as when dealing with dynamic changes in complex environments. This high-level executive function involves several sub-processes that include attention, classification, inhibition, updating, memory retrieval, and response to stimulus (Monsell, 2003). Past studies have documented that task-switching ability consistently declines with age. Compared to young adults, older adults present significantly poorer accuracy and slower reaction time while performing task-switching tasks (DiGirolamo et al., 2001; Gazes et al., 2012; Hakun et al., 2015; Kray and Lindenberger, 2000; Reimers and Maylor, 2005; Wasylyshyn et al., 2011; Zhu et al., 2014). Aged-related task-switching declines are associated with functional mobility declines in daily living (Blackwood et al., 2016; Gothe et al., 2014; Hawkes et al., 2012). Thus, the prevention or alleviation of declines in task-switching ability in older adults is an important cognitive aging issue that motivates this present study.

Tai Chi Chuan (TCC) exercise is a form of traditional Chinese exercise that involves physical activity, cognitive control, as well as social interaction when practiced in a group. Individuals who practice TCC often gain not only improvements in physical function and psychological well-being (Chan et al., 2017; Lan et al., 2013; Taylor-Piliae, 2008; Wang et al., 2010), but also in several domains of cognitive function, including global cognitive function, attention, language, perception, learning, memory, and in particular executive function (Taylor-Piliae et al., 2010; Wayne et al., 2014; Zheng et al., 2015). Indeed, the beneficial effects of TCC training on executive function in cognitively intact older adults have been consistently reported in Trail-Making-Test Part B (TMT-B) performance (Matthews and Williams, 2008; Mortimer et al., 2012; Nguyen

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and Kruse, 2012; Wayne et al., 2014). The TMT-B probes task-switching and working memory related abilities by requiring participants to process behavioral response rules that shift between two different stimulus categories (letter vs. number) (Reitan, 1958; Sanchez-Cubillo et al., 2009). In a one group pretest-posttest design study, TMT-B performance of older adults was shown to improve after a 10-week TCC training intervention (Matthews and Williams, 2008). Moreover, TMT-B performance also significantly improved after 6 months of TCC training in randomly assigned community-dwelling older adults compared to routine-care controls (Nguyen and Kruse, 2012).

Evidence also suggests that TCC related interventions may be associated with specific changes of brain structure as well as resting-state connectivity and activation of the brain (Li et al., 2014; Mortimer et al., 2012; Wei et al., 2013; Wei et al., 2014; Wei et al., 2017; Yin et al., 2014). Cross-sectional studies revealed that TCC experts with an average of 14 years of experience, compared with non-TCC practitioners, had greater gray matter cortical thickness in right middle frontal, insula, and precentral, and left superior temporal, medial occipito-temporal, and lingual regions (Wei et al., 2013), and showed smaller functional homogeneity in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex, with the latter findings suggesting enhanced functional specialization of brain regions involved in attention control (Wei et al., 2014). Also using resting-state fMRI, Wei et al. (2017) found a lower fractional amplitude of low frequency fluctuations (fALFF) in the blood oxygen level dependent (BOLD) signal of bilateral frontoparietal attention network during rest in these experienced TCC practitioners, compared to non-practitioners, with lower fALFF correlating with better attention control performance assessed using Attention Network Test response time. While these cross-sectional studies may indicate that long-term TCC practice is

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associated with altered brain structure and resting-state functional specialization of certain brain regions, it remains difficult to establish causal relationships between TCC practice and these brain changes because of the limitations of the cross-sectional nature of the study design.

Several longitudinal studies using resting-state fMRI have provided more direct evidence in support of the effects of TCC-related practice on changing functional connectivity of the brain and the associated cognitive function after intervention (Li et al., 2014; Tao et al., 2017; Yin et al., 2014). Li et al. (2014) reported that after a 6-week multimodal intervention program comprising TCC training, cognitive training, and group counseling, older adults increased brain functional connectivity between the medial prefrontal cortex and medial temporal lobe in their resting-state fMRI, and this increase of functional connectivity was associated with better task-switching and category fluency performance. Also using resting-state fMRI, Yin and colleagues (2014) found that after a similar 6-week multimodal training program, older adults enhanced the amplitude of low frequency fluctuations (ALFF), the regional spontaneous activation during rest, in the middle frontal gyrus (MFG), superior frontal gyrus (SFG), and the cerebellum, and that greater increases of ALFF in the right MFG were associated with better TMT-B performance improvement (Yin et al., 2014). Tao et al. (2017) also found that older adults who received a 12-week TCC intervention program also increased fALFF in the DLPFC, and this increase was associated with improvement of their memory function. Note, reduced fALFF of the resting-state frontoparietal network was found in TCC experts in one cross-sectional study (Wei et al., 2017), whereas increased ALFF or fALFF in the resting-state prefrontal network was found in older adults who undertook short-term TCC intervention in two longitudinal studies (Tao et al., 2017; Yin et al., 2014). This discrepancy may stem from differences

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in the duration of TCC practice (long- vs. short-term), study design (cross-sectional vs. longitudinal), or brain regions used to calculate the functional connectivity indices. Nevertheless, long- and short-term TCC training both resulted in detectable differences in resting-state functional connectivity in older adult participants. Importantly, intervention studies that investigate the effects of TCC training on task-switching related functional brain processes using task-fMRI in older adults are still lacking (Yu et al., 2018). Thus, it remains unclear whether and how TCC training alters task-switching associated brain functional responses and how these changes in functional responses correlate with improvement in task-switching ability.

Previous studies that investigated task-switching associated brain functional activation found that compared to non-switch trials, task-switching trials evoked higher neural activity in the SFG and MFG, inferior frontal gyrus pars triangularis (IFG_t) and opercularis (IFG_o), medial PFG, and superior and inferior parietal cortices (Crone et al., 2006; DiGirolamo et al., 2001; Gold et al., 2010; Hakun et al., 2015; Jimura and Braver, 2010; Sakai and Passingham, 2003; Zhu et al., 2014). Among these frontoparietal regions, age differences are characterized with young adults predominately recruiting the left DLPFC and inferior frontal gyrus (Dove et al., 2000; Kim et al., 2011; MacDonald et al., 2000) and older adults recruiting bilateral prefrontal regions (DiGirolamo et al., 2001; Gazes et al., 2012; Hakun et al., 2015; Zhu et al., 2014). However, over-recruitment in prefrontal regions was negatively associated or unassociated with task-switching performance during Switch conditions in older adults, indicating an attempted but unsuccessful compensatory mechanism (Cabeza and Dennis, 2013; Hakun et al., 2015; Zhu et al., 2014). Noting the above beneficial effects of TCC practice on task-switching performance, we aimed to more specifically determine how TCC training alters prefrontal functional responses associated with task-switching in cognitively normal older adults and how these changes were associated with their task-switching performance.

We conducted a randomized controlled clinical trial (RCT) task-switching fMRI study to investigate changes in task-switching performance and associated brain functional activation, focusing on bilateral prefrontal regions, before and after a 12-week TCC intervention in cognitively intact older adults. Bilateral prefrontal regions were our foci because they are heavily engaged during task-switching and evinced age differences in prior studies (Crone et al., 2006; DiGirolamo et al., 2001; Gold et al., 2010; Hakun et al., 2015; Jimura and Braver, 2010; Sakai and Passingham, 2003; Zhu et al., 2014). In addition, functional activation in prefrontal regions often increases during executive function tasks after aerobic or resistance exercise interventions (Colcombe et al., 2004; Liu-Ambrose et al., 2012). We hypothesized that older adults who received TCC intervention would improve task-switching ability and increase task-switching associated prefrontal functional activation during task-switching fMRI and that such activity increases would positively correlate with post-intervention task-switching performance improvement.

Task-switching fMRI experimental paradigms typically involve measuring brain and behavioral responses during Non-switch and Switch conditions. In Non-switch conditions, participants respond to consecutive trials involving the same single task rule (e.g., AAAAAA or BBBBBB for six trials with rules A and B). In Switch conditions, participants alternate, sometimes stochastically, between a mix of two task rules (e.g., ABAABBAB). Behavioral performance in task-switching can be assessed via accuracy and reaction time (RT) of responses in Switch conditions (Kray and Lindenberger, 2000; Reimers and Maylor, 2005). Alternatively, a global Switch cost measure can also be derived that uses differences in error rates and RTs between averages across trials for

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Non-switch and Switch conditions (Switch – Non-switch condition values) (Kray and Lindenberger, 2000; Wasylyshyn et al., 2011). Yet another approach is to compute a local Switch cost, which uses differences in error rates and RTs of consecutive Non-switch and Switch trials (Switch – Non-switch trial values) within the Switch condition (Monsell, 2003; Wasylyshyn et al., 2011). Past studies have shown that RT and accuracy in Switch conditions and global Switch cost in RTs are both sensitive to aging (Kray and Lindenberger, 2000; Reimers and Maylor, 2005; Wasylyshyn et al., 2011), whereas local Switch cost does not change with age (Wasylyshyn et al., 2011). Therefore, in this study, we focused on Switch condition and global Switch cost indices of the task-switching fMRI experiment to evaluate the effects of TCC training on task-switching behavioral and neural responses.

In addition to using task-switching behavioral measures in the fMRI experiment, we also included the Intra/Extra-Dimensional Set Shift (IED) test of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Ltd., Bottisham, Cambridge, UK) to assess whether the effects of TCC training could be detected by a clinical assessment of the construct of task-switching (Robbins et al., 1998) that was independent from our fMRI task-switching experiment. Importantly, the IED test has established construct validity (Kim et al., 2014), good test-retest reliability (Henry and Bettenay, 2010), and has been used to detect cognitive declines in aging (Robbins et al., 1998) or prefrontal/fronto-striatal dysfunction (Fray et al., 1996). IED use was also in consideration of potential ceiling effects on inside-fMRI task-switching performance due to the practice criterion set in our fMRI experiment (described in Section 2.4). Overall, we hypothesized that performance on the IED test would be improved after a 12-week intervention in the TCC group only and that this improvement would be associated with increases in prefrontal activation during task-switching from

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pre- to post-intervention.

3.2 Methods

Participants & Study Design

This was an assessor-blind RCT (Figure 3.1). Participants (N=31; age range 60-69 years old) were chosen from a larger sample of participants who were enrolled in a registered RCT study (URL: https://clinicaltrials.gov/ct2/show/NCT02270320) and were randomly assigned to either the TCC or the CON group using the stratified randomization method based on age range. The study protocol was registered at Clinical Trials.gov (NCT02270320). All participants underwent neuropsychological and physical function assessments, as well as structural and functional brain MRI scans before and after the 12-week intervention period. The study protocol was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of National Taiwan University Hospital, Taiwan. All participants provided written informed consent before participating in the study.

Participants were recruited from local communities in the Taipei metropolitan area. Inclusion criteria were aged between 60-69 years, education level ≥ 6 years, right-handedness (Oldfield, 1971), right-footedness (Elias et al., 1998), and native Mandarin speakers. Exclusion criteria were Montreal Cognitive Assessment Taiwan version (MoCA) score < 26 (Nasreddine et al., 2005; Tsai et al., 2012), Clinical Dementia Rating score > 0 (Hughes et al., 1982), Geriatric Depression Scale 15-item short-form (GDS-15) score > 8 (Nyunt et al., 2009), Instrumental Activities of Daily Living disability items ≥ 1 (Lawton and Brody, 1969), psychiatric and neurological illness, severe or uncontrolled cardiovascular diseases or musculoskeletal disorders, any MRI contraindications, regular moderate-intensity exercise habits (defined as > 30 mins per session and more than 3 sessions per week in the past 6 months), and prior

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experiences with TCC, yoga, qigong, or martial arts practice. To further understand the required sample size of participants, we calculated the sample size by using the G*Power 3.1.9.2 software (Faul et al., 2009). In this calculation, we assumed a moderate effect (effect size of Hedge's g= 0.51) of TCC training on executive function (Wayne et al., 2014) with the α level set at 0.05 and beta set at 0.2, using in a 2 (group) by 2 (time point) two-way repeated measures analysis of variance (RM ANOVA) design. The results showed that to reach a power of 0.8, the required total sample size was 26. Assuming a 20% dropout rate, the final total sample size of 31 was determined.

Tai Chi Chuan intervention and control procedures

The TCC group received three weekly sessions of 24-form Yang-style TCC (Liang and Wu, 1996) group training for 12 weeks. A 12-week intervention period was chosen because previous behavioral and resting-state fMRI studies suggested that a 12-week TCC program is sufficient to show cognitive effects and alter resting-state brain activation and connectivity in older adults (Tao et al., 2016; Tao et al., 2017; Wayne et al., 2014) and because the duration provided sufficient time for our older participants to steadily learn 2 to 3 new forms of the 24-form Yang-style TCC weekly. Each training session, consisting of 10 minutes of warm-up, 10 minutes of new TCC form learning, 30 minutes of continuous sequential practice of learned forms, and 10 minutes of cool-down, was led by a certified TCC coach with more than 10 years of TCC coaching experiences. Using the Polar Watch (Polar Electro Oy, Kempele, Finland) to monitor participants' heart rate during the exercise sessions, we found that the intensity of the 30-min continuous TCC practice reached approximately 65.4 ± 1.1% (range= 63.8% to 66.7%) of individual participant's age-predicted maximal heart rate (HR_{max}) on average, and thus could be considered moderate intensity (64% to 76% HR_{max}) endurance

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exercise according to the classification of American College of Sports Medicine (Garber et al., 2011; Lan et al., 2008). The CON group was instructed to maintain their original daily routines and physical activity habits and not to receive any new or additional exercise interventions. All CON participants received one telephone consultation biweekly during the 12-week period and their physical activity level and frequency of social interaction were recorded using the Physical Activity Scale for the Elderly (PASE) (Washburn et al., 1993). Free TCC training course was offered to them after the study period.

Neuropsychological and physical function assessments

Before and after the intervention period, we measured participants' task-switching behavioral performances by using the IED test, as well as the outside- and inside-fMRI task-switching behavioral performance measures (described in "fMRI Number Stroop Task and Procedure" section). The IED test has a maximum of nine stages of increasing difficulty, ranging from simple stimulus-response discrimination, reversal learning, compound discrimination, intra-dimensional set-shifts, to difficult extra-dimensional set-shifts. Having received no explicit instructions on when the intra- or extra-dimensional trials began or ended, participants had to figure out whether the intra- versus extra-dimensional rules have changed in each trial according to the "correct" or "wrong" feedback displayed from the computer screen to his/her response to the previous trial. In particular, in the stage of intra-dimensional set-shift trials, participants had to selectively maintain attention on the same specific dimension (such as form) of the stimuli across trials, whereas in the stage of extra-dimensional shift trials, they had to switch attention to a previously irrelevant stimulus dimension (such as line) (Fray et al., 1996; Robbins et al., 1998). Each stage has a maximum of fifty trials and could be

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ended prematurely when the participant correctly answered six trials of that stage consecutively. In this case, without notification, the subject would be prompted to the next stage, in which a different rule is used. The entire IED would be terminated at the end of the stage in which the subject could not correctly answer six trials consecutively of that stage. We used the number of completed stages and the number of total errors of all answered trials on the IED test in this study, with a higher number of completed stages or a smaller number of total errors indicating better task-switching performance.

To allow for understanding the associations among changes in physical function, cognitive function, and brain activation after TCC training, we also conducted pre- and post-intervention physical function tests of muscle strength, balance, mobility, and cardiorespiratory endurance. The muscle strength of bilateral knee extensors was measured twice with a handheld dynamometer (Lafayette Instrument Co., Lafayette, IN, USA; Wang et al., 2002). The better performance of the two trials was recorded for each leg and then averaged to represent the strength. Balance ability was assessed with the eyes-open one-legged stance test (OLST) up to 30 sec for each of 5 trials (Bohannon et al., 1984). The best trial performance of the dominant leg was recorded. Mobility was assessed with two trials each of the Four Square Step Test (FSST) (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 (6MWT) (Brooks et al., 2003). We also recorded each participant’s physical activity level using the PASE before, during, and after the intervention (Washburn et al., 1993). Participants’ frequency of being engaged in social interaction activities was extracted from narratives of their answers to questions 1 and 6 of the PASE.

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fMRI Number Stroop Task and Procedure

We adopted a hybrid block/event-related task-switching fMRI paradigm modified from Huang et al. (2012). The paradigm was implemented using E-prime 2.0 (Psychology Software Tools, Pittsburgh, PA, USA). For each participant, we applied two runs of fMRI scans (7 min/run) each in the before- and after-intervention time points. Each run included two Non-switch blocks (physical size and numerical magnitude blocks in counter-balanced order across subjects, 16 trials for each block) first, followed by a Switch block (32 trials) (Figure 3.2). In each trial, participants were presented with a pair of digits and were required to distinguish the digits by following the cues given before each block. In the physical size block, participants distinguished which digit of the two (with Arial font sizes of 73 and 55) were physically larger than the other, ignoring their numerical magnitude. In the numerical magnitude block, they distinguished which of the two digits (that differed by 3, 4, or 5) 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 stimuli color, with green indicating physical size distinction and red indicating numerical magnitude distinction. Each trial lasted 2 seconds, with pseudo-randomly jittered fixation inter-trial-intervals ranging between 2, 4, and 6 seconds. Each block was preceded by a 20-second fixation resting duration followed by 2 seconds of color-cued instructions on the relevant task dimension(s) for that block. Note that physical size and numerical magnitude of the two digits could be congruent or incongruent in a given trial. There were an equal number of congruent and incongruent trials for physical size, numerical magnitude, and Switch blocks in both runs. Before entering the scanner, all participants received two short-practice sessions with 40 trials

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each (10 physical size trials, 10 numerical magnitude trials, and 20 Switch trials) and reached ≥ 70% accuracy. The error rates (in percentage) during the practice sessions were used to compute the outside-fMRI Non-switch, Switch, and Switch cost behavioral performances, and the error rates and the mean RT collected during the fMRI scans were used to compute the inside-fMRI Non-switch, Switch, and Switch cost behavioral performances. In summary, key behavioral outcome measures for task-switching ability in our study included the inside- and outside-fMRI behavioral performance for the Non-switch and Switch blocks, and for Switch cost, as well as the number of completed stages and total errors of the IED test. We considered the IED and outside-fMRI behavioral performances could better represent participant's actual task-switching ability because the inside-fMRI task-switching performance may be influenced by ceiling effects, given that participants had practiced the non-switch and switch tasks and reached the ≥ 70% accuracy rate criterion before undertaking the fMRI scans.

Behavioral and physical data analyses

Between-group pre-intervention differences in demographics, physical tests, IED task-switching behavioral measure, and the inside- and outside-fMRI behavioral measures for the Non-switch, Switch, and Switch cost were analyzed by using the independent t-test. To analyze the effects of the TCC intervention on physical functions and social interaction, we performed separate two-way (group × time) RM ANOVAs on bilateral knee extensor strength, OLST, FSST, 6MWT, and frequency of social interaction, with time as the within-subject factor. To understand the effects of the TCC intervention on task-switching behavioral outcomes, we performed separate two-way (group × time) RM ANCOVAs on the number of completed stages and total errors of the IED test, on the error rate of the outside- and inside-fMRI Non-switch and Switch

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conditions and Switch cost, and on the RT of the inside-fMRI Non-switch and Switch conditions and Switch cost, controlling for education, because education is known to influence task-switching performance (Zahodne et al., 2014). We adjusted *p*-value for multiple comparisons wherever needed. Because the correlations among the four physical measures (the knee extensor strength, OLST, FSST, and 6MWT) ranged from -0.502 to 0.526, we adjusted the *p*-value to 0.0125 (= 0.05/4). The variable of frequency of social interaction had no significant correlation with these four physical variables (*r* ranged between -0.222 and 0.060; *p*> 0.05), therefore, this *p*-value was not adjusted and was set at *p*=0.05. For the task-switching behavioral variables, because we used three behavioral variables (outside-fMRI error, inside-fMRI error, and inside-fMRI RT) at the same time when we ran analyses of non-switch, switch, or switch cost performance, and these variables were to some extent related (r ranged from 0.193 to 0.599 for baseline data), we adjusted the *p*-value to 0.017 (= 0.05/3). For the IED variables, because there was no significant relationship between the numbers of IED completed stages and IED total errors (*r*= -0.229, *p*= 0.216), suggesting no multicollinearity concern between these two variables, we did not adjust the *p*-value (*p*-value was set at 0.05) when examining the group and time effects on these two IED variables.

Image acquisition parameters

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. Three types of brain images were collected for each participant: a T1-weighted image, using Magnetization-Prepared Rapid Acquisition Gradient Echo (repetition time (TR)/TE (echo time) 2000 ms/2.98 ms, flip angle (FA)= 9°, field of view (FOV)= 192 × 256 mm^2, coronal slice number= 208 slices, voxel size= 1 × 1 × 1 mm^3); a T2-weighted

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image (TR/TE= 7240 ms/101 ms, FA= 90°, FOV= 192 × 192 mm^2, axial slice number = 34 slices, voxel size= 0.8 × 0.8 × 4 mm^3); and two runs of T2* weighted echo planar image depicting BOLD contrast (TR/TE= 2000 ms/24 ms, FA= 90°, axial slice number= 34 slices, FOV= 192 × 192 mm^2, voxel size= 3 × 3 × 4 mm^3).

Image preprocessing and analysis

All preprocessing and general linear model (GLM) estimations were carried out using the Statistical Parametric Mapping 12 (SPM12) (Wellcome Trust Centre for Neuroimaging, London, UK) implemented in MATLAB version 16.0 (The MathWorks, Natick, MA, USA). During image acquisition for each participant, each run of the fMRI scan started with a 6-second dummy scan in consideration of signal equilibrium and subject' adaptation to imaging noise. These dummy scans were excluded from data analysis. For preprocessing of functional images, slice time correction and intra-session alignment were performed to spatially realign the images to the first image of each time series. Head motion correction was performed using a 6-parameter rigid body. Images with head motion greater than 3 mm in translation or 3 degrees in rotation in any run were excluded, based on our scanning voxel resolution. Functional images were then co-registered to co-planar T2 images, which was then used for co-registration to T1-weighted images. Co-registered images were normalized to the Montreal Neurological Institute (MNI) template using the segmentation approach in SPM12, and then spatially smoothed using an 8-mm full-width at half-maximum Gaussian filter.

For first-level whole-brain analysis, each participant's functional brain images for each session and each run were submitted to a GLM to estimate voxel-wise responses during physical size judgment, numerical magnitude judgment, and switching across runs. Specifically, first-level GLMs included three regressors based on the vectors of

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onsets convolved with the hemodynamic responses function (HRF) for trials with correct responses in physical size blocks, numerical size blocks, and switch (both physical size and numerical magnitude together) blocks, and one regressor based on the onsets of all incorrect trials across all blocks convolved with the HRF. These four task regressors with six motion covariates and a constant for the mean run response were replicated over the two runs for each of the two sessions resulting in a total of 44 regressors in each participant's first-level GLM. Individual contrast maps for Non-switch (average of numerical magnitude and physical size trial responses during physical size and numerical magnitude blocks relative to rest fixation) and Switch conditions (average of numerical magnitude and physical size trial responses during switch blocks relative to rest fixation) and Switch > Non-switch contrast were then generated and submitted as the dependent variable in a second-level random effects group analysis with group (TCC and CON) and time (pre- and post-intervention) as independent variables. The whole-brain analysis of the Switch > Non-switch contrast for each group and each time point was performed, and the threshold was set at a significance criterion of voxel-wise $p< 0.005$ corrected for FWE and a cluster size of at least 10 voxels. We then generated a disjunction activation map to identify voxels that showed significant Switch > Non-switch contrast in at least one of the groups for at least one of the time point (Smith et al., 2013). There are three reasons that we chose disjunction analysis. First, the disjunction method is fair to consider all brain functional activation sensitive to Switch > Non-switch contrast across groups and time points. Second, this method can reduce the multiple comparisons (within- and between-group contrasts) in fMRI data processing, and reduce the noise problem introduced from these multiple contrasts. By using the disjunction analysis and the RM ANCOVA with Bonferroni corrections, we could correct for multiple comparisons of the BOLD signals all at once. Third, we anticipated a relatively small difference in the changes of BOLD responses after the short-term TCC intervention and these small changes may not be discernable in group whole-brain contrast analysis that directly compares the significant differences of brain activation changes (post vs. pre) between the TCC and CON groups at the Switch > Non-switch contrast. Therefore, we chose the disjunction analysis and determined the critical ROIs for our analyses. Disjunctions were considered significance using the same threshold of voxel-wise $p< 0.005$ corrected for FWE and a cluster size of at least 10 voxels. Thus, a voxel was deemed to show a significant disjunction response if Switch > Non-switch contrast response passed the criterion for any group at any time point. We then evaluated BOLD response magnitude in functional regions-of-interest (ROIs) identified in this disjunction analysis.

ROI analysis

Because our *a priori* ROIs were in the prefrontal cortex, we delineated functional ROIs as 5mm radius spheres centered around voxels showing peak responses in prefrontal regions in the disjunction map generated above. For each participant, mean BOLD response magnitude for Non-switch and Switch conditions, and for Switch > Non-switch contrast, within each functional ROI were extracted using the Marsbar software (http://marsbar.sourceforge.net) (Brett et al., 2002). To evaluate the effect of TCC training on BOLD response magnitude in the *a priori* prefrontal ROIs, we first performed two-way ANCOVAs on BOLD response magnitudes in three identified ROIs for the Switch > Non-switch contrast with group and time as independent variables and age, gender, and years of education as the covariates. We adjusted the *p*-value to be 0.017 (=0.05/3) because there were three prefrontal ROIs. Post-hoc tests with Bonferroni corrections were performed. We also evaluated the relationships between

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changes in BOLD response magnitude during the Switch condition and in task-switching behavioral measures across time. The changes were all calculated as post-intervention values minus pre-intervention values for corresponding variables. Specifically, we ran partial correlation analyses of changes in Switch BOLD response magnitude in the ROIs with changes in the number of total errors and completed stages of the IED test, changes in error rate of the outside-fMRI Switch condition, and changes in error rate and RT of the inside-fMRI Switch condition, and controlled for age, gender, and years of education, for the TCC and CON groups. We used the Switch BOLD response magnitudes for these correlation analyses in consideration of their comparability with the task-switching behavioral measures, which were taken from direct task-switching performance rather than Switch > Non-switch contrasts. All statistical analyses were performed in SPSS version 18.0.

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3.3 Results

Participants

Two hundred and eleven people who volunteered to participate in this study were initially screened. Among them, 31 participants were eligible and randomly assigned to the TCC (N=16) or CON (N=15) groups. No participants in the TCC group dropped out (i.e., 100% completion rate). Four participants in the CON group dropped out due to personal reasons (i.e. 73.3% completion rate). In addition, one CON participant had excessive head motion during the post-intervention fMRI scan. After exclusions due to incompletion (N=4) and excessive head motion (N=1), the final sample for data analyses was 26 (N=16 for the TCC group and N=10 for the CON group) (Figure 3.1). Since this study was an RCT trial, we adopted the intention-to-treat analysis approach to treatment of data.

The baseline characteristics of the TCC and CON groups did not differ in age, education, body mass index, general cognitive function measured with MoCA, depression level measured with GDS-15, physical activity level measured with PASE, and frequency of social interaction activities (Table 3.1). There were no group differences in the results of pre-intervention physical function tests, number of completed stages and total errors of the IED test, the error rate of the outside-fMRI Non-switch and Switch conditions and Switch cost, and the error rate and RT of the inside-fMRI Non-switch and Switch conditions and Switch cost (all *p* values > 0.05).

In the last two weeks of the 12-week intervention, all participants in the TCC group learned the 24 forms of Yang-style TCC, by demonstrating the ability to execute the forms consecutively on their own as a group, in the absence of verbal instructions or cues from the coach. However, we did not rate individual skill level or fluency of movements because all these participants were novices to TCC before being enrolled into this study and thus could be considered as beginners of TCC only.

Behavioral performance

Results of the two-way RM ANCOVA analysis showed significant group × time interaction effects on the number of total errors of the IED performance ($F(1, 28)= 4.93$, $p= 0.035$) and error rate of the outside-fMRI Switch condition ($F(1, 28)= 16.86$, $p< 0.001$) (Figure 3.3). Post-hoc tests revealed that the TCC group, but not the CON group, significantly reduced the number of total errors of the IED performance ($t(15)= 3.13$, $p= 0.007$) and the error rate of the outside-fMRI Switch condition ($t(15)= 6.34$, $p< 0.001$) from pre- to post-intervention (Figure 3.3). There was a marginal interaction effect on the number of completed stages of the IED performance ($F(1, 28)= 4.16$, $p= 0.051$), error rate of the outside-fMRI Non-switch condition ($F(1, 28)= 3.99$, $p= 0.056$) and Switch cost contrast ($F(1, 28)= 3.31$, $p= 0.079$) with the TCC group showing a trend of increasing the number of completed stages of the IED test and reducing the error rate of the outside-fMRI Non-switch condition and Switch cost contrast, whereas the CON group lacking changes (Figure 3.3). There were no significant interaction effects on other behavioral measures of the inside-fMRI Non-switch, Switch, and Switch cost (Table S3.1).

The two-way RM ANOVA analysis on physical function and social interaction showed significant group × time interaction effects on knee extensor strength ($F(1, 29)= 13.52$, $p= 0.001$), the FSST ($F(1, 29)= 14.52$, $p= 0.001$), the 6MWT ($F(1, 29)= 12.70$, $p= 0.001$), and the frequency of social interaction ($F(1, 29)= 26.62$, $p< 0.001$). The post hoc tests revealed that the TCC group improved on knee extensor strength ($t(15)= -4.54$, $p< 0.001$), FSST ($t(15)= 5.88$, $p< 0.001$), 6MWT ($t(15)= -3.98$, $p= 0.001$), and

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frequency of social interaction (t(15)= -5.37, $p< 0.001$), but the CON group did not (Figure 3.4). There was no significant interaction on OLST ($F(1, 29)= 2.25$, $p= 0.145$).

Task-switching fMRI activation

The functional activations of the Switch > Non-switch contrast per group and per time point (Figure S3.1) were submitted to a disjunction analysis (see Methods). The resulting disjunction map identified functional ROIs over the left SFG, IFG$_t$, inferior parietal gyrus, and right MFG and angular gyrus (Table 3.2). These regions showed significant activation for Switch > Non-switch contrast in at least one of the groups for at least one of the time points. We further analyzed the BOLD response magnitudes in the *a priori* prefrontal functional ROI regions- the left SFG, left IFG$_t$, and right MFG (Figure 3.5A). We adjusted p-value to be 0.017 (= 0.05/3) for multiple comparisons of the BOLD response across group and time, and controlled for age, gender, and education. Two-way RM ANCOVA analysis on the mean BOLD response magnitude of Switch > Non-switch response contrast in these three ROIs revealed a significant group × time interaction effect in the left SFG ($F(1, 26)= 6.57$, $p= 0.017$) and a marginal significant interaction effect in the right MFG ($F(1, 26)= 3.31$, $p= 0.081$), but no interaction effects in the left IFG$_t$ (Table S3.2). Post hoc tests qualified that the left SFG interaction was due to marginally increased Switch > Non-switch BOLD response contrast in the TCC group (t(15)= -1.96, $p= 0.069$, two-tailed) but a non-significant difference in the CON group (t(14)= 1.72, $p= 0.107$, two-tailed) from the pre- to post-intervention scans (Figure 3.5B). Overall, the CON group showed a non-significant trend of decreased Switch > Non-switch neural response contrast in all three ROIs from the pre- to post-intervention scans ($p> 0.05$). In sum, after a 12-week intervention, the TCC group showed a trend of increased Switch > Non-switch BOLD response contrast in the left SFG and right MFG ROIs, whereas the CON group showed a trend of decreased Switch > Non-switch BOLD response contrast in all three ROIs. There were no regions showing significant functional activation for the reverse Non-switch > Switch contrast.

Associations between task-switching fMRI brain activation and behavioral performance

Results of partial correlation analysis between task-switching fMRI brain activation and behavioral performance for the TCC group showed negative moderate-to-good correlations between the changes in Switch BOLD response magnitude in the left SFG (r= -0.631, p= 0.021) and a marginal significant correlation in the right MFG (r= -0.551, p= 0.051) during the fMRI experiment with changes in the number of total errors of IED test (Figure 3.5C), suggesting that TCC participants who had greater activation increments in the left SFG and right MFG regions during the Switch condition also showed greater reductions of the number of total errors on the IED test (i.e., improved task-switching performance) after training. There were no other significant correlations between task-switching fMRI brain activation and other task-switching behavioral measures (all p values > 0.05) (Table S3.3) for the TCC group. As to the CON group, there was no significant correlation between any changes in task-switching fMRI brain activation and any changes in task-switching behavioral measures (all p values > 0.05) (Table S3.4).

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3.4 Discussion

To our knowledge, our study is the first RCT to investigate TCC training-induced changes in brain functional activation during a task-switching fMRI experiment in cognitively intact older adults (Yu et al., 2018) and the correlations between these functional neural processing changes and changes in task-switching performance. Behaviorally, the 12-week TCC training led to improved cognitive task-switching ability, as indicated by the reduced number of total errors on the IED test and the reduced error rate of the outside-fMRI Switch performance. The TCC training also resulted in improved physical performance, including muscle strength, mobility, and cardiorespiratory endurance, and better social interaction. With regard to changes of brain functional activation, we found that after the intervention period, the TCC group presented a marginally increased functional engagement and a trend of increased engagement in the left SFG and the right MFG (bilateral DLPFC), respectively, for the Switch > Non-switch contrast; whereas the CON group showed a trend of decreased engagement of all three prefrontal ROI regions. More importantly, individuals who showed greater increments of such DLPFC engagement had greater improvement in task-switching performance assessed with the IED test. These novel findings regarding functional brain activation provided evidence in support of enhanced DLPFC functional processing as a possible mechanism for the role of TCC training in modulating older adult task-switching performance.

Effects of TCC training on behavioral performance

Among the three task-switching behavioral measures, we found that after TCC training, the TCC group showed a reduced number of total errors on the IED test, and a

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reduced error rate of the outside-fMRI Switch performance, but not during the actual fMRI scans. We considered participants' performance on the outside-fMRI practice session as important outcome measures of their actual task-switching abilities because there were no practice influences on this performance. In contrast, participants underwent the fMRI scans after they had practiced 40 Non-switch and 40 Switch trials and reached *a priori* criterion of accuracy (≥ 70%), which could introduce practice-induced ceiling effects on the inside-fMRI task-switching performance and make this performance less representative of participant's actual task-switching ability. Indeed, when we ran paired-t tests on the Non-switch and Switch performances between the outside-fMRI and the inside-fMRI trials for the pre-intervention data, we found significantly smaller number of errors for both Non-switch and Switch performances on the inside-fMRI trials ($p = 0.039$ and 0.001, respectively, for the TCC group; and both $p < 0.001$ for the CON group). These significant differences suggested practice effects on the inside-fMRI performance. Furthermore, the IED test, designed to specifically tax the cognitive processes of shifting attention between different dimensions of visual stimuli, is a reliable and valid clinical instrument for measuring aspects of cognitive flexibility among executive function (Robbins et al., 1998). It has been shown that the number of total errors on the IED test has a moderate correlation with that on the Wisconsin Card Sorting Test (Kim et al., 2014), one of the gold standard neuropsychological tests for "set-shifting" or "task-switching" (Monchi et al., 2001). Therefore, our findings that the TCC group showed improvements on the IED test and the outside-fMRI Switch performance after training support the notion that TCC training has beneficial effects on task-switching behavioral performance in older adults.

In past research based on the TMT-B, it was difficult to tease out whether the beneficial effects of TCC training were on task-switching, working memory, or both

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(Matthews and Williams, 2008; Mortimer et al., 2012; Nguyen and Kruse, 2012). Our findings provided more direct evidence in support of the effects of TCC training on task-switching vis-à-vis our examination of effects on switch cost (Switch > Non-switch) rather than just non-switch or switch neural responses. While speculative, these beneficial effects on task-switching may stem from the requirement during TCC practice that participants smoothly shifted from one form of TCC to the next till the end of a total of 24 forms. Such drills may not only enhance their sustained attention and memory, but also the task-switching abilities (Chang et al., 2014; Fong et al., 2014; Zheng et al., 2015). Future experiments that break down the components of TCC training to evaluate each of their effects are needed to precisely isolate the specific mechanisms of TCC training in changing cognitive and neural processing.

Non-cognitive aspects of our findings consistent with past studies on TCC training should also be highlighted. Regarding physical performance, our findings that the TCC group improved their lower extremity extensor strength, mobility, and cardiorespiratory endurance are congruent with previous research (Lan et al., 2013; Li et al., 2001; Taylor-Piliae et al., 2006; Taylor-Piliae, 2008). Such improvements in physical performances might be attributed to the requirement to maintain a semi-squat posture while performing whole body movements in a continual manner during TCC practice (Lan et al., 2013). However, different from previous literature, we did not find TCC training effects on static balance performance- the OLST. Note that the majority of our participants already had good balance ability before training, with 81% of the TCC and 73% of the CON participants showing a score of 30 seconds on the OLST before training. More difficult tests may be needed to sensitively detect the effects of TCC training on balance ability in these participants. Finally, our results also showed that the TCC group increased the frequency of social interactions after training, supporting

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previous literature which revealed that practicing TCC enhances social support (Chan et al., 2017; Yeh et al., 2016). Together, these positive TCC training effects on cognitive and physical functions, and social interactions indicate that regular engagement in a TCC program three times a week for three months is sufficient to induce detectable cognitive and physical health benefits and enhance social support in cognitively intact older individuals.

Effects of TCC training on task-switching related brain activation

Our disjunction analysis of fMRI activations in the *a priori* prefrontal regions showed that the left SFG, right MFG, and left IFG_t were the main regions activated for Switch > Non-switch contrast among the participants. These identified prefrontal regions implicated in our task-switching number Stroop experiment were consistent with those reported in older adults in prior task-switching studies (DiGirolamo et al., 2001; Hakun et al., 2015; Zhu et al., 2014). Our results provided two lines of evidence supporting that the two task-switching specific DLPFC regions were particularly modulated after TCC training. First, after TCC training, the TCC group presented a marginally increased functional activation in the left SFG and a trend of increased activation in the right MFG for Switch > Non-switch contrast. Second, after TCC training, those participants who showed greater increases of activation in these two regions during task-switching presented better improvement on the IED test performance. These findings suggested that the left SFG and right MFG activation was specifically modulated during task-switching after TCC training to enhance task-switching performance in some, although not all, of the TCC participants. Intriguingly, previous research that used resting-state fMRI to investigate effects of a 6-week multimodality intervention program, comprising TCC, cognitive training, and

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group counseling, on resting-state brain activation also revealed modulation of brain activation in these two DLPFC regions (Yin et al., 2014). Yin and colleagues (2014) found significant increases in the resting-state brain activation in the left SFG and right MFG for participants who received the multimodality intervention program and that greater increases of the activation in the right MFG were correlated with greater improvements in TMT performance. Furthermore, using structural brain imaging, Wei et al. (2013) found that TCC experts with an average of 14-year TCC experiences had thicker cortex in right MFG as compared to age-matched TCC-naive control individuals. Together with our findings, we speculate that in some older adults, TCC training may specifically enhance neural processing in the left SFG and right MFG regions during resting and during task-switching and enlarge these regions, which in turn, could lead to more efficient task-switching performance. The three key cognitive processes of task-switching entail control of attention maintenance, inhibition, and working memory (Monsell, 2003). The left SFG is known to be involved in the implementation of top-down executive control by maintaining attention demands while switching between tasks (MacDonald et al., 2000) and contributing to working memory processing, such as loading, monitoring, and maintaining different stimulus-response rules (Cutini et al., 2008; du Boisgueheneuc et al., 2006). The right MFG is associated with inhibition control of ignoring irrelevant stimuli or inhibiting undesirable responses (Brass et al., 2001; Buchsbaum et al., 2005; Garavan et al., 1999). The fact that while practicing TCC, participants have to memorize a series of whole-body movements, maintain attention on coordinating breath and actions, and switch from one Tai Chi form to another smoothly may provide extensive drills on attention, working memory, and inhibition control and thereby enhances the engagement of the left SFG and right MFG regions and makes the activation in these regions more efficient.

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It is worth noting that our study showed that except for the left SFG region, TCC practice did not significantly increase brain activations in other prefrontal regions engaged in task-switching across all TCC practitioners. However, among the TCC practitioners, those who became better at increasing the prefrontal activations during task-switching could significantly reduce task-switching behavioral errors after TCC training. These findings suggested individual differences in their brain responses to short-term practice of TCC, which may potentially provide benefits to some, although not all, older adults to enhance the function of their prefrontal activations during task-switching. It remains to be studied whether a longer-term of TCC training could bring more homogenous positive effects on prefrontal activation to all TCC practitioners. Another possible account of the small amount of prefrontal activation changes after TCC training could be the practice-induced ceiling effects resulting from participants' practice of 40 non-switch and 40 switch trials outside the MRI scanner in order to ensure their fully understanding of the tasks and reaching the 70% performance accuracy criterion before being scanned. As such, the prefrontal activation changes due to TCC training per se may be attenuated and hence become less discernible. Nevertheless, we suggest that even if ceiling performance is reached behaviorally for the inside-MRI task because of the practice performance criterion, neural responses can still reflect level of ease or difficulty to reach the ceiling response, as seen with the correlations with the out of scanner IED performance.

We note that our finding of a non-significant trend of decreasing activation during task-switching activation in prefrontal ROIs for the CON group is consistent with previous studies which showed a non-significant trend for brain volume reduction of the control group who did not receive any exercise training (Mortimer et al., 2012). These findings suggest that normative age-related changes in brain structure and function

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might be observed in as little as 3 months, albeit not significant in our study. More importantly, we provide evidence suggesting that TCC training not only halts but reverses this normative trajectory of brain functional aging in target frontal brain areas in some older adults.

While we speculate that TCC practice particularly challenges learners' task-switching processing, and thereby improves learners' task-switching abilities, it remains possible that the TCC training effects on task-switching may come from the aerobic or social interaction effects of TCC practice (Chan et al., 2017; Lan et al., 2013; Li et al., 2001; Ma et al., 2018; Mortimer et al., 2012; Taylor-Piliae, 2008; Yeh et al., 2016). Aerobic training studies showed that enhanced cardiorespiratory fitness after such training was associated with improvements in cognitive function (Colcombe and Kramer, 2003; Smith et al., 2010) and changes in brain activation (Colcombe et al., 2004; Voelcker-Rehage et al., 2011). Participation in social activities is known to be associated with better cognitive function or protection against cognitive decline in older adults (Fu et al., 2018; Glei et al., 2005; Hikichi et al., 2017; Mortimer et al., 2012). Since we found our TCC participants had improvements on the knee extensor strength, mobility (FSST), cardiorespiratory fitness (6MWT) performance, and social interaction, we further performed correlation analyses of TCC participants' changes on these physical and social interaction measures with changes in activation in the three identified prefrontal ROIs during task-switching and changes in task-switching behavioral measures, using age, gender, and education as the covariates. The analyses yielded no significant relationships of task-switching abilities with physical measures (all $p > 0.05$) (Table S3.3), suggesting that it is unlikely that the improvements of task-switching behavioral performance after TCC training came from the physical effects of TCC. However, we found a significant correlation between the change in

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social interaction and the change in the outside-fMRI error rate of switch condition (*r*= -0.690; *p*= 0.009), and between the change in the knee extensor strength and the change in the Switch BOLD response magnitude of the left $\mathrm{IFG_t}$ (*r*= 0.802; *p*= 0.001) for the TCC group (Table S3.3). To further examine whether changes in social interaction influenced the relationships between changes in the outside-fMRI error rate of the switch condition and changes in the Switch BOLD response magnitude for the three ROIs, we re-ran the partial correlation analyses using age, gender, education, and social interaction as the covariates. The results remained the same and there were still no significant correlations between changes in the outside-fMRI error rate of the switch condition with changes in Switch BOLD response for these three ROIs (*r*= -0.324 – 0.148, *p*> 0.05; Figure S3.2). Similarly, to further test whether the change in the knee extensor strength affected the relationships between changes in task-switching performance and Switch BOLD response magnitude in the left $\mathrm{IFG_t}$, we controlled for age, gender, education, and the knee extensor strength as covariates. The results also showed no significant relationships between changes of all task-switching measures with changes in the Switch BOLD response magnitude in the left $\mathrm{IFG_t}$ (*r*= -0.081 – 0.403, *p*> 0.05; Figure S3.3). According to these results, it is unlikely that the newly emerged relationships between changes in brain activation and changes in switch performance after TCC training came from the improved social interaction or knee extensor strength for the TCC group. Rather, it is more possible that practicing TCC provides specific drills on cognitive processes needed for task-switching, and therefore leads to improved task-switching performance in most practitioners and altered neural activation in brain regions particularly engaged in task-switching in some practitioners. However, because we only performed the 6MWT and did not measure the maximum cardiorespiratory capacity, such as maximal VO_2 uptake, as reported in previous studies

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using aerobic exercises (Colcombe et al., 2004; Voelcker-Rehage et al. 2011), it remains to be tested as to whether TCC participants' changes in the maximum cardiorespiratory capacity relate to their changes in brain activations after TCC practice.

Comparisons of brain mechanisms of cognitive effects between TCC and other types of exercises

We note that there are similarities and differences in the effects of TCC training on cognition and neural processing, compared to other forms of exercises including aerobic, resistance, and cognitive-motor exercises. Aerobic or resistance exercises have been shown to improve inhibition control (Colcombe et al., 2004; Liu-Ambrose et al., 2012; Nagamatsu et al., 2012; Voelcker-Rehage et al., 2011), but not task-switching components of executive function (Liu-Ambrose et al., 2010; Voss et al., 2013) in cognitively intact older adults. By contrast, cognitive-motor exercises, a form of dual-task training comprising simultaneous cognitive and motor loads (Wollesen and Voelcker-Rehage, 2013), show positive effects on task-switching performance (Eggenberger et al., 2016; Nishiguchi et al., 2015), as well as greater spatial ability and working memory capacity compared to aerobic exercise (Moreau et al., 2015). These findings suggest that complex cognitive-motor training protocols are more effective in enhancing cognitive functions than simple motor training alone, consistent with the effects of TCC training in our study as well as others (Mortimer et al., 2012; Wayne et al., 2014).

Less consistency is seen in the effects of exercise interventions on brain responses during cognitive processing. Whereas some report aerobic or resistance exercise intervention increased prefrontal activation during a Flanker or associative memory task (Colcombe et al., 2004; Liu-Ambrose et al., 2012; Nagamatsu et al., 2012;

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Voelcker-Rehage et al., 2011), others report decreased prefrontal activation during similar tasks (Voelcker-Rehage et al., 2011; Smith et al., 2013). Decreased neural cognitive processing after training might reflect improved neural processing efficiency, whereas increased neural activity might reflect more specialized and enhanced cognitive operations. Thus, both types of exercise training related changes in neural processing can theoretically support improved cognition. However, we note that in our study, increases in prefrontal activity correlated with better task-switching ability in the TCC group, suggesting the latter enhancement of neural computations as the more likely outcome of TCC training effects on task-switching processing. Since TCC training also comprises the aerobic and resistance training components, it remains to be studied whether TCC training also improves inhibition and memory functions, and the associated neural mechanisms involved. Future studies directly comparing TCC training effects against aerobic/resistance exercises across different cognitive abilities and associated brain responses are required to evaluate the specific neural mechanisms that underlie the cognitive benefits afforded by TCC training.

Limitations

Four limitations are noted in this present study. First, there was a relatively small sample size and a higher dropout rate for the CON than TCC group (26.7% in CON group v.s. 0% in TCC group) (chi square, $p= 0.022$). The latter was possibly due to the lack of strong incentive to adhere to the study enrollment for the CON participants. Nevertheless, the independent t-test on baseline demographics and behavioral performance between the initial 15 CON participants and the remaining 10 CON participants yielded no significant group differences (all $p > 0.05$). Therefore, it is unlikely that the higher dropout rate in the CON group affected our results. Second,

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there were fewer male participants than female participants in this study, which could decrease the generalizability of the results to the general older population. Third, there was a lack of an active control group that performed another type of exercise during the intervention period. Adding an active control group could help differentiate whether our findings were due to TCC training per se from being engaged in any form of physical exercise. Fourth, this study only assessed the training effect immediately following the 12-week TCC training. Future research may extend the current findings by adding follow-up assessments after the end of training to explore the longer time influences and retention effects of a 12-week TCC program.

3.5 Conclusion

This study demonstrated that 12 weeks of TCC training improved task-switching ability and induced a positive relationship between changes in task-switching associated prefrontal activation and improvement in task-switching performance in older adults. These findings suggest TCC training could potentially provide benefits to some, although not all, older adults to enhance the function of their prefrontal activations during task-switching. Future studies involving a longer-term of training and using examinations of brain structural and functional connectivity are possible next steps to further understand whether a longer-term of TCC training could bring more homogenous positive effects on brain prefrontal activation to all TCC practitioners and the mechanisms underlying improved neural processing after TCC intervention in those who benefit from the training.

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3.6 Acknowledgements

This study was supported by grant NSC 102-2410-H-002-213-MY2 from the Ministry of Science and Technology of Taiwan and grant 06A1-PHSP08-028 from the National Health and Research Institutes of Taiwan. We thank Ms. Yue-Ju Wang and Mr. Gao-Teng Yang for coaching the Tai Chi Chuan courses. We thank the Taipei senior service centers in the Zhongzheng and Wanhua districts and Yonghe Cardinal Tien Hospital for providing space for training.

Table 3.1 Demographics of the TCC and CON groups at pre-intervention

	TCC (n= 16)	CON (n= 15)	*p*
Age (year)	64.9 ± 2.8	64.9 ± 3.2	0.989
Age range (year)	61 - 69	60 - 69	
Gender (female : male)	13 : 3	15 : 0	
Education (year)	13.8 ± 2.4	13.4 ± 2.6	0.645
BMI (kg/m^2)	22.5 ± 2.7	22.3 ± 3.2	0.863
MoCA (score)	28.3 ± 1.5	28.4 ± 1.5	0.868
GDS (score)	1.8 ± 2.0	1.9 ± 1.6	0.859
PASE (score)	50.3 ± 36.2	40.5 ± 18.4	0.352
Frequency of social interaction (times/week)	7.0 ± 2.0	7.1 ± 2.0	0.854

Data are presented as means ± standard deviations. Independent t test was used for all other group comparisons. Abbreviations: BMI, body mass index; GDS, Geriatric Depression Scale; MoCA, Montreal Cognitive Assessment; PASE, Physical Activity Scale for the Elderly.

Table 3.2 Peak MNI coordinates and activation details in frontoparietal regions identified in the disjunction map of the Switch > Non-switch contrast across groups and time points

Brain area	x	y	z	T	No. of voxels
L Superior Frontal Gyrus	-22	-4	58	6.48	238
R Middle Frontal Gyrus	32	18	54	7.39	54
L Inferior Frontal Gyrus pars Triangularis	-50	20	26	6.72	245
L Inferior Parietal Gyrus	-32	-60	46	7.92	744
R Angular Gyrus	32	-64	42	6.95	283

Whole-brain analysis with threshold set at voxel-wise $p < 0.005$ corrected for FWE and a cluster size at least 10 voxels. Positive t-values indicate stronger activation in the Switch condition than in the Non-switch condition.

Table S3.1 Outside- and inside- fMRI Non-switch, Switch, and Switch cost performance (error and RT) of the TCC and CON groups at pre- and post-intervention tests

	TCC (N= 16)		CON (N= 15)		Group × Time	Group	Time
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention			
Non-switch							
Outside-fMRI error (%)	6.9 ± 6.6	2.8 ± 2.7	9.3 ± 6.2	9.7 ± 7.7	0.056	0.021	0.168
Inside-fMRI error (%)	2.8 ± 2.4	1.8 ± 2.1	2.3 ± 1.5	3.1 ± 3.9	0.096	0.728	0.363
Inside-fMRI RT (ms)	878.5 ± 96.4	877.5 ± 125.1	897.4 ± 95.7	949.8 ± 98.6	0.176	0.282	0.962
Switch							
Outside-fMRI error (%)	17.3 ± 11.7	7.0 ± 8.1†	20.3 ± 11.9	20.0 ± 11.4	< 0.001*	0.046	0.642
Inside-fMRI error (%)	4.9 ± 3.9	3.1 ± 3.8	6.6 ± 6.0	5.2 ± 3.0	0.849	0.237	0.711
Inside-fMRI RT (ms)	1079.4 ± 119.3	1061.5 ± 93.9	1147.9 ± 122.8	1181.4 ± 112.2	0.224	0.042	0.687
Switch cost							
Outside-fMRI error (%)	10.5 ± 9.8	4.2 ± 8.3	11.0 ± 8.3	10.3 ± 9.2	0.079	0.263	0.467
Inside-fMRI error (%)	2.1 ± 4.0	1.4 ± 3.4	4.2 ± 5.4	2.0 ± 4.5	0.515	0.255	0.889
Inside-fMRI RT (ms)	201.0 ± 76.5	184.0 ± 84.3	250.5 ± 62.4	231.6 ± 82.0	0.904	0.086	0.722

Values are means ± standard deviations. Outside-fMRI error means performance during practice trials. * adjusted p< 0.017: showing a significant difference, using RM ANCOVA and controlling for education. $^{\dagger}p$< 0.001: post hoc analysis of repeated measures ANCOVA, showing a significant difference from pre-intervention test data. Abbreviations: error, error rate; RT, reaction time.

Table S3.2 BOLD response magnitude for the Switch > Non-switch contrast of the TCC and CON groups at pre- and post- intervention

	TCC (N= 16)		CON (N= 15)		Group × Time	Group	Time
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention			
L SFG	3.0 ± 2.8	4.9 ± 3.9	3.2 ± 3.2	1.9 ± 3.1	0.017*	0.157	0.563
R MFG	4.8 ± 3.6	5.6 ± 3.6	3.5 ± 3.0	2.4 ± 3.0	0.081	0.048	0.876
L IFG_t	7.4 ± 5.2	6.2 ± 5.0	4.7 ± 4.0	3.3 ± 3.1	0.764	0.096	0.742

Values are means ± standard deviations. *adjusted $p \leq 0.017$: showing a significant difference using RM ANCOVA, controlling for age, education, and gender. Abbreviations: L SFG, left superior frontal gyrus; R MFG, right middle frontal gyrus; L IFG_t, left inferior frontal gyrus pars triangularis.

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Table S3.3 Inter-relationships among changes in task-switching performance, changes in physical function and social interaction, and changes in BOLD response magnitude in the prefrontal cortex during the Switch condition from pre-intervention to post-intervention in the TCC group

	△ IED Completed Stages	△ IED Total Errors	△ Outside-fMRI Error$_{sw}$ (%)	△ Inside-fMRI Error$_{sw}$ (%)	△ Inside-fMRI RT$_{sw}$ (ms)	△ Frequency of social interaction	△ BOLD in L SFG	△ BOLD in R MFG	△ BOLD in L IFG$_t$
△ Knee extensor strength (kg)	*r*= 0.041 *p*= 0.895	*r*= -0.234 *p*= 0.442	*r*= -0.123 *p*= 0.689	*r*= 0.134 *p*= 0.663	*r*= -0.086 *p*= 0.781	*r*= 0.110 *p*= 0.721	*r*= 0.458 *p*= 0.116	*r*= 0.314 *p*= 0.296	*r*= 0.802 *p*= 0.001*
△ Four Square Step Test (sec)	*r*= 0.199 *p*= 0.514	*r*= 0.075 *p*= 0.808	*r*= 0.128 *p*= 0.676	*r*= -0.093 *p*= 0.762	*r*= -0.053 *p*= 0.863	*r*= -0.237 *p*= 0.435	*r*= -0.307 *p*= 0.308	*r*= 0.048 *p*= 0.876	*r*= -0.210 *p*= 0.492
△ Six Minute Walk Test (m)	*r*= -0.087 *p*= 0.778	*r*= 0.066 *p*= 0.830	*r*= 0.316 *p*= 0.292	*r*= -0.346 *p*= 0.247	*r*= -0.247 *p*= 0.415	*r*= -0.216 *p*= 0.479	*r*= 0.213 *p*= 0.485	*r*= -0.336 *p*= 0.262	*r*= -0.026 *p*= 0.933
△ IED Completed Stages		*r*= -0.162 *p*= 0.598	*r*= 0.063 *p*= 0.838	*r*= -0.310 *p*= 0.303	*r*= -0.309 *p*= 0.304	*r*= 0.248 *p*= 0.413	*r*= -0.197 *p*= 0.518	*r*= 0.076 *p*= 0.804	*r*= 0.050 *p*= 0.870
△ IED Total Errors			*r*= 0.252 *p*= 0.406	*r*= 0.060 *p*= 0.846	*r*= 0.194 *p*= 0.526	*r*= -0.310 *p*= 0.303	*r*= -0.631 *p*= 0.021*	*r*= -0.551 *p*= 0.051	*r*= -0.100 *p*= 0.746
△ Outside-fMRI Error$_{sw}$ (%)				*r*= -0.084 *p*= 0.785	*r*= 0.165 *p*= 0.590	*r*= -0.690 *p*= 0.009*	*r*= -0.046 *p*= 0.882	*r*= 0.014 *p*= 0.965	*r*= 0.140 *p*= 0.648
△ Inside- fMRI Error$_{sw}$ (%)					*r*= 0.519 *p*= 0.069	*r*= -0.156 *p*= 0.610	*r*= 0.062 *p*= 0.839	*r*= 0.199 *p*= 0.514	*r*= 0.059 *p*= 0.847
△ Inside- fMRI RT$_{sw}$ (ms)						*r*= -0.487 *p*= 0.091	*r*= 0.105 *p*= 0.733	*r*= -0.032 *p*= 0.917	*r*= 0.043 *p*= 0.890

△ Frequency of social interaction	*r*= -0.262 *p*= 0.387	*r*= 0.134 *p*= 0.662	*r*= -0.053 *p*= 0.863
△BOLD in L SFG		*r*= 0.389 *p*= 0.152	*r*= 0.224 *p*= 0.462
△ BOLD in R MFG			*r*= 0.361 *p*= 0.225

Partial correlation analyses were performed, controlling for age, gender, and education. △= post-intervention value – pre-intervention value.

Abbreviations: BOLD, blood oxygenation level dependent; Error, error rate; IED, Intra-Extra Dimensional Set Shift; L SFG, left superior frontal gyrus; R MFG, right middle frontal gyrus; L IFG$_t$, left inferior frontal gyrus pars triangularis; RT, reaction time; sw, Switch condition.

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Table S3.4 Inter-relationships among changes in task-switching performance, changes in physical function and social interaction, and changes in BOLD response magnitude in the prefrontal cortex during the Switch condition from pre-intervention to post-intervention in the CON group

	△ IED Completed Stages	△ IED Total Errors	△ Outside-fMRI Error$_{sw}$ (%)	△ Inside-fMRI Error$_{sw}$ (%)	△ Inside-fMRI RT$_{sw}$ (ms)	△ Frequency of social interaction	△ BOLD in L SFG	△ BOLD in R MFG	△ BOLD in L IFG$_{t}$
△ Knee extensor strength (kg)	*r*= -0.502 *p*= 0.204	*r*= -0.413 *p*= 0.309	*r*= -0.518 *p*= 0.188	*r*= 0.903 *p*= 0.002*	*r*= -0.112 *p*= 0.792	*r*= 0.100 *p*= 0.814	*r*= -0.184 *p*= 0.662	*r*= 0.058 *p*= 0.891	*r*= 0.329 *p*= 0.426
△ Four Square Step Test (sec)	*r*= 0.594 *p*= 0.121	*r*= 0.343 *p*= 0.406	*r*= 0.040 *p*= 0.926	*r*= -0.098 *p*= 0.818	*r*= 0.045 *p*= 0.916	*r*= -0.363 *p*= 0.377	*r*= -0.217 *p*= 0.606	*r*= 0.306 *p*= 0.461	*r*= -0.501 *p*= 0.206
△ Six Minute Walk Test (m)	*r*= -0.048 *p*= 0.911	*r*= 0.248 *p*= 0.553	*r*= -0.396 *p*= 0.332	*r*= 0.495 *p*= 0.213	*r*= -0.075 *p*= 0.860	*r*= 0.495 *p*= 0.213	*r*= 0.495 *p*= 0.212	*r*= 0.200 *p*= 0.634	*r*= 0.221 *p*= 0.599
△ IED Completed Stages		*r*= 0.782 *p*= 0.022*	*r*= 0.258 *p*= 0.538	*r*= -0.340 *p*= 0.409	*r*= 0.213 *p*= 0.613	*r*= 0.012 *p*= 0.977	*r*= 0.202 *p*= 0.632	*r*= 0.238 *p*= 0.570	*r*= -0.043 *p*= 0.920
△ IED Total Errors			*r*= 0.203 *p*= 0.629	*r*= -0.341 *p*= 0.409	*r*= 0.076 *p*= 0.857	*r*= -0.045 *p*= 0.916	*r*= 0.509 *p*= 0.198	*r*= 0.231 *p*= 0.581	*r*= 0.241 *p*= 0.565
△ Outside-fMRI Error$_{sw}$ (%)				*r*= -0.382 *p*= 0.350	*r*= 0.848 *p*= 0.008*	*r*= -0.423 *p*= 0.296	*r*= 0.052 *p*= 0.903	*r*= 0.138 *p*= 0.745	*r*= -0.019 *p*= 0.965
△ Inside- fMRI Error$_{sw}$ (%)					*r*= 0.119 *p*= 0.778	*r*= -0.017 *p*= 0.968	*r*= -0.292 *p*= 0.483	*r*= 0.150 *p*= 0.722	*r*= 0.076 *p*= 0.858
△ Inside- fMRI RT$_{sw}$ (ms)						*r*= -0.298 *p*= 0.473	*r*= -0.032 *p*= 0.940	*r*= 0.256 *p*= 0.540	*r*= -0.009 *p*= 0.983

△ Frequency of social interaction	*r*= 0.434 *p*= 0.282	*r*= -0.213 *p*= 0.612	*r*= 0.107 *p*= 0.801
△BOLD in L SFG		*r*= 0.496 *p*= 0.211	*r*= 0.694 *p*= 0.056
△ BOLD in R MFG			*r*= 0.564 *p*= 0.145

Partial correlation analyses were performed, controlling for age, gender, and education. △= post-intervention value – pre-intervention value.

Abbreviations: BOLD, blood oxygenation level dependent; Error, error rate; IED, Intra-Extra Dimensional Set Shift; L SFG, left superior frontal gyrus; R MFG, right middle frontal gyrus; L IFG_t, left inferior frontal gyrus pars triangularis; RT, reaction time; sw, Switch condition.

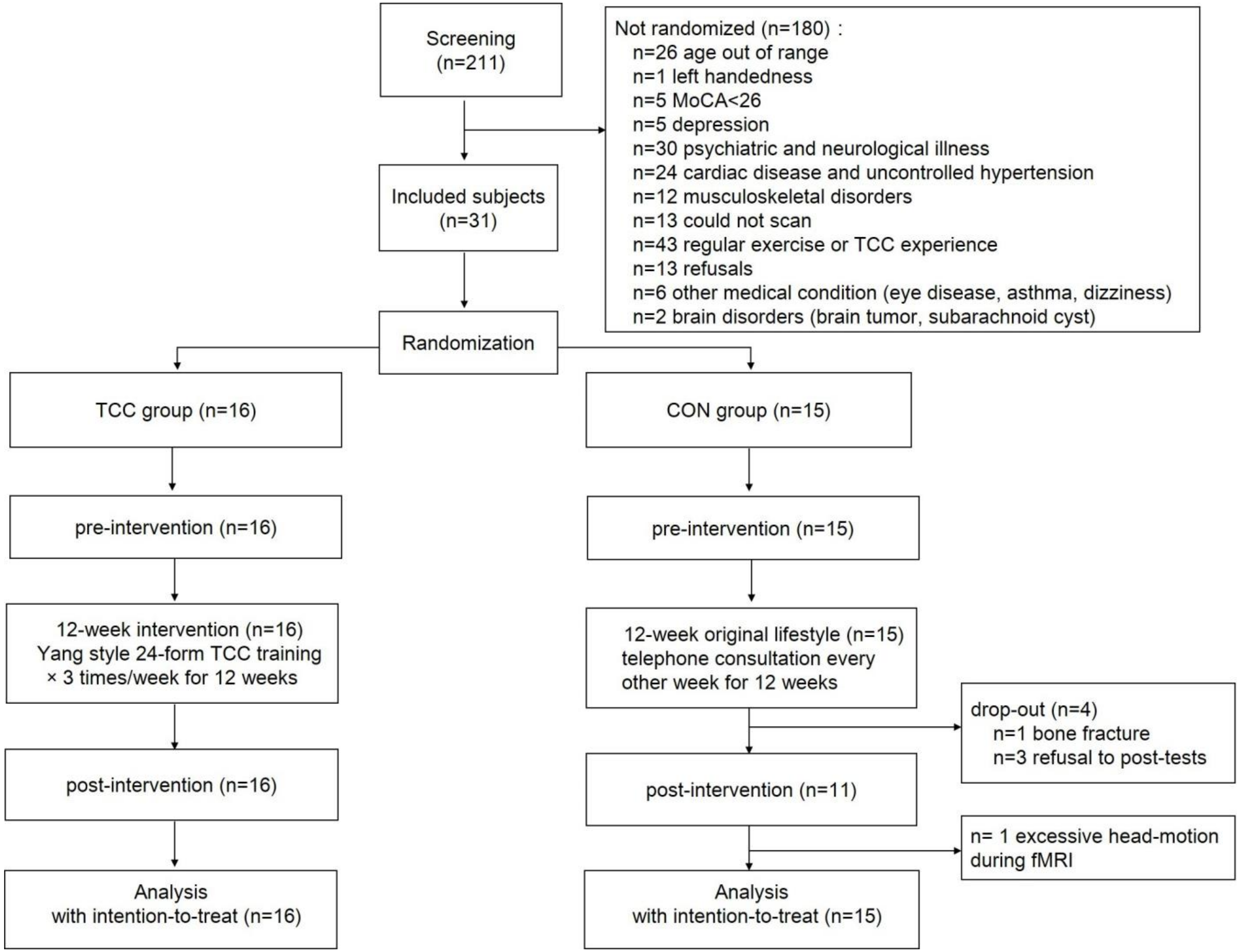

Figure 3.1 Consort chart of the randomized controlled trial

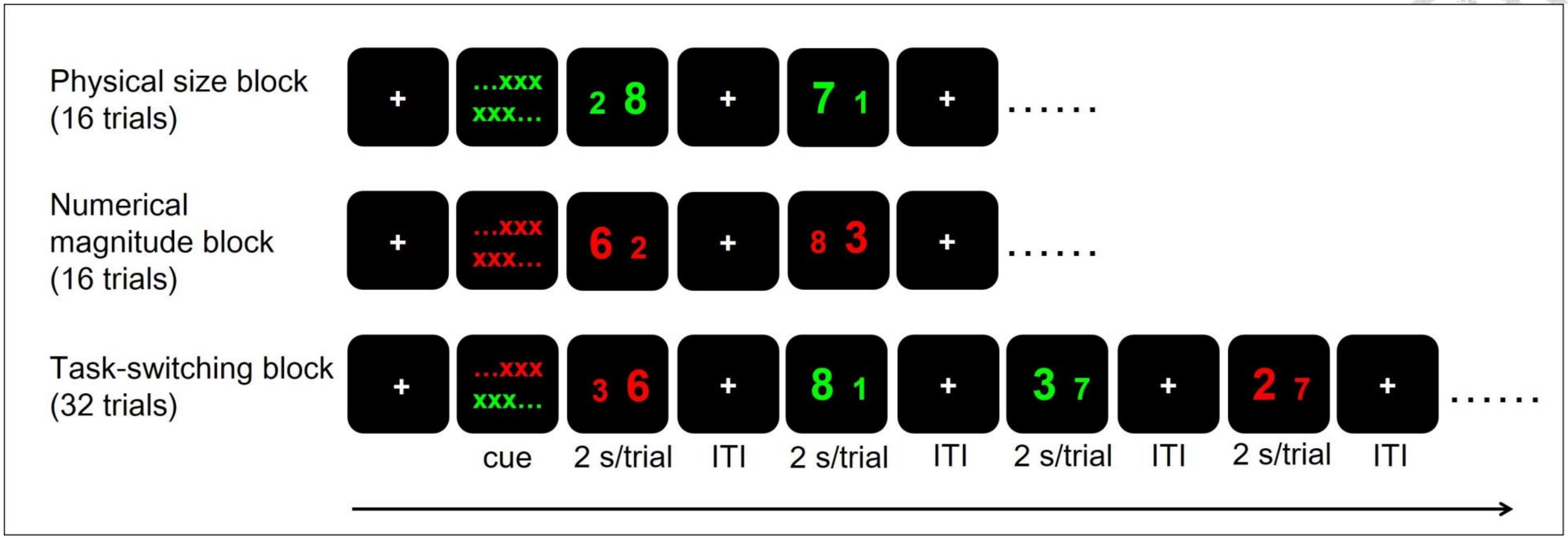

Figure 3.2 The hybrid block/event-related task-switching fMRI paradigm. Each trial lasted 2 seconds and the inter-trial interval (ITI) varied among 2, 4, and 6 seconds. Cue: color-cued instructions, with green indicating physical size rule and red indicating numerical magnitude rule.

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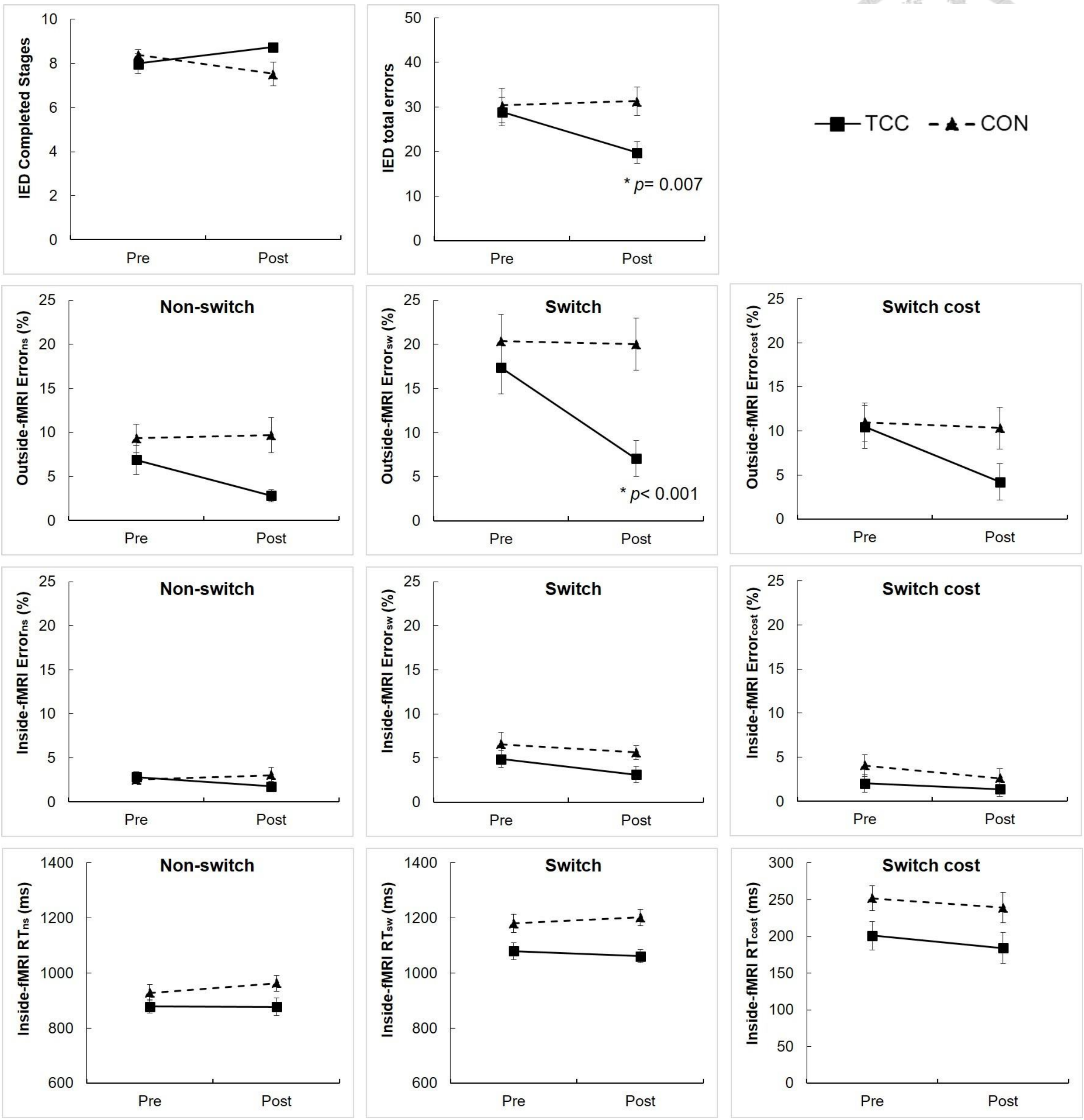

Figure 3.3 Intra-Extra Dimensional Set Shift (IED) performance and outside-fMRI and inside-fMRI Non-switch, Switch, and Switch cost performances of the TCC and CON groups at the pre- and post-intervention tests.

Values are means ± standard errors. There were no significant group differences at pre-intervention tests using independent t test. We set *p*= 0.05 for the IED variables, and adjusted *p*-value= 0.017 for testing group × time interaction, group, and time effects on outside-fMRI and inside-fMRI Non-switch, Switch, and Switch cost performances using RM ANCOVA. *significantly different from pre-intervention in post-hoc analysis. cost= value in Switch condition – value in Non-switch condition; Abbreviations: Error, error rate; ns, Non-switch condition; sw, Switch condition.

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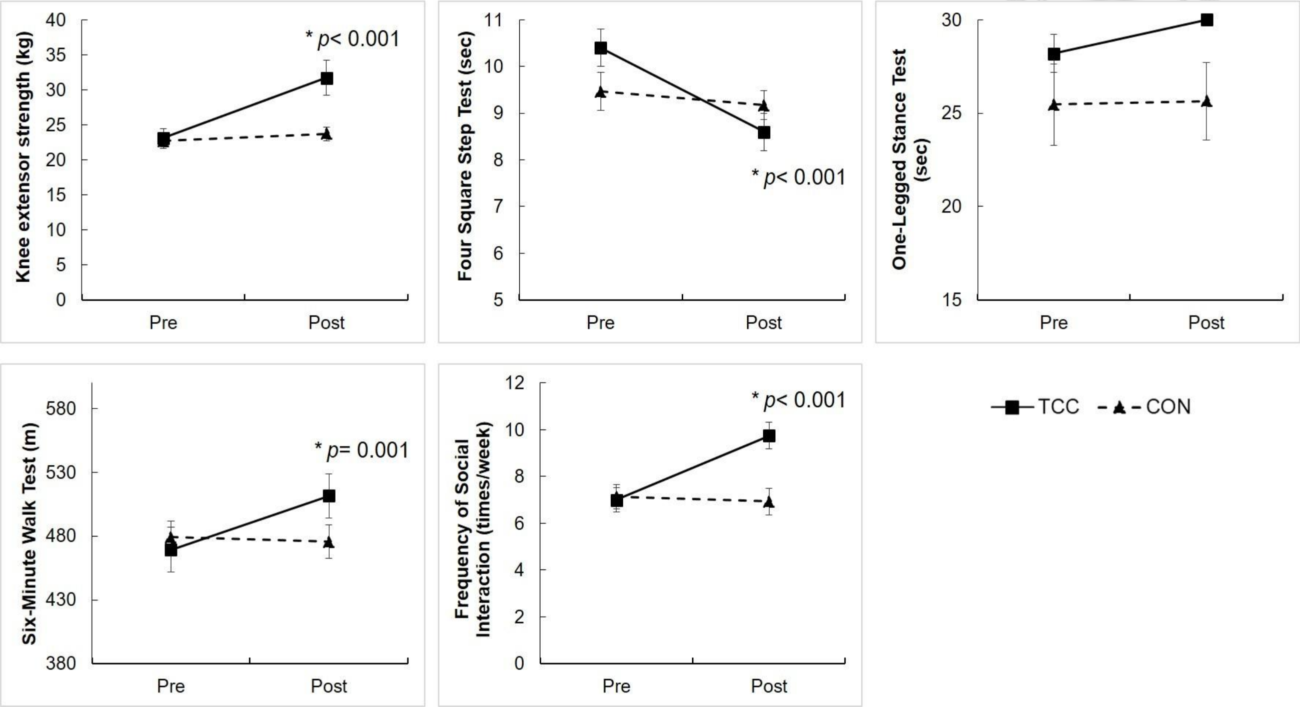

Figure 3.4 Physical function performance and frequency of social interaction of the TCC and CON groups at the pre- and post-intervention tests.

Values are means ± standard errors. We set adjusted *p*-value= 0.0125 for testing group × time interaction, group, and time effects on four physical variables (knee extensor strength, Four Square Step Test, One-Legged Stance Test, Six-Minute Walk Test), and set *p*-value= 0.05 for testing group × time interaction, group, and time effects on frequency of social interaction using RM ANCOVA. *significantly different from pre-intervention in post-hoc analysis. There were no significant group differences at pre-intervention tests, using independent t test.

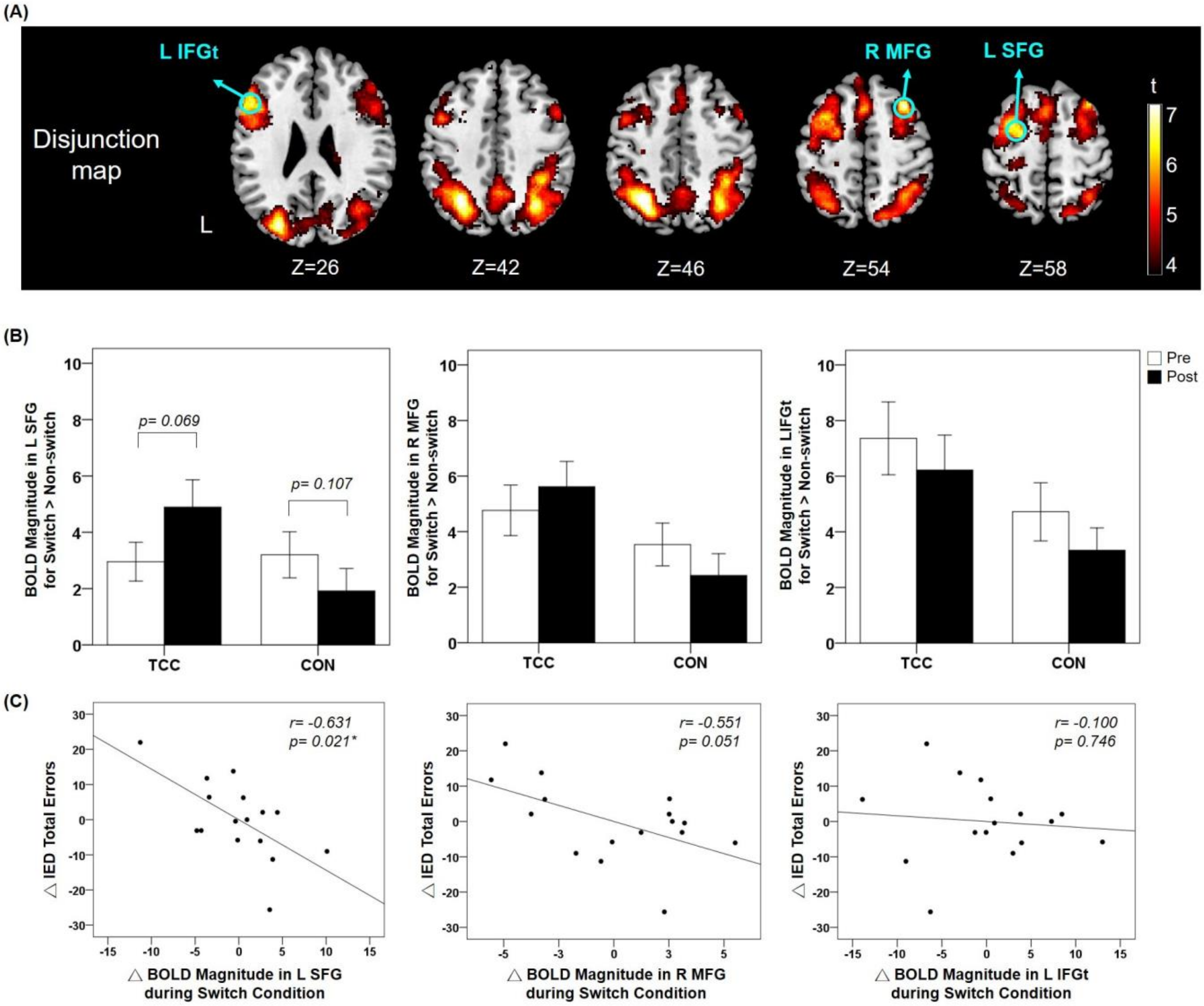

Figure 3.5 (A) Disjunction map of the Switch > Non-switch contrast across groups and time points (voxel-wise *p*< 0.005 with FWE correction). The locations of the functional ROIs in the prefrontal regions are indicated using green colored circles. (B) Mean and standard errors of BOLD response magnitude in these three functional ROIs for Switch > Non-switch contrast for the TCC and CON groups at the pre- and post-intervention scans. For the left SFG, the group × time interaction effect was significant (*p*= 0.017) with the TCC group showing a marginal increase (*p*= 0.069) in BOLD response magnitude in Switch > Non-Switch contrast after training in contrast to a non-significant change in the CON group. (C) Partial

correlation plots showing that the changes of BOLD response magnitude during the Switch condition in the left SFG and right MFG ROIs significantly ($p = 0.021$) and marginally ($p = 0.051$) correlated with the changes of the number of total errors of the IED test from pre- to post-intervention tests for the TCC group, respectively, after controlling for age, gender, and education.

△BOLD= post-intervention BOLD value – pre-intervention BOLD value; △IED total errors= post-intervention number of IED total errors – pre-intervention number of IED errors. Abbreviations: BOLD, blood oxygenation level dependent; IED, Intra-Extra Dimensional Set Shift; L SFG, left superior frontal gyrus; R MFG, right middle frontal gyrus; L IFG$_t$, left inferior frontal gyrus pars triangularis. *Significant correlation between △IED total errors and △BOLD, $p < 0.05$.

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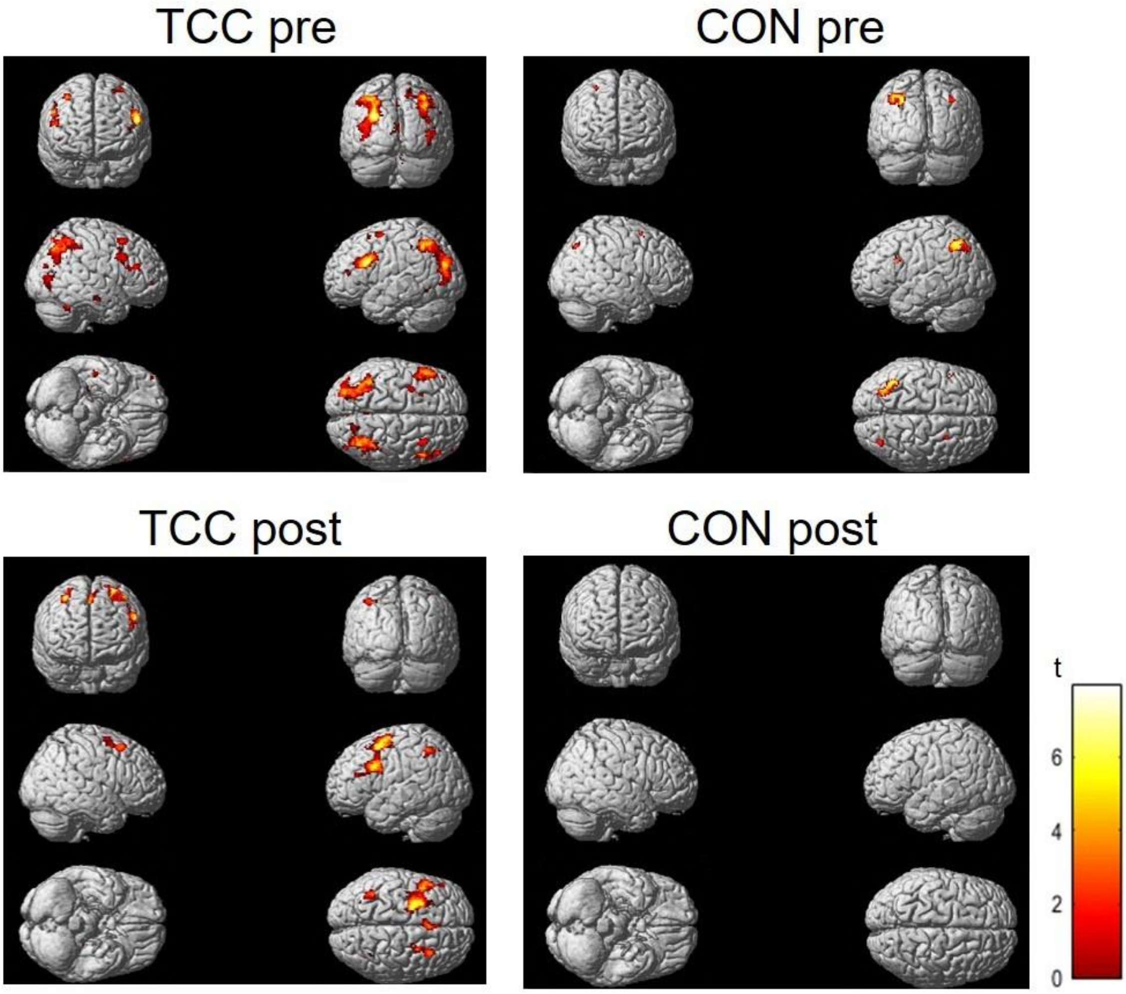

Figure S3.1 Brain activation of Switch > Non-switch contrast at pre- and post-intervention in the TCC and CON groups. Whole-brain analysis with threshold set at p< 0.005 (FWE corrected), k≥ 10 voxels.

Abbreviations: TCC, Tai Chi Chuan group; CON, control group; pre, pre-intervention; post, post-intervention.

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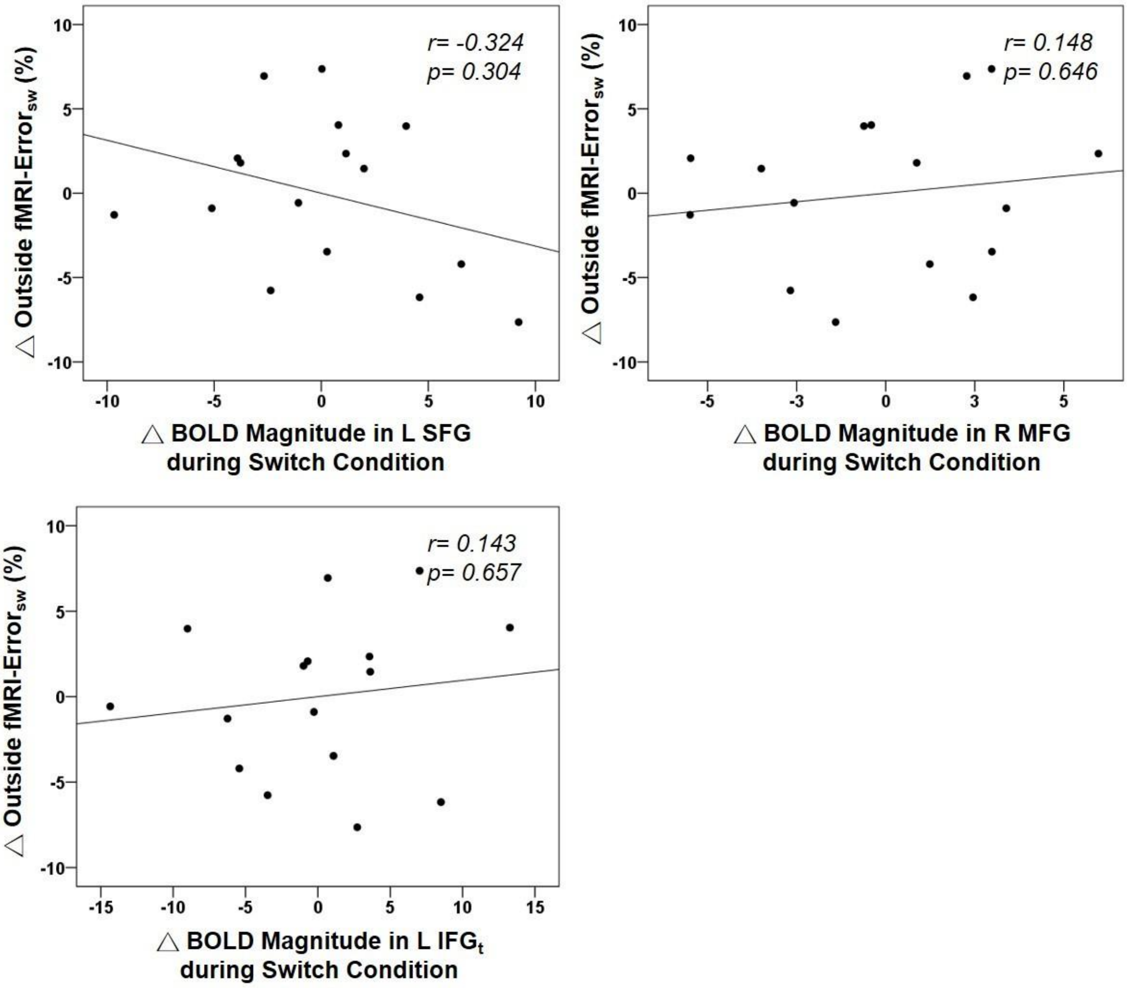

Figure S3.2 Partial correlation plots showing that no significant relationships between the changes of the outside fMRI error during the switch condition with Switch BOLD response in the three prefrontal ROIs, controlling for age, gender, education, and social interaction.

△BOLD= post-intervention BOLD value – pre-intervention BOLD value; △Outside fMRI-Errorsw= post-intervention outside fMRI error rate – pre-intervention outside fMRI error rate. Abbreviations: BOLD, blood oxygenation level dependent; sw, switch condition; L SFG, left superior frontal gyrus; R MFG, right middle frontal gyrus; L IFG$_t$, left inferior frontal gyrus pars triangularis.

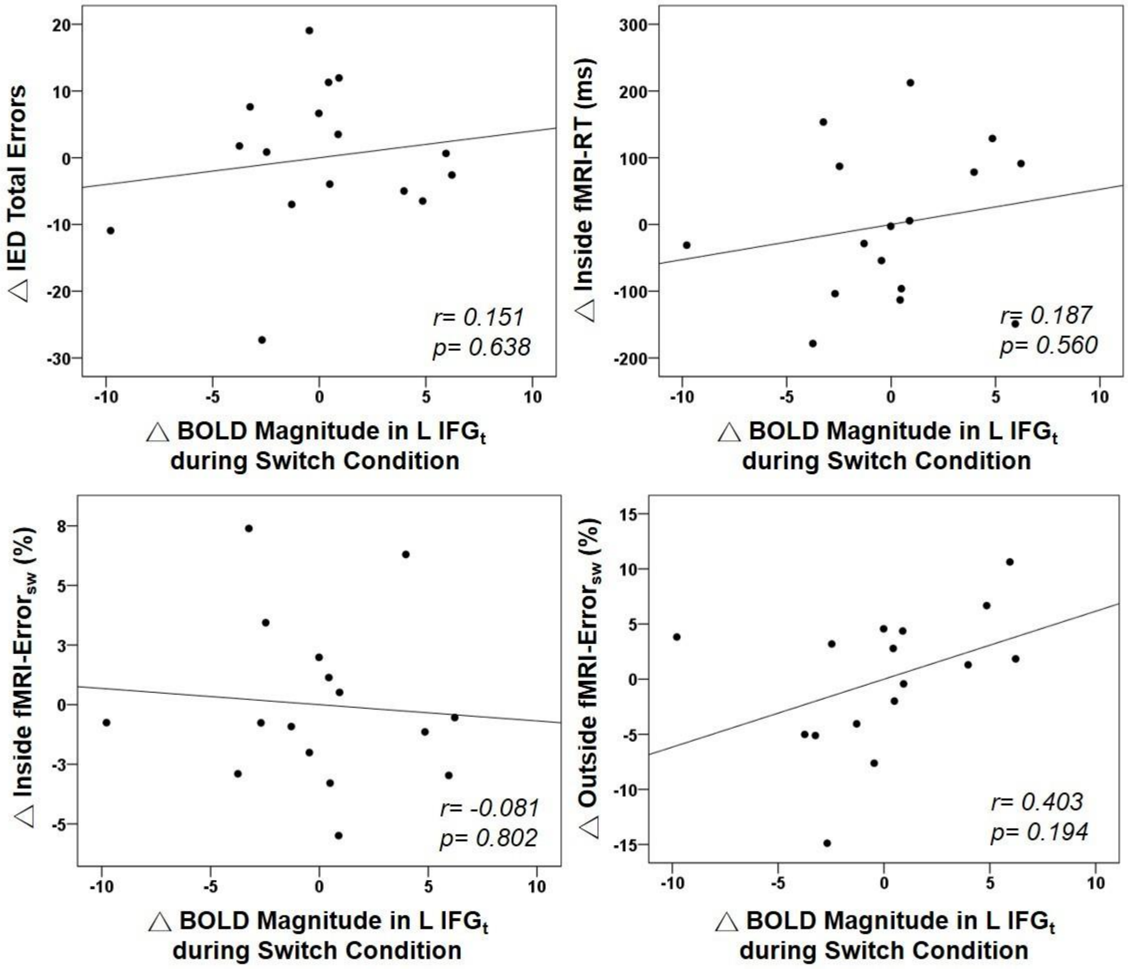

Figure S3.3 Partial correlation plots showing that no significant relationships between the changes of BOLD response magnitude during the Switch condition in the L IFGt ROIs with the changes of the number of total errors of the IED test, the changes of inside fMRI-RT, the changes of inside fMRI error rate, and the changes in outside fMRI-error during the Switch condition from pre- to post-intervention tests for the TCC group, controlling for age, gender, education, and knee extensor strength.

△= post-intervention value – pre-intervention value. Abbreviations: IED, Intra-Extra Dimensional Set Shift; RT, reaction time; Error, error rate; sw, switch condition; BOLD, blood oxygenation level dependent; L IFG$_t$, left inferior frontal gyrus pars triangularis.

CHAPTER 4

Integrity of Fiber Tracts in the Prefronto-striatal-thalamo-prefrontal Loop Predicts Task-switching Improvement after Tai Chi Chuan Training in Middle-aged and Older Adults

前額葉-紋狀體-視丘-前額葉迴路之神經纖維束完整性能預測中老年人接受太極拳運動訓練後之轉換任務效益

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中文摘要

背景：太極拳運動訓練已知有益於改善轉換任務能力。本隨機對照試驗探討太極拳運動訓練是否能促進轉換任務相關之特定白質神經纖維束完整性、及此特定的白質神經纖維束完整性之基準值是否能預測太極拳運動訓練後之轉換任務表現之進步量。**方法：**三十八位中老年人被隨機分派至太極拳組($n = 19$)及控制組($n = 19$)。本研究比較兩組於介入前、後之轉換任務功能、身體功能、及以擴散頻譜磁振造影(diffusion spectrum MR images)評估之白質神經纖維束完整性。此白質神經纖維束完整性以普擴散不等向性分數(generalized fractional anisotropy, GFA)表示，並以相關性分析，探討特定白質神經纖維束完整性之基準值與訓練後轉換任務表現之進步量之關係。**結果：**唯有太極拳組在訓練介入後，能有效增進轉換任務功能及身體功能($p < 0.025$)，控制組未有此效益。在太極拳運動訓練參與者之中，其基準期之全腦神經纖維束($r = -0.747$, $p = 0.001$)、前額葉-紋狀體-視丘-前額葉迴路神經纖維束(prefronto-striatal-thalamo-prefrontal loop fiber group; $r = -0.800$, $p < 0.001$)及前額葉-頂葉/枕葉神經纖維束(prefronto-parietal/occipital fiber group; $r = -0.782$, $p < 0.001$)之完整性(GFA 值)愈高者，在太極拳運動訓練後，其轉換任務錯誤數減少愈多。多元迴歸分析結果發現，前額葉-紋狀體-視丘-前額葉迴路之白質神經纖維束完整性基準值，為最主要可預測訓練後轉換任務錯誤數減少之因子($\beta = -0.875$, $p < 0.001$)。**結論：**本研究是首篇論文顯示，前額葉-基底核迴路之白質神經纖維束完整性基準值，強力影響太極拳運動訓練促進轉換任務之效益，也突顯老年族群維持白質神經纖維束完整性之重要，以期能最佳化訓練之認知效果。

關鍵詞：執行功能、身心運動介入、擴散頻譜磁振造影、白質、隨機對照試驗

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English Abstract

Background: Tai Chi Chuan (TCC) training is known to improve task-switching ability. This randomized controlled trial tested whether TCC training improves the integrity of task-switching specific brain white matter (WM) tracts and whether the baseline integrity of these WM tracts predicts task-switching improvement after TCC training. **Methods:** Thirty-eight middle-aged and older adults were randomly assigned into a TCC group ($n = 19$) and a control group ($n = 19$). Task-switching and physical performances, and brain diffusion spectrum MR images, were collected and compared before and after training. Relationships between baseline integrity, indexed as general fractional anisotropy (GFA), of specific WM tract groups and task-switching improvement after training were also analyzed. **Results:** After training, the TCC group, but not the control group, showed significant task-switching and physical improvements ($p < 0.025$). Among the TCC participants, those who had better baseline GFAs of WM tracts of the whole brain ($r = -0.747$, $p = 0.001$), prefronto-striatal-thalamo-prefrontal loop ($r = -0.800$, $p < 0.001$), and prefronto-parietal/occipital ($r = -0.782$, $p < 0.001$) fiber group showed greater reductions of task-switching errors after training. Multiple regression analysis revealed that baseline GFA of the tracts in the prefronto-striatal-thalamo-prefrontal loop was the primary independent predictor of reductions of task-switching errors after training ($\beta = -0.875$, $p < 0.001$). **Conclusions:** This is the first study to illustrate that the baseline integrity of prefrontal-basal ganglia circuits strongly influences TCC training benefits on task-switching, highlighting the importance of preserving WM integrity in the aging population to optimize the training effects on cognition.

Key words: Executive function, Mind-body exercise intervention, Diffusion spectrum imaging, White matter, Randomized controlled trial

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4.1 Introduction

Age-related declines in task-switching performance

Task-switching is a critical ability that allows a person to shift between cognitive tasks or mental sets (Monsell, 2003). Task-switching experimental paradigms typically consist of non-switch blocks, in which one simple task rule (e.g., AAAAAA) is implemented repeatedly across trials, and a switch block, in which two simple task rules (e.g., BABBAB) are randomly implemented (Kray and Lindenberger, 2000; Monsell et al., 2003; Reimers and Maylor, 2005). Aging studies have revealed that older adults show declines in task-switching abilities as manifested by a longer reaction time (RT) or a greater error rate in the switch blocks, or a greater switch cost (i.e., greater reduction of performance from non-switch to switch blocks), compared to young adults (Gold et al., 2010; Kray and Lindenberger, 2000; Reimers and Maylor, 2005).

Relationships between integrity of specific white matter tracts and task-switching performance in middle-aged and older adults

Diffusion tensor imaging (DTI) studies have shown that task-switching performance in middle-aged and older adults is associated with the integrity of their white matter (WM) tracts in the frontoparietal regions (Gold et al., 2010; Jolly et al., 2017; Madden et al., 2009). The DTI technology allows for *in vivo* measurement of water molecule diffusion in the WM to reflect WM microstructure properties such as fiber orientation and density, axonal diameter, degree of myelination, and membrane integrity. The four DTI parameters commonly used to represent WM integrity are mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA) (Beaulieu, 2014). The MD represents the overall water diffusion, but it lacks information about diffusion directionality. The AD and RD indicate the diffusivity

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of water molecules parallel and orthogonal to the fiber tract direction, respectively. Reduced AD and increased RD values are associated with axonal injury and myelin degeneration, respectively (Beaulieu, 2014; Concha et al., 2006; Song et al., 2003). The FA value, derived from the combination of the AD and RD values, indicates the degree of water diffusion anisotropy in the WM and ranges from zero (meaning fully isotropic) to one (meaning fully anisotropic). Hence, a higher FA value represents better WM integrity and could be due to higher AD, smaller RD, or both (Beaulieu, 2014; Johansen-Berg and Rushworth, 2009; Le Bihan, 2003). Previous DTI studies have shown that older adults with greater FA values of the left superior longitudinal fasciculus (SLF) and splenium-parietal callosal fibers (CFs), and of the genu-center region of the corpus callosum, present better task-switching performance, regardless of whether age is controlled as a confounding factor or not (Gold et al., 2010; Madden et al., 2009). Moreover, Jolly et al. (2017) also found that middle-aged and older adults who had lower RD values of the left SLF, inferior longitudinal fasciculus (ILF), or inferior fronto-occipital fasciculus (IFOF) performed better in task-switching after age was taken into consideration. These findings suggested that association fibers connecting the prefrontal and parietal regions and commissural fibers connecting bi-hemispheric prefrontal and parietal regions may be relevant to task-switching processing for the aging population.

In addition, the prefronto-striatal-thalamo-prefrontal loop is also implicated in task-switching performance. This loop originates in the dorsolateral prefrontal cortex (DLPFC) and projects to the caudate nucleus, then to the internal segment of the globus pallidus and the rostral substantia nigra pars reticulata, and finally to the ventral anterior and mediodorsal nuclei of the thalamus before returning to the DLPFC (Wichmann and Delong, 2006; Wichmann and Delong, 2013). DTI research has shown that better

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integrity of the WM tracts connecting the prefrontal and striatum regions are associated with better task-switching performance in various populations, including youths with and without attention deficit hyperactivity disorder (Chiang et al., 2016; Shang et al., 2013;), patients with traumatic injury (Leunissen et al., 2014), and older adults (Serbruyns et al., 2016; Ystad et al., 2011). In particular, using magnetization transfer imaging, Serbruyns et al. (2016) found that compared to young adults, older adults had decreased magnetization transfer ratios (MTR) of the superior corona radiata fibers projecting from the prefrontal regions to the internal capsule surrounding the striatum (Jellison et al., 2004; Mori et al., 2008; Wakana et al., 2004), and this decreased MTR, indicating poorer myelin integrity, significantly contributed to age-related increases in task-switching cost in RT by 27% in variance. Using a combination of DTI and resting-state functional magnetic resonance imaging (fMRI), Ystad et al. (2011) found that older adults with lower FA values of prefrontal-striatal fibers connecting the dorsal attention network and the putamen showed poorer executive function, primarily measured with the Stroop tests. Further support of the prefronto-striatal involvement in task-switching can be found in research that shows that patients with Parkinson’s disease, known to have deficits in the dopaminergic fronto-striatal pathways, present task-switching deficits (Cools et al., 2001) and that medication that ehnances the dopaminergic function of these patients reduces task-switching deficits (Aarts et al., 2014).

Together, current literature suggests that brain association fibers connecting the prefrontal and parietal/occipital regions, commissural fibers connecting bi-hemispheric prefrontal and parietal/occipital regions, and projection fibers of the prefrontal-basal ganglia loop are all relevant to task-switching processing.

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Effects of Tai Chi Chuan (TCC) Training on task-switching related brain functions

Much evidence has provided strong support that Tai Chi Chuan (TCC) exercise has beneficial effects on task-switching ability for older adults (Mortimer et al., 2012; Nguyen and Kruse, 2012; Wayne et al., 2014; Wu et al., 2018). In a resting-state fMRI study, Tao et al. (2017) found that after a 12-week TCC exercise program, older adults exhibited increases in the fractional amplitude of low frequency fluctuations in the DLPFC during rest and showed memory improvements. Also using 12 weeks of TCC training, Wu et al. (2018) found that older adults who presented greater prefrontal activation increases during task-switching after training also showed greater task-switching improvements. However, little is known regarding whether TCC training would change task-switching associated WM tracts.

Studies involving motor or cognitive training intervention have shown positive training effects on WM integrity in both young and older adults (Engvig et al., 2012; Hofstetter et al., 2013; Scholz et al., 2009; Svatkova et al., 2015). Specifically, motor training intervention alters specific WM integrity in the frontal, parietal, and temporal regions (Scholz et al., 2009; Svatkova et al., 2015; Voss et al., 2013). In young adults, a 6-week intensive juggling training intervention increased WM integrity of the intraparietal sulcus (Scholz et al., 2009), and a 6-month training intervention combining aerobic and resistance exercises increased WM integrity in the frontoparietal regions, including the SLF, ILF, IFOF, anterior thalamic radiation (ATR), and the body and splenium of the corpus callosum (Svatkova et al., 2015). In older adults, not all participants could significantly increase WM integrity after one year of aerobic training, but it was found that those who showed greater increases in WM integrity of the prefrontal and temporal regions gained better aerobic fitness improvements after

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training (Voss et al., 2013). Moreover, one cognitive training study also showed that baseline WM tract integrity of ATR, CF, and IFOF was predictive of cognitive improvements after training for older adults (de Lange et al., 2016). Therefore, in this study, it was of interest to know whether TCC training could alter WM integrity and whether baseline WM integrity could be predictive of task-switching improvement after TCC training in older adults.

Aims and hypotheses

In this study, we aimed to study whether a 12-week TCC exercise training intervention could induce changes in the integrity of the whole brain and three specific fiber groups of WM tracts that are implicated in processing task-switching—the prefronto-parietal/occipital fiber group, the CF group connecting bi-hemispheric prefrontal and parietal cortices, and the prefronto-striatal-thalamo-prefrontal loop fiber group. We also investigated whether the baseline integrity of the whole brain WM tracts and these three fiber groups was predictive of task-switching improvement after TCC training in middle-aged and older adults. We used diffusion spectrum imaging (DSI) to study tract integrity because DSI could better resolve tracking difficulties of crossing fibers compared to DTI (Wedeen et al., 2008). We hypothesized that in the middle-aged and older adults, WM integrity of the whole brain and the three fiber groups would not significantly increase after the short-term TCC training; however, those who had higher WM integrity at baseline would show better task-switching improvements after TCC intervention.

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4.2 Methods

Data in the present study were extracted from a registered assessor-blind and stratified randomized controlled trial (RCT) (ClinicalTrials.gov ID: NCT02270320) which enrolled 65 participants who met the inclusion criteria of aged between 50 and 85 years old, years of education ≥ 6 years, Mandarin as the native language, right-handedness (Oldfield, 1971) and right-footedness (Elias et al., 1998). Participants were excluded if they scored < 26 on the Montreal Cognitive Assessment Taiwan version (MoCA) (Tsai et al., 2012), scored > 0 on Clinical Dementia Rating (Hughes et al., 1982), scored > 8 on the Geriatric Depression Scale 15-item short-form (GDS-15) (Nyunt et al., 2009), had any disability in Instrumental Activities of Daily Living (Lawton and Brody, 1969), had any neurological or psychiatric diseases, had severe cardiovascular diseases or musculoskeletal disorders, had any contraindications to MRI, were engaged in moderate-intensity exercises regularly (> 30 mins/session × 3 sessions/week) in the 6 months prior to enrollment, and had any TCC exercise experiences. We also used the Physical Activity Scale for the Elderly (PASE) (Washburn et al., 1993) to quantify participants' physical activity levels at baseline and weekly during the intervention period. All participants provided signed informed consent approved by the Research Ethics Committee of the National Taiwan University Hospital (No. 20121216RIND) and were stratified by age and then randomly assigned to the TCC or control (CON) group.

To reduce potential confounding effects from age heterogeneity on outcomes of interest, we adopted an approach similar to that used in a previous fMRI publication based on the same RCT dataset (Wu et al., 2018) and used data from 38 participants only, aged between 55 and 69 years old, in the present study. There were 19 in the TCC

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group and 19 in the CON group (Figure 4.1). All participants underwent a 12-week intervention period, as well as behavioral tests of cognitive task-switching ability and physical functions, plus DSI scans, at baseline and post-intervention. At the end of the 12-week intervention, all TCC participants remained enrolled, but four CON participants dropped out the study because of fracture (n = 1) and refusal to complete post-tests (n = 3). All behavioral and imaging data were analyzed using the intention-to-treat analyses in this study.

TCC exercise intervention and CON intervention

The TCC participants undertook a 12-week TCC exercise program consisting of three one-hour sessions of weekly training for a total of 36 sessions, conducted in a group format. The TCC program, taught by a certified and experienced TCC coach, was the 24-form Yang style TCC (Liang and Wu, 1996). Details of the TCC program protocol were previously described in Wu et al. (2018). The CON participants did not change their lifestyles and received one telephone consultation every other week during the corresponding 12 weeks.

Task-switching and physical function tests

The Intra/Extra-dimensional set shift (IED) test of the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd., Bottisham, Cambridge, UK) was used to test participants’ task-switching ability. The IED test is a validated computerized analog of the Wisconsin Card Sorting test (Kim et al., 2014) and has been widely used (Chamberlain et al., 2011; Chiang et al., 2016; Gau and Shang, 2010; Stefanova et al., 2014). Briefly, there are 9 stages of trials of increasing complexity in the IED test. Participants have to maintain attention on the same untold relevant stimulus dimension (“shape” or “line”) of visual patterns shown on the screen across trials in the intra-dimensional set-shift stages, and to shift attention to previously irrelevant stimulus dimensions of visual patterns across trials in the extra-dimensional set-shift stage (Luciana and Nelson, 1998). The transition from intra-dimensional to extra-dimensional set-shifting stages is not made known to the participants. More details about the IED test can be found in Wu et al. (2018). We chose to use the number of total errors ($\mathrm{IED_{errors}}$) of all answered trials to indicate participant’s task-switching ability, with a smaller $\mathrm{IED_{errors}}$ indicating better task-switching ability.

Regarding physical functions, we tested participants’ muscle strength of bilateral knee extensors using a handheld dynamometer (Lafayette Instrument Co., Lafayette, Indiana, USA) (Wang et al., 2002) and balance ability with the eyes-open one-legged stance test (OLST) (Bohannon et al., 1984). Their mobility and agility were tested with the Four Square Step Test (FSST) (Dite and Temple, 2002), and cardiorespiratory endurance was tested with the Six-Minute Walk Test (6MWT) (Brooks et al., 2003).

Imaging data acquisition

Image data were collected on a 3-Tesla Trio MRI scanner with a 32-channel phased-array head coil (Siemens Healthcare, Erlangen, Germany) at the National Taiwan University Hospital. Two types of brain structural images were acquired for each participant: T1-weighted images and DSI. The T1-weighted images, mainly for subsequent registration of DSI in standard stereotactic space, were acquired using a 3D Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence with repetition time (TR)/echo time (TE) = 2000 ms/2.98 ms, flip angle = 9°, field of view (FOV) = $192 \times 256\ \mathrm{mm}^2$, coronal slice number = 208, and voxel size = $1 \times 1 \times 1\ \mathrm{mm}^3$. The DSI was acquired using a single-shot spin-echo echo planar imaging sequence with a twice-refocused balanced echo (Reese et al., 2003), with TR/TE = 9600/130 ms, flip angle = 90°, FOV = 200 × 200 mm^2, matrix size = 80 × 80, slice number = 56, and slice thickness = 2.5 mm. The acquisition scheme of DSI consisted of 102 diffusion-weighted image volumes (101 diffusion gradient vectors + 1 null image), corresponding to the grid points in a half sphere of the q-space with the maximum diffusion b-values (bmax) equal to 4000 sec/mm^2 (Kuo et al., 2008). The total time for MPRAGE and DSI acquisition was approximately 20 minutes.

DSI reconstruction

Before reconstructing the DSI, we first assessed the image quality of the entire dataset by using a quality assurance pipeline (Chen et al., 2015), which included the procedures of estimating the signal-to-noise ratio and motion-induced signal dropout in diffusion-weighted images, and the degree of alignment between T1-weighted images and spatial maps of DSI-derived diffusion indices. All images in the present study passed the criteria of quality assurance. The qualified DSI data were transformed to obtain the probability density function (PDF) based on the Fourier relationship between the PDF and q-space signal (Callaghan et al., 1991). Within each voxel, there were 102 samples at the grid points within a half sphere of the q-space. These 102 samples were first projected around the origin to fill the other half sphere based on the fact that the q-space data were symmetric around the origin. The eight corners outside of the sphere were filled with zeros, resulting in a 7 × 7 × 7 data grid in the q-space. A Hanning filter of 17 units in width was applied to the q-space data, followed by a 3D Fourier transform of the q-space signal to obtain the PDF. The orientation distribution function (ODF, $\psi(u)$) was computed by obtaining the second moment of the PDF along each of the 362 radial directions (6-fold tessellated icosahedron). At each voxel, generalized fractional

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anisotropy (GFA) was quantified in terms of SD(ψ)/RMS(ψ), where SD was the standard deviation and RMS was the root mean square. The value of GFA indicates the directionality of the ODF and ranges from zero (when the diffusion is completely isotropic) to one (when the diffusion is restricted to only one direction) (Tuch, 2004) and has served as the index of white matter integrity in previous DSI studies (Fritzsche et al., 2010; Gorczewski et al., 2009).

Tract-specific sampling of GFA values

The tract-based automatic analysis (TBAA) was used to reconstruct 76 WM tracts of the whole brain in each participant, including 32 projection tracts, 26 association tracts, and 18 commissural tracts (Chen et al., 2015). The procedures of TBAA were described in detail previously (Chen et al., 2015). In brief, the T1-weighted images and DSI datasets from the study subjects served as the input of TBAA. These data were registered to form a study-specific template (SST), and the SST was further registered to a standard DSI template NTU-DSI-122 (Chen et al., 2015; Hsu et al., 2015). The registration was achieved through a two-step process, which included anatomical information provided by the T1-weighted images (Ashburner and Friston, 2011) and microstructural information provided by DSI datasets (Hsu et al., 2012). Once the registration was completed, the transformation between NTU-DSI-122 and individual DSI was established. The coordinates of WM tracts built in the DSI template were transformed from the template to individual DSI datasets, and GFA values were sampled along the coordinates of each WM tract automatically.

Afterwards, we analyzed the integrity of whole brain tracts and four groups of WM tracts reconstructed with the TBAA procedure (Figure 4.2 and Table 4.1). The first group was the prefronto-parietal/occipital (association) fiber group, which consisted of

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eight prefronto-parietal/occipital tracts—the bilateral SLF I, SLF II, SLF III, and IFOF tracts (Chen et al., 2015). The SLF I connects the superior frontal gyrus with the precuneus, the SLF II connects the pars triangularis of the inferior frontal gyrus with the middle occipital gyrus, and the SLF III connects the pars opercularis of the inferior frontal gyrus with the angular gyrus. The IFOF connects the orbitofrontal gyrus with the occipital lobe. The second group was the CF (commissural) group, which included five callosal CFs—namely, those connecting the bi-hemispheric orbitofrontal gyri (CF_{OFG}), dorsolateral prefrontal cortices (CF_{DLPFC}), ventrolateral prefrontal cortices (CF_{VLPFC}), superior parietal lobules (CF_{SPL}), and inferior parietal lobules (CF_{IPL}). The third group was the prefronto-striatal-thalamo-prefrontal loop (projection) fiber group, which included four prefronto-striatal tracts, i.e., the bilateral DLPFC-striatum (FS_{DLPFC}) and VLPFC-striatum (FS_{VLPFC}) tracts, and four thalamo-prefrontal tracts, i.e., the bilateral thalamus-DLPFC (TR_{DLPFC}) and thalamus-VLPFC (TR_{VLPFC}) tracts. In addition, we also analyzed the integrity of the thalamic radiation auditory fiber group ($\text{TR}_{\text{auditory}}$), consisting of fibers connecting the Heschl’s gyri with the thalamus in bilateral hemispheres. We chose this fourth WM fiber group to serve as the reference group because this group was expected to be irrelevant to performing the IED test, in which visual stimuli were used. We hypothesized that unlike the above-mentioned three task-switching relevant fiber groups, the baseline integrity of this reference fiber group would not influence training effects on task-switching ability tested with the IED. Such differential relationships with training effects between task-switching relevant and irrelevant fiber groups would be important to validate the specificity of the neural correlate of the IED test.

For the integrity of whole brain WM tract, we calculated the average GFA value across GFA values of the 76 TBAA-reconstructed WM tracts. For each of the four group fiber tracts, we calculated the average GFA value across all the WM tracts in each group to indicate the overall WM integrity of the group. Hence, to represent the overall WM integrity of whole brain tracts and four fiber groups, we derived five average GFA values: the prefronto-parietal/occipital, callosal, prefronto-striatal-thalamo-prefrontal, and auditory fiber groups, respectively, for both pre- and post-intervention DSI data of each group of participants.

Statistical analyses

First, the baseline group difference in gender distribution was analyzed by chi-square analysis, and differences in age, education, body mass index, general cognitive function (MoCA), depression status (GDS-15), physical activity level (PASE), task-switching ability ($\mathrm{IED}_{\mathrm{errors}}$), physical function tests, and five GFA values were analyzed using independent t test, all with the significance level set at $p < 0.05$. Then we applied the mixed-model repeated measures analysis of covariance (RM ANCOVA) to investigate group, time, and group × time effects on task-switching and physical performances and GFA values, with group as the between-subject factor and time as the within-subject factor. For the RM ANCOVA on task-switching performance, age, education, and gender served as the covariates because these variables are all known to influence task-switching ability (Perry et al., 2017; Reimers and Maylor, 2005). For the RM ANCOVA on physical performances, age and gender served as the covariates because these two factors affect physical functions (Bongard et al., 2007; Sugimoto et al., 2014). The significance level of the RM ANCOVA test on task-switching performance was set at $p < 0.05$. However, because of the multiple comparisons and significant correlations among three of the four physical function measures (Table 4.2), and among the five GFA values (Table 4.3), after controlling for age and gender, we

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adjusted the significance levels to $p < 0.0125$ (= 0.05/4), and $p < 0.01$ (= 0.05/5) for the RM ANCOVA tests on physical performances and GFA values, respectively. Bonferroni corrections were performed in *post hoc* analyses.

The relationships of the whole brain tracts, prefronto-parietal/occipital, callosal, prefronto-striatal-thalamo-prefrontal loop, and auditory fiber groups with the changes (= post – pre) of task-switching performance after the 12-week intervention were analyzed by using five separate partial correlation analyses, controlling for age, education, and gender for the TCC group. Because of the multiple comparisons, the significance level was set at $p < 0.01$ (= 0.05/5) for these partial correlation analyses. Next, to identify the most important baseline tract integrity that could best predict task-switching improvement after TCC training, we further conducted a multiple linear regression analysis using the stepwise method and included the integrity of fiber groups that showed significance in the partial correlation analyses as the potential predictors, controlling for age, education, and gender. The significance level was set at $p < 0.05$ for regression analyses. All statistical analyses were performed using SPSS Statistics for Windows, version 18.0 (SPSS Inc., Chicago, Ill., USA).

4.3 Results

Behavioral improvements and changes in WM integrity

There were no baseline group differences in age, gender, education, body mass index, MoCA, GDS-15, PASE, $\text{IED}_{\text{errors}}$, knee extensor strength, OLST, or 6MWT (all $p > 0.05$) (Tables 4.4 and 4.5). The only baseline difference was observed for the FSST, with the TCC group showing poorer FSST performance than the CON group ($p = 0.018$). Therefore, we also controlled for the baseline FSST performance for subsequent RM ANCOVA on this variable.

There were significant group × time interaction effects for $\text{IED}_{\text{errors}}$ ($F(1, 33) = 7.36$, $p = 0.010$), knee extensor strength ($F(1, 34) = 14.37$, $p = 0.001$), FSST ($F(1, 33) = 16.25$, $p < 0.001$), and 6MWT performances ($F(1, 34) = 11.65$, $p = 0.002$) (Table 4.5). The *post hoc* analyses revealed that the TCC group significantly reduced the $\text{IED}_{\text{errors}}$ ($t(18) = 2.60$, $p = 0.018$), increased knee extensor strength ($t(18) = -5.79$, $p < 0.001$), and improved FSST ($t(18) = 7.25$, $p < 0.001$) and 6MWT ($t(18) = -4.26$, $p < 0.001$) performances from the pre- to post-test, but the CON group did not. Moreover, at the post-test, the TCC group showed greater knee extensor strength than the CON group ($t(36) = 2.97$, $p = 0.005$). There were no significant group × time interaction effects on the OLST, the GFA values for whole brain tracts, GFA values for all four WM fiber groups (Tables 4.5 and 4.6), or GFA values for individual WM tracts (Table 4.7).

Relationships between baseline WM integrity and task-switching improvement

The results of partial correlation analyses revealed that in the TCC group, higher baseline GFA values of the whole brain tracts ($r = -0.747$, $p = 0.001$), prefronto-parietal/occipital ($r = -0.782$, $p < 0.001$), and prefronto-striatal-thalamo-prefrontal loop (r = -0.800, p < 0.001) fiber groups correlated with greater reductions of the IED$_{\text{errors}}$ (Figure 4.2). There were no significant correlations of baseline GFA values of the callosal fiber group and of the auditory fiber groups with the changes of IED$_{\text{errors}}$ (r = -0.416, p = 0.109 and r = -0.243, p = 0.363), respectively.

Therefore, in the multiple regression model, we entered three covariates (age, gender, and education) first, followed by baseline GFA values of the whole brain tracts, prefronto-parietal/occipital, and prefronto-striatal-thalamo-prefrontal loop fiber groups as the potential predictors for the reduction of the IED$_{\text{errors}}$. The results of the stepwise multiple regression analyses showed that among the three GFA values, only the baseline GFA value of the prefronto-striatal-thalamo-prefrontal loop fiber group was a significant independent predictor of the change in IED$_{\text{errors}}$ (β = -0.875, p < 0.001), and that together with age (β = -0.731, p = 0.001), gender (β = -0.594, p = 0.002), and education (β = -0.463, p = 0.01), the final model accounted for 72.2% of the variance in change in IED$_{\text{errors}}$, with the baseline GFA value of the prefronto-striatal-thalamo-prefrontal loop fiber group alone accounting for 49.5% of the variance (Model 2 in Table 4.8). This model suggested that TCC participants with younger age, female gender, higher education, and higher baseline GFA values of the prefronto-striatal-thalamo-prefrontal loop fiber group showed greater reduction of task-switching errors after the 12-week TCC training.

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4.4 Discussion

To our knowledge, this is the first RCT study that investigated whether brain WM integrity changes after a short-term TCC training program, and whether baseline WM tract integrity could predict the extent of cognitive task-switching improvement after the training in middle-aged and older adults. Our findings indicated that the TCC group showed significant task-switching and physical function improvements after training, but the integrity of their whole brain WM tracts, as well as of the three task-switching relevant fiber groups—the prefronto-parietal/occipital, callosal, and prefronto-striatal-thalamo-prefrontal loop fiber groups—remained unchanged. Notably, among the participants in the TCC group, those who had better baseline WM integrity of the whole brain tracts, the prefronto-parietal/occipital, and the prefronto-striatal-thalamo-prefrontal loop fiber groups showed better task-switching improvement after the TCC intervention. Furthermore, the regression analysis showed that the baseline integrity of the prefronto-striatal-thalamo-prefrontal loop fiber group was the most important independent predictor of the task-switching improvement. Our study highlights the importance of preserving the WM health of the prefrontal-basal ganglia circuits to gain the best benefits of TCC training effects on cognitive task-switching in the aging population.

Task-switching and physical improvements after TCC training

In concordance with previous studies using short-term TCC training for 10 to 12 weeks (Matthews and Williams, 2008; Tao et al., 2017; Tao et al., 2016; Wu et al., 2018), our results also showed that middle-aged and older adults improved task-switching and physical performances after 12 weeks of Yang Style TCC training. In most of these

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previous studies, the TCC effects on task-switching ability were measured with the Trail Making Test-part B (Matthews and Williams, 2008; Mortimer et al., 2012; Nguyen and Kruse, 2012; Wayne et al., 2014), which required both task-switching and working memory processing (Sanchez-Cubillo et al., 2009). To specifically examine TCC effects on task-switching processing alone, we used the IED test of the CANTAB, a reliable and valid clinical instrument for cognitive flexibility (Robbins et al., 1998). The significant reductions of $\text{IED}_{\text{errors}}$ in our TCC participants provided direct, strong support that 12 weeks of TCC training was sufficient to improve cognitive flexibility in community-dwelling sedentary middle-aged and older adults. We speculated that this cognitive flexibility effect of TCC might come from the nature of TCC practice, which emphasizes mind-body integration, concentration, and repeated switching between sequential forms. These practices may enhance the prefrontal activations necessarily for performing task-switching and hence lead to improvements in task-switching behaviors. Indeed, previous fMRI studies showed that, after 12 weeks of TCC training, older adults were able to increase prefrontal-hippocampal functional connectivity at rest (Tao et al., 2016), and also that those who could increase the prefrontal activation during task-switching to a greater extent showed better task-switching improvement after training (Wu et al., 2018).

Our findings of improved physical functions of the TCC group are also consistent with those of previous studies showing that TCC training improves knee extensor strength, mobility, and cardiorespiratory endurance (Li et al., 2001; Taylor-Piliae, 2008; Taylor-Piliae et al., 2010). However, inconsistent with previous studies, we did not find a significant improvement on balance in the TCC group. We speculated that this might be due to the fact that most of the TCC participants reached the highest 30-second score on the eyes-opened OLST at pre- (78.9%) and post-tests (100.0%), suggesting this test

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may not be sensitive enough to detect changes in balance ability in this group.

Baseline WM integrity of the prefronto-striatal-thalamo-prefrontal loop fiber group was most predictive of task-switching improvement after TCC intervention

Our most important novel finding was that when the baseline integrity of the whole brain WM tracts and three task-switching relevant WM fiber groups, as well as age, gender, and education, were all taken into consideration together, the baseline integrity of fiber tracts in the prefronto-striatal-thalamo-prefrontal loop appeared to be the only independent baseline WM tract predictor of task-switching improvement after TCC training. It is also worth noting that the predictive power of the integrity of this loop alone even surpassed that of age, gender, and education in combination. This finding pinpoints the strong influence of the integrity status of this loop on the gain of task-switching ability after training. This model predicted that with the same amount and intensity of TCC training, middle-aged and older individuals with poorer structural integrity of the prefronto-striatal-thalamo-prefrontal pathway would not benefit from the training effects on task-switching performance as much as those with better structural integrity of this pathway. Most previous diffusion imaging and fMRI studies supported the importance of the prefronto-striatal-thalamo-prefrontal circuit on task-switching performance (Cools et al., 2004; Coxon et al., 2010; Serbruyns et al., 2016; van Schouwenburg et al., 2015; Ystad et al., 2011). Our finding is the first one implying the predictive role of the integrity of this circuit on gain in cognitive function after training.

The prefronto-striatal pathway is relevant to task-switching due to its roles in action programming, inhibitory control, and decision making (Aron and Poldrack, 2006; Neubert et al., 2010; Ratcliff and Frank, 2012). Aron and Poldrack (2006) conducted a Stop-signal fMRI task and found that the prefronto-striatal pathway was relevant to

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response inhibitory control. Using neurocomputational and diffusion models, Ratcliff and Frank (2012) found that the cortico-subcortical pathway connecting the prefrontal and basal ganglia/subthalamic nucleus was involved in decision-making processes to modulate conflicts. Both inhibitory control and decision making are cognitive processes required while performing task-switching. Indeed, evidence from fMRI studies revealed that young adults showed concurrent activation in the prefrontal cortex and basal ganglia (caudate, putamen, and pallidum) during task-switching (Coxon et al., 2010; van Schouwenburg et al., 2015), suggesting that the prefrontal-striatal network was relevant to task-switching.

More evidence that supports the importance of the integrity of the prefrontal-striatal-thalamo-prefrontal network in task-switching can be found in studies on older adults and on patients with Parkinson’s disease. Zhu et al. (2015) found that older adults with poorer WM integrity of the corona radiata for the prefronto-striatal and parietal-insula connections presented greater prefrontal activation for task-switching, suggesting that poorer integrity of these WM tracts may induce compensatory prefrontal activations during task-switching. Moreover, striatal dopamine function was found to be involved in the regulation of task-switching performance (Klanker et al., 2013), and patients with Parkinson’s disease showed task-switching deficits related to dopamine depletion in prefronto-striatal pathways (Cools et al., 2001).

Another possible explanation for the influence of the baseline integrity of the prefronto-striatal-thalamo-prefrontal pathways on task-switching improvement after TCC is related to its role in motor sequence learning, one type of implicit learning (Dennis and Cabeza, 2011). Motor training studies have shown that prefronto-striatal circuits are implicated in motor sequence learning (Dennis and Cabeza, 2011) and that baseline higher WM integrity of specific prefronto-striatal tracts is associated with

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better motor learning ability in both young and older adults (*r* = 0.55–0.82) (Bennett et al., 2011; Song et al., 2012). In the present study, all participants were novices with regard to TCC exercise. They had to learn each TCC posture and form accurately and be able to perform a series of 24 TCC forms fluently in 12 weeks. We speculated that the TCC participants who had higher baseline prefronto-striatal-thalamo-prefrontal loop WM integrity might have been able to better learn the entire 24 sequential forms of Yang-Style TCC and hence become better at transferring the motor form-switching to cognitive task-switching. However, this speculation needs to be further tested.

Baseline WM integrity of the prefronto-parietal/occipital fiber group was associated with task-switching improvement after TCC intervention

We also found that the baseline WM integrity of the prefronto-parietal/occipital fiber group was related to task-switching improvement after TCC training and that a greater baseline GFA value of the prefronto-parietal/occipital fiber group tracts was associated with greater reductions of $\text{IED}_{\text{errors}}$. The prefronto-parietal/occipital fiber group included bilateral SLF I, SLF II, SLF III, and IFOF fiber tracts. Previous DTI studies have shown that the white matter microstructure of the SLF and IFOF was related to task-switching performance in middle-aged and older adults (Gold et al., 2010; Jolly et al., 2017; Madden et al., 2009), and that that of the SLF was also related to motor information processing (Braddick et al., 2017; Rodriguez-Herreros et al., 2015), visuo-spatial attention (Bennett et al., 2012; Chechlacz et al., 2015; Mayer and Vuong, 2014), and working memory (Rizio and Diaz, 2016). Furthermore, the IFOF is known to be involved in semantic processing (Bookheimer, 2002; de Zubicaray et al., 2011), and the parietal cortex is particularly involved in integrating perception, recognition, and action (Seghier, 2013). We speculated that as TCC beginners, our TCC participants

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would have to pay close attention to their own postures and movements, as well as to those of the coach, and to integrate the constantly changing visuo-spatial information, in order to carry out the 24 TCC forms in a coordinated and sequential manner with smooth transitions between forms. Better WM integrity of the prefronto-parietal/occipital fiber group may have helped these participants to have deeper prefrontal, parietal, and occipital engagement during the TCC practices, which in turn may subsequently have also helped with the task-switching ability because it requires similar brain regions for processing visuo-spatial attention, selection, inhibition, and working memory. However, because of the high correlation ($r = 0.801$, $p < 0.001$) between the baseline integrity of this fiber group and that of the prefrontal-striatal-thalamo-prefrontal loop, the integrity of this fiber group was not an independent predictor of the task-switching improvement according to our regression analysis model.

Contrary to our hypothesis, we found that the baseline WM integrity of the prefrontal/parietal CFs was not related to task-switching improvement after TCC training. Madden et al. (2009) showed positive relationships of WM integrity of the genu of the corpus callosum and right splenium-parietal CFs with task-switching performance in older adults. We speculated that the differences in calculating the integrity of the entire prefrontal/parietal CF tracts, as shown in our study, versus calculating the integrity of various segments of the corpus callosum, as shown in Madden et al. (2009), might have contributed to the discrepancy in research findings. Therefore, we further analyzed the relationships of the WM integrity of five individual CFs (CF_{OFG}, CF_{DLPFC}, CF_{VLPFC}, CF_{SPL}, and CF_{IPL}) with task-switching improvement. Using parcellations of callosal fibers could help us clarify which fronto-parietal regions connecting with the corpus callosum influenced TCC-induced task-switching improvement. The results showed that higher baseline WM integrity of only the CF_{DLPFC} was associated with greater reductions of the IED_{errors} in the TCC group (r = -0.544, p = 0.030), controlling for age, gender, and education (Table 4.9). The DLPFC plays a crucial role in attention maintenance and selection of task-relevant information during task-switching (Banich et al., 2000; MacDonald et al., 2000) and is one of the primary parts of the prefrontal regions to which callosal fibers passing the genu connect (Hofer and Frahm, 2006). Therefore, it is reasonable that the baseline integrity of the CF_{DLPFC} is more important for task-switching improvement after TCC training, compared with other CFs.

It is worth noting that although the baseline WM integrity of whole brain tracts was also positively associated with task-switching improvement after the TCC training, this integrity value did not turn out to be the most important integrity predictor of task-switching improvement after TCC training. This finding supports the specificity of neural correlates related to task-switching and TCC training. de Lange et al. (2016) reported similar findings and concepts about the specificity of neural correlates related to cognitive training on memory function. Using DTI, de Lange et al. (2016) found that the WM integrity of the anterior corpus callosum, thalamic radiation, and IFOF tracts, but not that of other brain regions, predicted memory improvement after memory training in older adults. Further support for this specific concept came from our finding about the auditory fiber group, the baseline integrity of which was not related to task-switching improvement. Therefore, our findings suggested that the TCC-induced task-switching improvement were influenced by the baseline integrity of WM tracts relevant to task-switching, but not by that of WM tracts irrelevant to task-switching.

No significant increases in WM integrity after TCC intervention

Our results showed no significant changes in the WM integrity of whole brain tracts or all investigated fiber groups after the 12-week TCC intervention. The changes in GFA values after training were small, ranging from -0.032 to 0.025. We speculated that the short-term motor training might have been insufficiently long to change the WM integrity. In a short-term motor learning study, Kwon et al. (2012) found that 10 days of intensive motor training in young adults induced behavioral improvement and cortical activation changes on a serial RT task, but no changes in WM integrity. Previous studies suggested that a long-term 40-week TCC training program could alter cortical structures by increasing brain volume (Mortimer et al., 2012), whereas a short-term 12-week TCC program might only induce brain functional changes and behavioral improvement associated with task-switching (Tao et al., 2016; Wu et al., 2018). Similarly, Voss and colleagues (2013) found that not all older adults showed increased FA values of the prefrontal, parietal, temporal, and occipital regions after one year of walking exercise training. Together with our findings, one may conclude that training-induced changes in WM integrity may be difficult to observe after a short-term exercise program due to insufficient exercise intensity and large individual differences.

Limitations

The primary limitations of this study were the relatively small sample size and the use of short-term intervention, which may lead to difficulty in observing changes in WM integrity after training. Future research using a longer term of training is needed.

4.5 Conclusion

The results of this study demonstrated that TCC training-induced task-switching improvement can be primarily attributed to baseline WM integrity of the fiber tracts of the prefronto-striatal-thalamo-prefrontal loop. Better integrity of these fiber tracts may help with the TCC skills, and better TCC skills may in turn help with cognitive task-switching. Findings of this study also provided strong support for the importance of WM health in predicting cognitive gains after exercise training in the aging population.

4.6 Acknowledgements

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Table 4.1 Names and related ROIs of the four white matter fiber groups

Name		**Connected ROIs**	**Connected ROIs**
Prefronto-parietal/occipital fiber group			
1.	L SLFI	L superior frontal gyrus	L precuneus
2.	R SLFI	R superior frontal gyrus	R precuneus
3.	L SLFII	L inferior frontal gyrus pars triangularis	L middle occipital gyrus
4.	R SLFII	R inferior frontal gyrus pars triangularis	R middle occipital gyrus
5.	L SLFIII	L inferior frontal gyrus pars opercularis	L angular gyrus
6.	R SLFIII	R inferior frontal gyrus pars opercularis	R angular gyrus
7.	L IFOF	L orbitofrontal gyrus	L occipital lobe
8.	R IFOF	R orbitofrontal gyrus	R occipital lobe
Callosal fiber group			
1.	CF$_{\text{OFG}}$	L orbitofrontal gyrus	R orbitofrontal gyrus
2.	CF$_{\text{DLPFC}}$	L medial frontal gyrus + superior frontal gyrus	R medial frontal gyrus + superior frontal gyrus
3.	CF$_{\text{VLPFC}}$	L inferior frontal gyrus + middle frontal gyrus	R inferior frontal gyrus + middle frontal gyrus
4.	CF$_{\text{SPL}}$	L superior parietal lobules	R superior parietal lobules
5.	CF$_{\text{IPL}}$	L inferior parietal lobules	R inferior parietal lobules
Prefronto-striatal-thalamo-prefrontal loop fiber group			
1.	L FS$_{\text{DLPFC}}$	L striatum	L medial frontal gyrus + superior frontal gyrus
2.	R FS$_{\text{DLPFC}}$	R striatum	R medial frontal gyrus + superior frontal gyrus

3.	L FS$_{\text{VLPFC}}$	L striatum	L inferior frontal gyrus + middle frontal gyrus
4.	R FS$_{\text{VLPFC}}$	R striatum	R inferior frontal gyrus + middle frontal gyrus
5.	L TR$_{\text{DLPFC}}$	L thalamus	L medial frontal gyrus + superior frontal gyrus + SMA
6.	R TR$_{\text{DLPFC}}$	R thalamus	R medial frontal gyrus + superior frontal gyrus + SMA
7.	L TR$_{\text{VLPFC}}$	L thalamus	L orbitofrontal gyrus + middle frontal gyrus + inferior frontal gyrus
8.	R TR$_{\text{VLPFC}}$	R thalamus	R orbitofrontal gyrus + middle frontal gyrus + inferior frontal gyrus
Reference fiber group: Auditory fiber group			
1.	L TR$_{\text{auditory}}$	L thalamus	L Heschl’s gyrus
2.	R TR$_{\text{auditory}}$	R thalamus	R Heschl’s gyrus

The table is adapted from Chen et al. (2015). Abbreviations: CF, callosal fibers; CST, corticospinal tract; DLPFC, dorsolateral prefrontal cortex; FS, frontal-striatum; IFOF, inferior fronto-occipital fasciculus; IPL, inferior parietal lobules; L, left; OFG, orbitofrontal gyru; R, right; ROIs, regions of interest; SLF, superior longitudinal fasciculus; SPL, superior parietal lobules; SMA, supplementary motor area; TR, thalamic radiation; VLPFC, ventrolateral prefrontal cortex.

Table 4.2 Correlations among four physical function measures

	Knee strength (kg)	One-legged stance test (sec)	Four Square Step Test (sec)	Six-Minute Walk Test (m)
Knee strength (kg)	1	$r = 0.097$ $p = 0.575$	$r = -0.459$ $p = 0.005^*$	$r = 0.510$ $p = 0.001^*$
One-legged stance test (sec)		1	$r = 0.006$ $p = 0.973$	$r = 0.186$ $p = 0.277$
Four Square Step Test (sec)			1	$r = -0.460$ $p = 0.005^*$
Six-Minute Walk Test (m)				1

Results from partial correlation analyses, controlling for age and gender. $^*p < 0.05$: significant correlation.

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Table 4.3 Correlations among five GFA values of whole brain tracts, and the prefronto-parietal/occipital, callosal, prefronto-striatal-thalamo-prefrontal loop, and auditory fiber groups

	GFA value of the whole brain tracts	GFA value of the prefronto-parietal/occipital fiber group	GFA value of the callosal fiber group	GFA value of the prefronto-striatal-thalamo-prefrontal loop fiber group	GFA value of the auditory fiber group
GFA value of the whole brain tracts	1	$r = 0.878$ $p < 0.001^*$	$r = 0.780$ $p < 0.001^*$	$r = 0.906$ $p < 0.001^*$	$r = 0.617$ $p < 0.001^*$
GFA value of the prefronto-parietal/occipital fiber group		1	$r = 0.510$ $p = 0.001^*$	$r = 0.801$ $p < 0.001^*$	$r = 0.542$ $p = 0.001^*$
GFA value of the callosal fiber group			1	$r = 0.693$ $p < 0.001^*$	$r = 0.371$ $p = 0.026^*$
GFA value of the prefronto-striatal-thalamo-prefrontal loop fiber group				1	$r = 0.544$ $p = 0.001^*$
GFA value of the auditory fiber group					1

Results from partial correlation analyses, controlling for age and gender. $^*p < 0.05$: significant correlation. Abbreviations: GFA, generalized fractional anisotropy.

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Table 4.4 Demographics of the TCC and CON groups at baseline

	TCC (n = 19) mean (SD)	CON (n = 19) mean (SD)	Differences between two groups [95% CI]	*P*-value
Age (year)	63.6 (4.0)	63.2 (4.4)	[-2.4 – 3.1]	0.801
Age range (year)	55–69	55–69		
Gender (female : male)	15:4	18:1		0.150
Education (year)	13.6 (2.2)	13.4 (2.4)	[-1.3 – 1.7]	0.781
Body mass index (kg/m^2)	22.6 (2.5)	22.8 (3.3)	[-2.1 – 1.7]	0.849
MoCA (score)	28.3 (1.4)	28.5 (1.4)	[-1.1 – 0.8]	0.734
GDS-15 (score)	1.5 (1.9)	1.7 (1.5)	[-1.4 – 0.9]	0.640
PASE (score)	54.6 (43.5)	58.4 (52.9)	[-35.7 – 28.1]	0.810

Abbreviations: CI, confidence interval; CON, control group; GDS-15, Geriatric Depression Scale 15-item Short-form; MoCA, Montreal Cognitive Assessment; PASE, Physical Activity Scale for the Elderly; SD, standard deviation; TCC, Tai Chi Chuan group.

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Table 4.5 Behavioral performances of the TCC and CON groups at pre- and post-tests

	TCC group			CON group			*P*-value			Differences between two groups [95% CI]
	Pre-test mean (SD)	Post-test mean (SD)	Differences within group [95% CI]	Pre-test mean (SD)	Post-test mean (SD)	Differences within group [95% CI]	Group × Time	Time	Group	
Task-switching functions										
$\mathrm{IED}_{\mathrm{errors}}$	27.1 (13.2)	$19.2^{\dagger}$ (10.5)	[1.5 – 14.3]	25.1 (15.7)	27.2 (14.3)	[-7.7 – 3.5]	0.010^{*}	0.099	0.325	[-9.9 – 3.4]
Physical functions										
Knee strength (kg)	22.8 (5.8)	$31.9^{\ddagger}$ (9.5)	[-12.4 – -5.8]	23.1 (4.1)	$24.9^{\S}$ (3.9)	[-3.3 – -0.3]	0.001^{**}	0.115	0.241	[-1.3 – 4.9]
OLST (sec)	28.1 (4.0)	30.0 (0.0)	[-3.9 – 0.03]	27.2 (6.2)	27.7 (6.0)	[-1.6 – 0.6]	0.205	0.633	0.276	[-1.4 – 4.6]
FSST (sec)	10.4 (1.6)	$8.4^{\ddagger}$ (1.7)	[1.4 – 2.5]	9.1 (1.4)	9.0 (1.3)	[-0.3 – 0.5]	$<0.001^{**}$	0.148	$<0.001^{*}$	[-1.0 – -0.3]
6MWT (m)	474.4 (75.0)	$518.2^{\ddagger}$ (66.4)	[-65.4 – -22.2]	492.1 (49.7)	490.2 (51.7)	[-13.3 – 17.1]	0.002^{**}	0.355	0.747	[-39.4 – 28.5]

Abbreviations: 6MWT, Six-Minute Walk Test; CI, confidence interval; CON, control group; FSST, Four Square Step Test; $\mathrm{IED}_{\mathrm{errors}}$, total errors of Intra/Extra-dimensional set shift test; OLST, one-legged stance test; SD, standard deviation; TCC, Tai Chi Chuan group. $^{*}p < 0.05$: significant group × time interaction effect on task-switching performance; $^{**}p < 0.0125$: significant group × time interaction or group main effects on physical performances; $^{\dagger}p < 0.025$: significantly different from the pre-test score with Bonferroni adjustments on task-switching performance;

[‡] $p < 0.006$: significantly different from the pre-test score with Bonferroni adjustments on physical performances; [§] $p < 0.006$: a significant difference between groups at the post-test with Bonferroni adjustments.

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Table 4.6 White matter integrity (GFA values) of the five groups of white matter tracts of the TCC and CON groups at pre- and post-tests

	TCC group			CON group			*P*-value			Differences between two groups [95% CI]
	Pre-test mean (SD)	Post-test mean (SD)	Differences within group [95% CI]	Pre-test mean (SD)	Post-test mean (SD)	Differences within group [95% CI]	Group × Time	Time	Group	
Whole brain tracts	0.492 (0.013)	0.492 (0.013)	[-0.003 – 0.003]	0.484 (0.017)	0.484 (0.018)	[-0.003 – 0.002]	0.654	0.687	0.102	[-0.002– 0.016]
Prefronto-parietal/ occipital fiber group	0.498 (0.023)	0.496 (0.022)	[-0.002 – 0.005]	0.486 (0.022)	0.484 (0.023)	[-0.002 – 0.005]	0.997	0.413	0.108	[-0.003 – 0.024]
Callosal fiber group	0.513 (0.022)	0.514 (0.023)	[-0.007 – 0.004]	0.502 (0.027)	0.503 (0.029)	[-0.004 – 0.003]	0.878	0.749	0.144	[-0.004 – 0.025]
Prefronto-striatal-thalamo-prefrontal loop fiber group	0.476 (0.022)	0.477 (0.022)	[-0.006 – 0.005]	0.459 (0.030)	0.459 (0.028)	[-0.003 – 0.004]	0.868	0.904	0.016*	[0.004 – 0.031]
Auditory fiber group	0.361 (0.013)	0.362 (0.015)	[-0.006 – 0.003]	0.366 (0.017)	0.365 (0.019)	[-0.003 – 0.003]	0.626	0.341	0.245	[-0.016 – 0.004]

Abbreviations: CI, confidence interval; CON, control group; GFA, generalized fractional anisotropy; SD, standard deviation; TCC, Tai Chi Chuan group. No significant findings were found.

Table 4.7 GFA values of the 23 individual white matter tracts of the TCC and CON groups at pre- and post-tests

	TCC (N= 19)		CON (N= 19)		*P*-value		
	Pre-test	Post-test	Pre-test	Post-test	Group × Time	Time	Group
Prefronto-parietal/occipital fiber group							
L SLF I	0.530 ± 0.029	0.529 ± 0.034	0.512 ± 0.028	0.514 ± 0.027	0.459	0.499	0.076
R SLF I	0.551 ± 0.033	0.550 ± 0.038	0.526 ± 0.038	0.523 ± 0.047	0.539	0.123	0.032*
L SLF II	0.491 ± 0.031	0.489 ± 0.031	0.482 ± 0.026	0.477 ± 0.027	0.364	0.790	0.312
R SLF II	0.485 ± 0.029	0.485 ± 0.027	0.476 ± 0.028	0.473 ± 0.029	0.456	0.846	0.330
L SLF III	0.516 ± 0.035	0.514 ± 0.033	0.504 ± 0.028	0.499 ± 0.029	0.398	0.984	0.223
R SLF III	0.446 ± 0.033	0.441 ± 0.032	0.435 ± 0.030	0.436 ± 0.030	0.255	0.501	0.624
L IFOF	0.496 ± 0.023	0.497 ± 0.021	0.493 ± 0.023	0.493 ± 0.023	0.748	0.679	0.635
R IFOF	0.466 ± 0.022	0.467 ± 0.020	0.459 ± 0.023	0.458 ± 0.024	0.494	0.903	0.309
Callosal fiber group							
CF$_{\text{OFG}}$	0.458 ± 0.043	0.463 ± 0.041	0.440 ± 0.035	0.444 ± 0.042	0.687	0.216	0.179
CF$_{\text{DLPFC}}$	0.503 ± 0.027	0.505 ± 0.030	0.481 ± 0.035	0.484 ± 0.034	0.810	0.583	0.013*
CF$_{\text{VLPFC}}$	0.491 ± 0.032	0.490 ± 0.030	0.485 ± 0.039	0.482 ± 0.040	0.867	0.855	0.608
CF$_{\text{SPL}}$	0.545 ± 0.025	0.548 ± 0.023	0.547 ± 0.033	0.549 ± 0.030	0.980	0.348	0.936
CF$_{\text{IPL}}$	0.567 ± 0.023	0.564 ± 0.026	0.559 ± 0.023	0.555 ± 0.029	0.676	0.982	0.202
Prefronto-striatal-thalamo-prefrontal loop fiber group							
L FS$_{\text{DLPFC}}$	0.509 ± 0.030	0.508 ± 0.028	0.487 ± 0.036	0.486 ± 0.038	0.940	0.387	0.017*
R FS$_{\text{DLPFC}}$	0.514 ± 0.028	0.512 ± 0.031	0.499 ± 0.041	0.494 ± 0.042	0.853	0.144	0.113
L FS$_{\text{VLPFC}}$	0.393 ± 0.033	0.393 ± 0.029	0.371 ± 0.039	0.371 ± 0.034	0.902	0.355	0.019*
R FS$_{\text{VLPFC}}$	0.380 ± 0.026	0.386 ± 0.033	0.353 ± 0.036	0.355 ± 0.039	0.423	0.886	0.006*
L TR$_{\text{DLPFC}}$	0.551 ± 0.020	0.550 ± 0.020	0.538 ± 0.032	0.539 ± 0.031	0.480	0.654	0.098

R TR$_{\text{DLPFC}}$	0.548 ± 0.022	0.547 ± 0.021	0.539 ± 0.029	0.536 ± 0.031	0.657	0.649	0.209
L TR$_{\text{VLPFC}}$	0.458 ± 0.024	0.460 ± 0.023	0.443 ± 0.027	0.447 ± 0.022	0.390	0.317	0.046^{*}
R TR$_{\text{VLPFC}}$	0.457 ± 0.027	0.459 ± 0.023	0.440 ± 0.024	0.442 ± 0.024	0.598	0.431	0.029^{*}
Auditory fiber group							
L TR$_{\text{auditory}}$	0.359 ± 0.013	0.361 ± 0.015	0.366 ± 0.019	0.368 ± 0.021	0.707	1.000	0.114
R TR$_{\text{auditory}}$	0.362 ± 0.018	0.364 ± 0.018	0.365 ± 0.021	0.363 ± 0.020	0.318	0.206	0.598

Values are means ± standard deviations. GFA values of white matter tracts were analyzed by a RM ANCOVA with age, gender, and education as covariates. Abbreviations: CF, callosal fibers; CON, control group; DLPFC, dorsolateral prefrontal cortex; FS, frontal-striatal fiber group; GFA, generalized fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; IPL, inferior parietal lobules; L, left; OFG, orbitofrontal gyrus; R, right; SD, standard deviation; SLF, superior longitudinal fasciculus; SPL, superior parietal lobules; TCC, Tai Chi Chuan group; TR, thalamic radiation; VLPFC, ventrolateral prefrontal cortex.

$^{*}p < 0.05$.

Table 4.8 Stepwise multiple linear regression analyses showing the predictors of the reduction of IEDerrors in the TCC group after training

	Unstandardized coefficients		Standardized coefficients		R^2	R^2 change	*F*	*P*-value
	B	Standard error	Beta	*P*-value				
Model 1					0.227	0.227	1.471	0.262
(Constant)	85.777	57.775		0.158				
Age	-0.773	0.748	-0.237	0.318				
Gender	-14.615	7.624	-0.463	0.074				
Education	-1.349	1.421	-0.229	0.358				
Model 2					0.722	0.495	9.087	0.001^{*}
(Constant)	467.187	84.431		$< 0.001^{*}$				
Age	-2.389	0.566	-0.731	0.001^{*}				
Gender	-18.728	4.805	-0.594	0.002^{*}				
Education	-2.732	0.925	-0.463	0.010^{*}				
GFA_{pre} of the prefronto-striatal-thalamo-prefrontal loop fiber group	-530.193	106.244	-0.875	$< 0.001^{*}$				

Age, gender, and education were entered as covariates in Models 1 and 2. The GFA_{pre} values of the whole brain tracts, prefronto-parietal/occipital fiber group, and prefronto-striatal-thalamo-prefrontal loop fiber group were originally entered into the Model 2, but only the GFA_{pre} of prefronto-striatal-thalamo-prefrontal loop fiber group remained in the model. Abbreviations: GFA_{pre}, generalized fractional anisotropy at baseline; IED_{errors}, the number of total errors of the Intra/Extra-dimensional set shift test; TCC, Tai Chi Chuan group. $^{*}p < 0.05$.

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Table 4.9 Correlations between the five baseline GFA values of parcellated callosal fibers with the changes in total errors on the Intra/Extra-dimensional set shift test

	GFA value of CF_{OFG}	GFA value of CF_{DLPFC}	GFA value of CF_{VLPFC}	GFA value of CF_{SPL}	GFA value of CF_{IPL}
$\triangle IED_{errors}$	r= -0.393 p= 0.132	r= -0.544 p= 0.030*	r= 0.025 p= 0.926	r= -0.252 p= 0.347	r= -0.409 p= 0.116

Results from partial correlation analyses, controlling for age, gender, and education. Abbreviations: △ = post-pre; CF, callosal fibers; DLPFC, dorsolateral prefrontal cortex; GFA, generalized fractional anisotropy; IED_{errors}, total errors of Intra/Extra-dimensional set shift test; IPL, inferior parietal lobules; OFG, orbitofrontal gyrus; SPL, superior parietal lobules; VLPFC, ventrolateral prefrontal cortex. $^{*}p < 0.05$: significant correlation.

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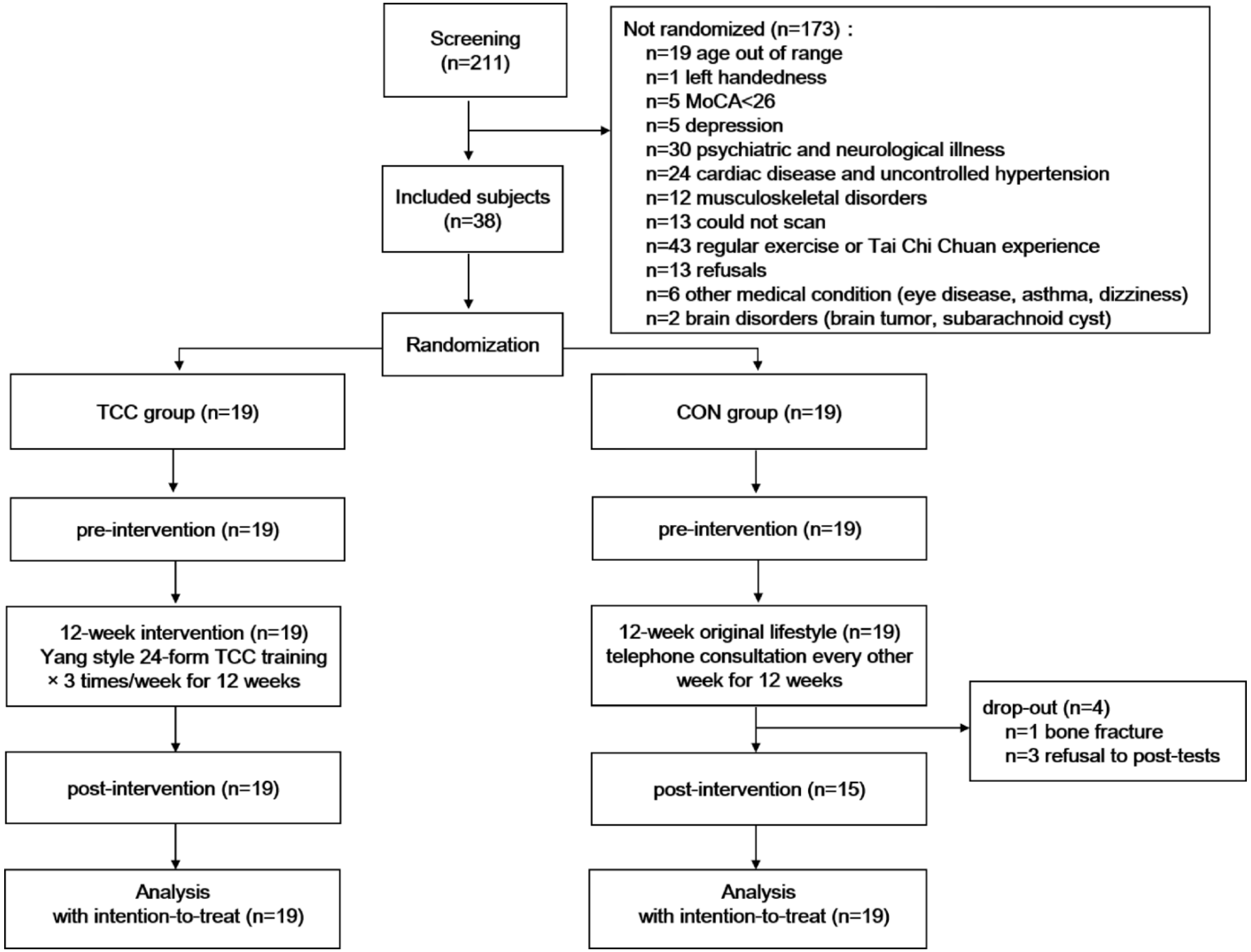

Figure 4.1 Consort chart of the randomized controlled trial

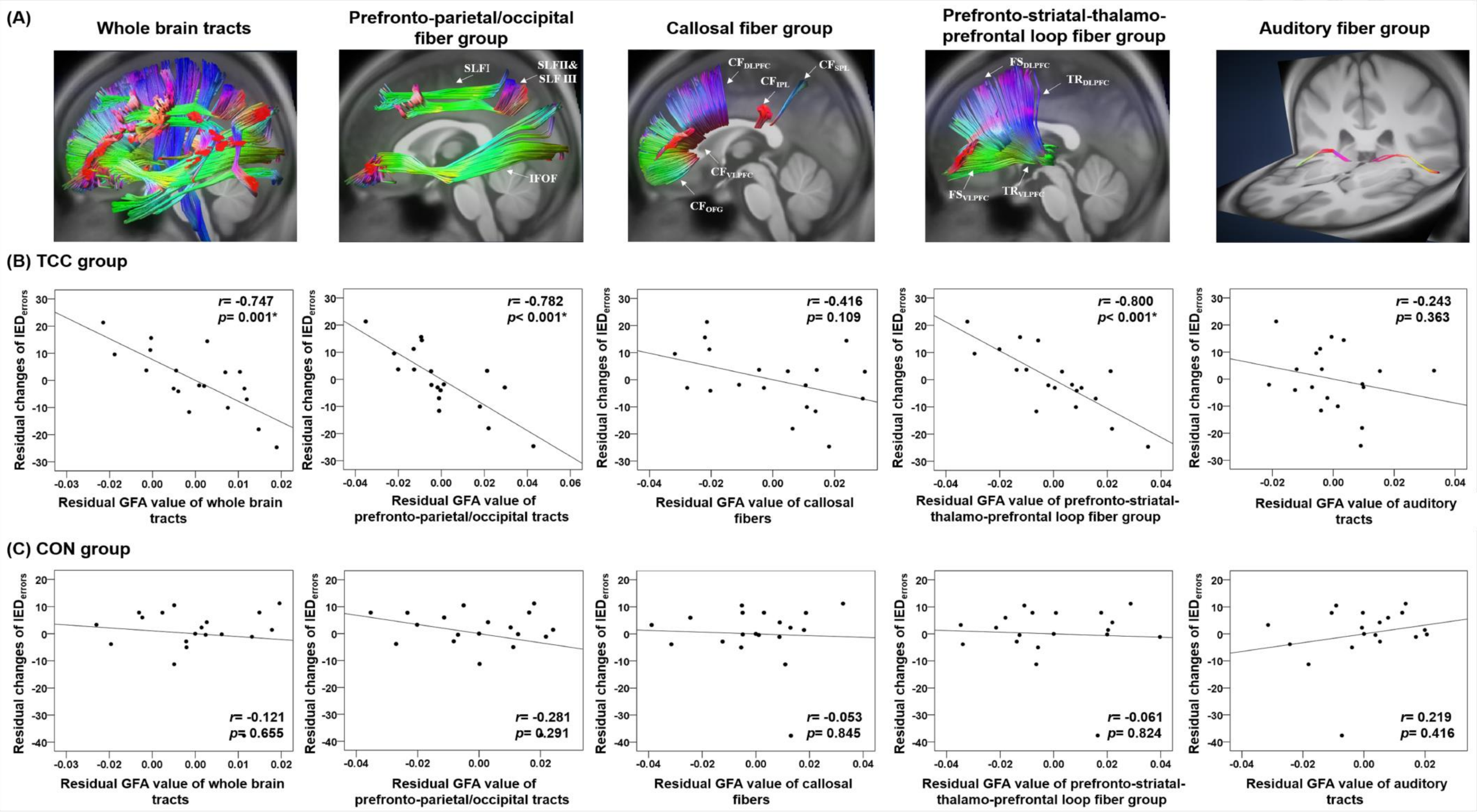

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Figure 4.2 (A) Reconstruction of the whole brain tracts and the prefronto-parietal/occipital, callosal, prefronto-striatal-thalamo-prefrontal, and auditory fiber groups using the TBAA procedure. (B) Partial correlation plots of the GFA values of the whole brain tracts, prefronto-parietal/occipital, callosal, prefronto-striatal-thalamo-prefrontal, and auditory fiber groups with the changes of the number of total errors of the IED test from pre- to post-intervention tests for the TCC group. (C) Partial correlation plots of these five GFA values with the changes of the number of total errors of the IED test from pre- to post-intervention tests for the CON group.

Abbreviations: △= post – pre; CON, control group; GFA, generalized fractional anisotropy; IED, Intra-Extra Dimensional Set Shift; TCC, Tai Chi Chuan group. * $P < 0.01$: significant correlations.

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CHAPTER 5

GENERAL DISCUSSION AND CONCLUSIONS

Task-switching is an important executive function in daily life and shows significant age-related declines. TCC exercise training has been shown to improve task-switching ability in older adults. The goals of this dissertation were to investigate the functional neural mechanisms of task-switching across young, middle-aged, and older adults in order to understand changes in these mechanisms across the lifespan, and to investigate how TCC exercise intervention might affect the structural and functional neural mechanisms associated with task-switching in cognitively intact aging populations. The intent was to further understand the underlying neural mechanisms affected by TCC exercise training and to identify the contributions of brain functional activation and white matter integrity to task-switching improvement after TCC training in middle-aged and older adults.

Age differences in task-switching performance and associated brain functional activation

In Study One, the findings indicated that the middle-aged adults preserved the ability to perform non-switch and switch tasks as accurately as young adults, but more slowly, whereas the older adults performed more poorly than young adults on accuracy and speed in both non-switch and switch tasks. These findings showed that task-switching declines at midlife were mainly manifested by slower speed, not poorer accuracy, suggesting that middle-aged adults may use the speed-accuracy tradeoff strategy to deal with task-switching demands (Starns and Ratcliff, 2010).

Regarding age differences in brain activations during the non-switch and switch

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tasks, it was found that compared to young adults, older and middle-aged adult groups additionally recruited the right prefrontoparietal regions predominantly during non-switch and switch conditions, respectively. During the non-switch condition, older adults showed such overactivation over the right SFG and IFG$_o$, whereas during the switch condition, middle-age adults showed such overactivation over the right IFG$_o$, IPL, and AG. These additional increases in right prefrontal activation, together with the commonly recruited left frontal activation across the three age groups, resulted in a decreased lateralization of brain activation during task-switching in the middle-aged and older adults, a phenomenon supporting the HAROLD model of neural mechanisms associated with cognitive aging (Cabeza, 2002). Therefore, our findings suggest that unlike older adults, who exhibited the HAROLD phenomenon during easy non-switch tasks, the middle-aged exhibited it only during difficult switching tasks. However, results of relationship analyses showed that the right prefrontoparietal recruitments were not associated with non-switch and switch performances in either middle-aged or older adults. It suggests that right prefrontoparietal overactivation is not effective in compensating for their declines in task-switching behaviors (Zhu et al., 2015).

Another age difference in brain activations during the non-switch and switch tasks was that although all three groups were able to increase brain activations from the non-switch to switch tasks, only in the middle-aged did we find relationships between the amount of brain activation and behavioral performance. Among middle-age adults, those who recruited less functional activation in the left MFG and IFG$_t$ during the non-switch condition had better non-switch performance; conversely, those who recruited greater functional activation in the left MFG and IFG$_o$ during the switch condition had better switch performance. Furthermore, from the non-switch to switch conditions, middle-aged adults who increased functional activation in the left MFG to a greater extent had better switch performance. In brief, these findings shed light on individual differences in functional activation at midlife and suggest that middle-aged individuals who are better at adapting neural functional activation in the relevant left prefrontal regions according to low and high levels of task-switching demands could perform better on task-switching. Past research on middle-aged and older adults showed that those who had lower gray matter volume had poorer task-switching performance (Adolfsdottir et al., 2014). Thus, we found that individual differences in the functional activation–behavioral performance relationship during task-switching in middle-aged adults may be affected by structural differences in their brains. This speculation needs to be further tested in future studies.

In Study One, the importance of left prefrontal activation during task-switching was noted. It was interesting to determine whether TCC exercise training, well known to have positive effects on improving task-switching ability in older adults, would alter their ability of modulating left prefrontal activation during task-switching. This question was further answered in Study Two. The results of Study Two indeed support that TCC training enhances the function of the left prefrontal activation during task-switching in some individuals who receive the exercise training.

TCC exercise training-induced task-switching improvements were associated with increases in prefrontal activation during task-switching

As expected, the 12-week TCC exercise training intervention had effects on improving task-switching performance, which was consistent with previous studies (Mortimer et al., 2012; Nguyen and Kruse, 2012; Wayne et al., 2014). In addition, the results of Study Two also showed that the TCC group marginally increased functional activation in the bilateral dorsolateral prefrontal cortex (DLPFC) regions after a

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12-week intervention, compared to the control group. With regard to brain functions on behavioral controls, the left DLPFC is known to be involved in task-switching and working memory processing (du Boisgueheneuc et al., 2006; MacDonald et al., 2000), and the right DLPFC is related to inhibitory control of ignoring irrelevant information (Brass et al., 2001; Buchsbaum et al., 2005). Specifically, the TCC participants who showed greater increases of functional activation in bilateral DLPFC, especially in the left SFG, during task-switching gained better task-switching improvement on the IED test. Previous rs-fMRI studies have shown that TCC-related training has benefits on enhancing functional connectivity between the prefrontal and temporal regions with improvements of memory function, category fluency, and task-switching ability for older adults (Li et al., 2014; Tao et al., 2016). Study Two of this dissertation provided direct evidence in support of the effects of TCC exercise training on enhancing prefrontal activation with improvement of task-switching ability for older adults, using task-fMRI. During TCC exercise training, the participants were required to maintain attention for shifting through a series of movements, memorize actions, and coordinate body postures. Indeed, practicing TCC exercise helps older adults improve multiple cognitive abilities, including task-switching, attention, working memory, memory, and learning (Tao et al., 2016; Taylor-Piliae et al., 2010; Wayne et al., 2014; Zheng et al., 2015). According to the findings of Study Two, TCC exercise training-induced task-switching improvement was positively associated with individual abilities to modulate prefrontal activation during task-switching. Furthermore, it was intriguing to know whether, in addition to causing changes in brain functional activation, TCC exercise training would enhance the WM integrity of whole brain tracts and specific task-switching related WM tracts, or whether the individual WM integrities of these tracts at baseline would influence the TCC effects on task-switching ability. Therefore,

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Study Three was designed to investigate these research questions.

White matter integrity at baseline was predictive of task-switching improvement after TCC exercise intervention

In Study Three, the findings showed that the cognitively intact middle-aged and older adults who had higher baseline WM integrity of the whole brain tracts and specific prefronto-parietal/occipital and prefronto-striatal-thalamo-prefrontal loop fiber groups showed greater task-switching improvement on the IED test after the 12-week TCC intervention. These improvements suggest that an individual’s baseline WM integrity level can influence TCC training-induced cognitive effects. de Lange and colleagues (2016) also found the influences of baseline WM integrity on training effects on cognitive function. They showed that higher baseline WM integrity of the anterior corpus callosum, left anterior thalamic radiation, and right inferior fronto-occipital fasciculus was associated with better memory improvements after 10 weeks of memory training. To our knowledge, Study Three was the first RCT to demonstrate that the WM integrity of whole brain tracts and specific WM tracts was predictive of TCC exercise training-induced task-switching effects. In addition, the contributions of the WM integrity of the prefronto-parietal/occipital and prefronto-striatal-thalamo-prefrontal loop fiber groups to TCC training-induced task-switching effects were further revealed. The results showed that the WM integrity of the prefronto-striatal-thalamo-prefrontal loop fiber group was the major independent WM integrity contributor to task-switching improvement after the TCC training. The prefronto-striatal-thalamo-prefrontal loop WM tracts connect the prefrontal regions with the striatum and thalamus (Alexander et al., 1986) and play a critical role in adapting cognitive and motor behavioral performance (Bennett et al., 2011; Seghete et al., 2013; Serbruyns et al., 2016; Song et al., 2012;

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Ystad et al., 2011). Previous studies revealed that in both young and older adults, higher WM integrity of the specific prefronto-striatal-thalamo-prefrontal loop WM tracts was associated with better task-switching performance (Seghete et al., 2013; Serbruyns et al., 2016; Ystad et al., 2011) and better motor learning ability (Bennett et al., 2011; Song et al., 2012). Thus, it was also speculated that TCC participants who had higher baseline WM integrity of the prefronto-striatal-thalamo-prefrontal loop fiber group might also have higher motor learning ability to learn a series of TCC movements more accurately and fluently and thus gain greater TCC effects on task-switching. However, this speculation needs to be explored in the future.

The contributions of the increased prefrontal activation and the baseline WM integrity of prefronto-parietal/occipital and prefronto-striatal-thalamo-prefrontal loop fiber groups to TCC training-induced task-switching improvements were found in Study Two and Study Three, respectively. It was interesting to know whether the observed relationships between the baseline WM integrity and the task-switching improvements could be better accounted for (i.e., mediated) by the changes in functional activation. Following the criterion of mediation analysis (Baron and Kenny, 1986), all three variables should be correlated with each other before being entered into a mediation model. Using the same participants in Study Three (n = 38; the TCC group, n = 19; the control group, n = 19), the results of partial correlation analyses revealed that in the TCC group, greater functional activation in the left MFG was associated with greater reductions of the number of errors on the IED test ($r = -0.533$, $p = 0.034$; Figure 5.1A & B) after controlling for age, gender, and years of education, and that higher baseline GFA values of the prefronto-parietal/occipital ($r = -0.782$, $p < 0.001$) and prefronto-striatal-thalamo-prefrontal loop fiber groups ($r = -0.792$, $p < 0.001$) were correlated with greater reductions of the number of errors on the IED test. However,

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these GFA values of the prefronto-parietal/occipital ($r = 0.314$, $p = 0.236$; Figure 5.1A) and prefronto-striatal-thalamo-prefrontal loop fiber groups ($r = 0.390$, $p = 0.136$; Figure 5.1B) were not correlated with the changes in functional activation in the left middle frontal gyrus. Therefore, the criteria of doing mediation analysis were not met. It was speculated that perhaps due to our relatively small sample size, the statistical power for running mediation analysis to answer this question was not sufficient.

Implications for clinical intervention

There are three major implications that can be drawn from the three studies in this dissertation. First, for middle-aged adults to be able to modulate functional activations in the left prefrontal regions efficiently during task-switching, early intervention emphasizing various task difficulty levels is suggested for middle-aged adults to improve their cognitive flexibility. Second, TCC exercises could be offered to middle-aged and older adults not only to improve their task-switching ability but also to enhance their prefrontal activity modulation during task-switching. Third, the WM integrity of the prefronto-parietal/occipital and prefronto-striatal-thalamo-striatal WM tracts is crucial in influencing TCC training-induced task-switching behavioral improvement. Therefore, maintenance of the structural integrity of WM is crucial in middle-aged and older adults. Overall, the results of this dissertation provide insights into the neural mechanisms of task-switching across the lifespan and the neural mechanisms of task-switching improvement after TCC training in middle-aged and older adults.

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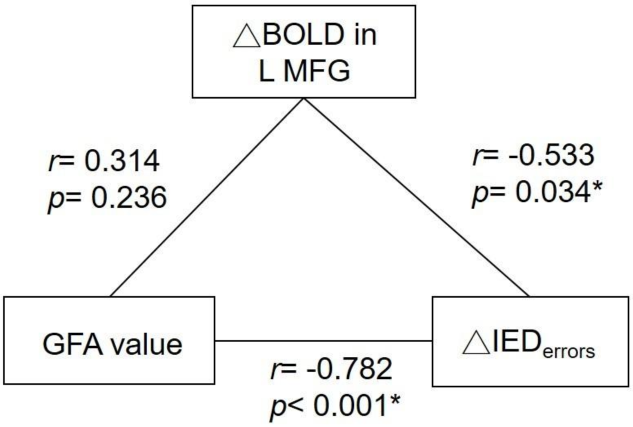
(A) Prefronto-parietal/occipital fiber group



(B) Prefronto-striatal-thalamo-prefrontal loop fiber group

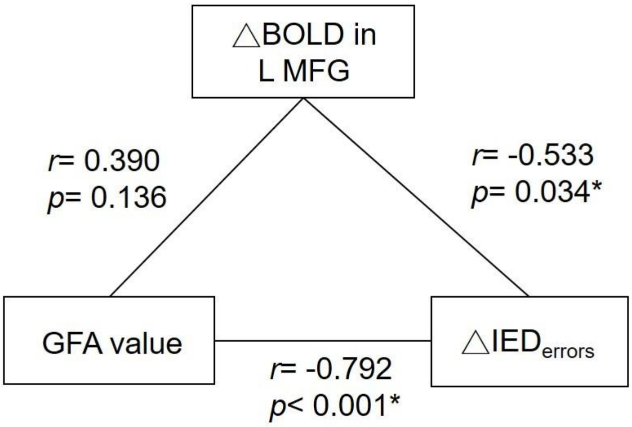


Figure 5.1 Relationship of baseline WM integrity of the prefronto-parietal/ occipital, prefronto-striatal-thalamo-prefrontal loop fiber groups with prefrontal activation in the left middle gyrus and with the task-switching improvements after TCC training in the TCC group.

Abbreviations: △= post – pre; BOLD, blood-oxygenation-level dependent; GFA, generalized fractional anisotropy; IED$_{errors}$, the number of errors on the Intra-Extra Dimensional Set Shift test; L MFG, left middle frontal gyrus; $^{*}p < 0.05$.

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REFERENCES

Aarts, E., Nusselein, A. A., Smittenaar, P., Helmich, R. C., Bloem, B. R., & Cools, R. (2014). Greater striatal responses to medication in Parkinsons disease are associated with better task-switching but worse reward performance. *Neuropsychologia, 62*, 390-397. doi:10.1016/j.neuropsychologia.2014.05.023

Adolfsdottir, S., Haasz, J., Wehling, E., Ystad, M., Lundervold, A., & Lundervold, A. J. (2014). Salient measures of inhibition and switching are associated with frontal lobe gray matter volume in healthy middle-aged and older adults. *Neuropsychology, 28*(6), 859-869.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci, 9,* 357-381. doi:10.1146/annurev.ne.09.030186.002041

Ankudowich, E., Pasvanis, S., & Rajah, M. N. (2016). Changes in the modulation of brain activity during context encoding vs. context retrieval across the adult lifespan. *Neuroimage, 139,* 103-113. doi:10.1016/j.neuroimage.2016.06.022

Aron, A. R., & Poldrack, R. A. (2006). Cortical and subcortical contributions to Stop signal response inhibition: Role of the subthalamic nucleus. *J Neurosci, 26*(9), 2424-2433. doi:10.1523/jneurosci.4682-05.2006

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage, 38*(1), 95-113. doi:10.1016/j.neuroimage.2007.07.007

Ashburner, J., & Friston, K. J. (2011). Diffeomorphic registration using geodesic shooting and Gauss-Newton optimisation. *Neuroimage, 55*(3), 954-967. doi:10.1016/j.neuroimage.2010.12.049

Badre, D., & Wagner, A. D. (2006). Computational and neurobiological mechanisms underlying cognitive flexibility. *Proceedings of the National Academy of*

doi:10.6342/NTU201900503

Sciences of the United States of America, 103(18), 7186-7191. doi:10.1073/pnas.0509550103

Banich, M. T., Milham, M. P., Atchley, R. A., Cohen, N. J., Webb, A., Wszalek, T., Kramer, A. F., Liang, Z., Barad, V., Gullett, D., Shah, C., Brown, C. (2000). Prefrontal regions play a predominant role in imposing an attentional 'set': evidence from fMRI. *Brain Res Cogn Brain Res, 10*(1-2), 1-9.

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol, 51*(6), 1173-1182.

Beaulieu, C. (2014). The biological basis of diffusion anisotropy. In H. Johansen-Berg & T. E. J. Behrens (Eds.), *Diffusion MRI* (2nd Edition ed., pp. 155-178): Academic Press.

Bennett, I. J., Madden, D. J., Vaidya, C. J., Howard, J. H., Jr., & Howard, D. V. (2011). White matter integrity correlates of implicit sequence learning in healthy aging. *Neurobiol Aging, 32*(12), 2317 e2311-2312.

Bennett, I. J., Motes, M. A., Rao, N. K., & Rypma, B. (2012). White matter tract integrity predicts visual search performance in young and older adults. *Neurobiol Aging, 33*(2), 433.e421-431. doi:10.1016/j.neurobiolaging.2011.02.001

Blackwood, J., Shubert, T., Forgarty, K., & Chase, C. (2016). Relationships between performance on assessments of executive function and fall risk screening measures in community-dwelling older adults. *J Geriatr Phys Ther, 39*(2), 89-96. doi:10.1519/jpt.0000000000000056

Bohannon, R. W., Larkin, P. A., Cook, A. C., Gear, J., & Singer, J. (1984). Decrease in timed balance test scores with aging. *Phys Ther, 64*(7), 1067-1070.

Bongard, V., McDermott, A. Y., Dallal, G. E., & Schaefer, E. J. (2007). Effects of age and gender on physical performance. *Age (Dordr), 29*(2-3), 77-85. doi:10.1007/s11357-007-9034-z

Bookheimer, S. (2002). Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci, 25*, 151-188. doi:10.1146/annurev.neuro.25.112701.142946

Braddick, O., Atkinson, J., Akshoomoff, N., Newman, E., Curley, L. B., Gonzalez, M. R., Brown, T., Dale, A., & Jernigan, T. (2017). Individual differences in children's global motion sensitivity correlate with TBSS-based measures of the superior longitudinal fasciculus. *Vision Res, 141*, 145-156. doi:10.1016/j.visres.2016.09.013

Brass, M., Zysset, S., & von Cramon, D. Y. (2001). The inhibition of imitative response tendencies. *Neuroimage, 14*(6), 1416-1423. doi: 10.1006/nimg.2001.0944

Braver, T. S., Reynolds, J. R., & Donaldson, D. I. (2003). Neural mechanisms of transient & sustained cognitive control during task switching. *Neuron, 39*(4), 713-726. doi:10.1016/s0896-6273(03)00466-5

Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002). Region of interest analysis using an SPM toolbox. *Neuroimage, 16*, 1140-1141. doi:10.1016/S1053-8119(02)90013-3

Brooks, D., Solway, S., & Gibbons, W. J. (2003). ATS statement on six-minute walk test. *Am J Respir Crit Care Med, 167*(9), 1287. doi:10.1164/ajrccm.167.9.950

Buchsbaum, B. R., Greer, S., Chang, W. L., & Berman, K. F. (2005). Meta-analysis of neuroimaging studies of the Wisconsin card-sorting task and component processes. *Hum Brain Mapp, 25*(1), 35-45. doi: 10.1002/hbm.20128

Bunce, D., Anstey, K. J., Cherbuin, N., Burns, R., Christensen, H., Wen, W., & Sachdev,

P. S. (2010). Cognitive deficits are associated with frontal and temporal lobe white matter lesions in middle-aged adults living in the community. *PLoS One, 5*(10), e13567. doi:10.1371/journal.pone.0013567

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging, 17*(1), 85-100.

Cabeza, R., & Dennis, N. A. (2013). Frontal lobes and aging: Deterioration and compensation. In D. T. Stuss and R. T. Knight (Eds.), *Principles of Frontal Lobe Function* (2nd ed., pp. 628-652). New York: Oxford University Press.

Callaghan, P. T., Coy, A., MacGowan, D., Packer, K. J., & Zelaya, F. O. (1991). Diffraction-like effects in NMR diffusion studies of fluids in porous solids. *Nature, 351*, 467. doi:10.1038/351467a0

Cansino, S., Trejo-Morales, P., Estrada-Manilla, C., Pasaye-Alcaraz, E. H., Aguilar-Castaneda, E., Salgado-Lujambio, P., & Sosa-Ortiz, A. L. (2015). Brain activity during source memory retrieval in young, middle-aged and old adults. *Brain Res, 1618*, 168-180. doi:10.1016/j.brainres.2015.05.032

Cepeda, N. J., Kramer, A. F., & Gonzalez de Sather, J. C. (2001). Changes in executive control across the life span: examination of task-switching performance. *Dev Psychol, 37*(5), 715-730.

Chamberlain, S. R., Robbins, T. W., Winder-Rhodes, S., Muller, U., Sahakian, B. J., Blackwell, A. D., & Barnett, J. H. (2011). Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. *Biol Psychiatry, 69*(12), 1192-1203. doi:10.1016/j.biopsych.2010.08.019

Chan, A. W., Yu, D. S., & Choi, K. C. (2017). Effects of Tai Chi Qigong on psychosocial well-being among hidden elderly, using elderly neighborhood volunteer approach: A pilot randomized controlled trial. *Clin Interv Aging, 12*, 85-96. doi:10.2147/cia.s124604

Chang, Y. K., Nien, Y. H., Chen, A. G., & Yan, J. (2014). Tai Ji Quan, the brain, and cognition in older adults. *Journal of Sport and Health Science, 3*(1), 36-42. doi:10.1016/j.jshs.2013.09.003

Chechlacz, M., Gillebert, C. R., Vangkilde, S. A., Petersen, A., & Humphreys, G. W. (2015). Structural Variability within Frontoparietal Networks and Individual Differences in Attentional Functions: An Approach Using the Theory of Visual Attention. *J Neurosci, 35*(30), 10647-10658. doi:10.1523/jneurosci.0210-15.2015

Chen, Y. J., Lo, Y. C., Hsu, Y. C., Fan, C. C., Hwang, T. J., Liu, C. M., Chien, Y. L., Hsieh, M. H., Liu, C. C., Hwu, H. G., & Tseng, W. Y. (2015). Automatic whole brain tract-based analysis using predefined tracts in a diffusion spectrum imaging template and an accurate registration strategy. *Hum Brain Mapp, 36*(9), 3441-3458. doi:10.1002/hbm.22854

Chiang, H. L., Chen, Y. J., Shang, C. Y., Tseng, W. Y., & Gau, S. S. (2016). Different neural substrates for executive functions in youths with ADHD: A diffusion spectrum imaging tractography study. *Psychol Med, 46*(6), 1225-1238. doi:10.1017/s0033291715002767

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., Webb, A., Jerome, G. J., Marquez, D. X., & Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A, 101*(9), 3316-3321. doi:10.1073/pnas.0400266101

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol Sci, 14*(2), 125-130.

doi:10.1111/1467-9280.t01-1-01430

Concha, L., Gross, D. W., Wheatley, B. M., & Beaulieu, C. (2006). Diffusion tensor imaging of time-dependent axonal and myelin degradation after corpus callosotomy in epilepsy patients. *Neuroimage, 32*(3), 1090-1099. doi:10.1016/j.neuroimage.2006.04.187

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain, 124*(Pt 12), 2503-2512.

Cools, R., Clark, L., & Robbins, T. W. (2004). Differential responses in human striatum and prefrontal cortex to changes in object and rule relevance. *J Neurosci, 24*(5), 1129-1135. doi:10.1523/jneurosci.4312-03.2004

Coxon, J. P., Goble, D. J., Van Impe, A., De Vos, J., Wenderoth, N., & Swinnen, S. P. (2010). Reduced basal ganglia function when elderly switch between coordinated movement patterns. *Cereb Cortex, 20*(10), 2368-2379. doi:10.1093/cercor/bhp306

Crone, E. A., Wendelken, C., Donohue, S. E., & Bunge, S. A. (2006). Neural evidence for dissociable components of task-switching. *Cereb Cortex, 16*(4), 475-486. doi:10.1093/cercor/bhi127

Cutini, S., Scatturin, P., Menon, E., Bisiacchi, P. S., Gamberini, L., Zorzi, M., & Dell'Acqua, R. (2008). Selective activation of the superior frontal gyrus in task-switching: An event-related fNIRS study. *Neuroimage, 42*(2), 945-955. doi:10.1016/j.neuroimage.2008.05.013

de Lange, A. G., Brathen, A. C., Grydeland, H., Sexton, C., Johansen-Berg, H., Andersson, J. L., Rohani, D. A., Nyberg, L., Fjell, A. M., & Walhovd, K. B. (2016). White matter integrity as a marker for cognitive plasticity in aging. *Neurobiol Aging, 47*, 74-82. doi:10.1016/j.neurobiolaging.2016.07.007

de Zubicaray, G. I., Rose, S. E., & McMahon, K. L. (2011). The structure and connectivity of semantic memory in the healthy older adult brain. *Neuroimage, 54*(2), 1488-1494. doi:10.1016/j.neuroimage.2010.08.058

D'Elia, L. F., Satz, P., Uchiyama, C. L., & White, T. (1996). *Color Trails Test*. USA: Psychological Assessment Resources.

Dennis, N. A., & Cabeza, R. (2011). Age-related dedifferentiation of learning systems: an fMRI study of implicit and explicit learning. *Neurobiol Aging, 32*(12), 2318.e2317-2330. doi:10.1016/j.neurobiolaging.2010.04.004

Derrfuss, J., Brass, M., Neumann, J., & von Cramon, D. Y. (2005). Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. *Hum Brain Mapp, 25*(1), 22-34. doi:10.1002/hbm.20127

Diamond, A. (2013). Executive functions. *Annu Rev Psychol, 64*, 135-168. doi:10.1146/annurev-psych-113011-143750

DiGirolamo, G. J., Kramer, A. F., Barad, V., Cepeda, N. J., Weissman, D. H., Milham, M. P., Wszalek, T. M., Cohen, N. J., Banich, M. T., Webb, A., Belopolsky, A. V., & McAuley, E. (2001). General and task-specific frontal lobe recruitment in older adults during executive processes: a fMRI investigation of task-switching. *Neuroreport, 12*(9), 2065-2071.

Dite, W., & Temple, V. A. (2002). A clinical test of stepping and change of direction to identify multiple falling older adults. *Arch Phys Med Rehabil, 83*(11), 1566-1571.

Dove, A., Pollmann, S., Schubert, T., Wiggins, C. J., & Yves von Cramon, D. (2000). Prefrontal cortex activation in task switching: An event-related fMRI study. *Cognitive Brain Research, 9*(1), 103-109. doi:10.1016/s0926-6410(99)00029-4

du Boisgueheneuc, F., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., et al. (2006). Functions of the left superior frontal gyrus in humans: a lesion study. *Brain, 129*(Pt 12), 3315-3328. doi: 10.1093/brain/awl244

Eggenberger, P., Wolf, M., Schumann, M., & de Bruin, E. D. (2016). Exergame and balance training modulate prefrontal brain activity during walking and enhance executive function in older adults. *Front Aging Neurosci, 8*, 66. doi:10.3389/fnagi.2016.00066

Elias, L. J., Bryden, M. P., & Bulman-Fleming, M. B. (1998). Footedness is a better predictor than is handedness of emotional lateralization. *Neuropsychologia, 36*(1), 37-43.

Engvig, A., Fjell, A. M., Westlye, L. T., Moberget, T., Sundseth, O., Larsen, V. A., & Walhovd, K. B. (2012). Memory training impacts short-term changes in aging white matter: A longitudinal diffusion tensor imaging study. *Hum Brain Mapp, 33*(10), 2390-2406. doi:10.1002/hbm.21370

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods, 41*(4), 1149-1160. doi:10.3758/brm.41.4.1149

Ferreira, D., Machado, A., Molina, Y., Nieto, A., Correia, R., Westman, E., & Barroso, J. (2017). Cognitive variability during middle-age: Possible association with neurodegeneration and cognitive reserve. *Front Aging Neurosci, 9*, 188. doi:10.3389/fnagi.2017.00188

Fong, D. Y., Chi, L. K., Li, F., & Chang, Y. K. (2014). The benefits of endurance exercise and Tai Chi Chuan for the task-switching aspect of executive function in older adults: An ERP study. *Front Aging Neurosci, 6*, 295. doi:10.3389/fnagi.2014.00295

Fray, P. J., Robbins, T. W., & Sahakian, B. J. (1996). Neuorpsychiatyric applications of

doi:10.6342/NTU201900503

CANTAB. *Int J Geriatr Psychiatry, 11*(4), 329-336. doi:10.1002/(sici)1099-1166(199604)11:4<329::aid-gps453>3.0.co;2-6

Fritzsche, K. H., Laun, F. B., Meinzer, H. P., & Stieltjes, B. (2010). Opportunities and pitfalls in the quantification of fiber integrity: What can we gain from Q-ball imaging? *Neuroimage, 51*(1), 242-251. doi:10.1016/j.neuroimage.2010.02.007

Fu, C., Li, Z., & Mao, Z. (2018). Association between social activities and cognitive function among the elderly in China: A cross-sectional study. *Int J Environ Res Public Health, 15*(2). doi:10.3390/ijerph15020231

Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proc Natl Acad Sci U S A, 96*(14), 8301-8306.

Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I. M., Nieman, D. C., & Swain, D. P. (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc, 43*(7), 1334-1359. doi:10.1249/MSS.0b013e318213fefb

Gau, S. S., & Shang, C. Y. (2010). Executive functions as endophenotypes in ADHD: Evidence from the Cambridge Neuropsychological Test Battery (CANTAB). *J Child Psychol Psychiatry, 51*(7), 838-849. doi:10.1111/j.1469-7610.2010.02215.x

Gazes, Y., Rakitin, B. C., Habeck, C., Steffener, J., & Stern, Y. (2012). Age differences of multivariate network expressions during task-switching and their associations with behavior. *Neuropsychologia, 50*(14), 3509-3518. doi:10.1016/j.neuropsychologia.2012.09.039

Glei, D. A., Landau, D. A., Goldman, N., Chuang, Y. L., Rodriguez, G., & Weinstein, M. (2005). Participating in social activities helps preserve cognitive function: An analysis of a longitudinal, population-based study of the elderly. *Int J Epidemiol, 34*(4), 864-871. doi:10.1093/ije/dyi049

Gold, B. T., Powell, D. K., Xuan, L., Jicha, G. A., & Smith, C. D. (2010). Age-related slowing of task switching is associated with decreased integrity of frontoparietal white matter. *Neurobiol Aging, 31*(3), 512-522. doi:10.1016/j.neurobiolaging.2008.04.005

Gorczewski, K., Mang, S., & Klose, U. (2009). Reproducibility and consistency of evaluation techniques for HARDI data. *Magma, 22*(1), 63-70. doi:10.1007/s10334-008-0144-0

Gothe, N. P., Fanning, J., Awick, E., Chung, D., Wojcicki, T. R., Olson, E. A., Mullen, S. P., Voss, M., Erickson, K. I., Kramer, A. F., & McAuley, E. (2014). Executive function processes predict mobility outcomes in older adults. *J Am Geriatr Soc, 62*(2), 285-290. doi:10.1111/jgs.12654

Gunstad, J., Paul, R. H., Brickman, A. M., Cohen, R. A., Arns, M., Roe, D., Lawrence, J. J., & Gordon, E. (2006). Patterns of cognitive performance in middle-aged and older adults: A cluster analytic examination. *J Geriatr Psychiatry Neurol, 19*(2), 59-64. doi:10.1177/0891988705284738

Hakun, J. G., & Johnson, N. F. (2017). Dynamic range of frontoparietal functional modulation is associated with working memory capacity limitations in older adults. *Brain Cogn, 118,* 128-136. doi:10.1016/j.bandc.2017.08.007

Hakun, J. G., Zhu, Z., Johnson, N. F., & Gold, B. T. (2015). Evidence for reduced efficiency and successful compensation in older adults during task switching. *Cortex, 64,* 352-362. doi:10.1016/j.cortex.2014.12.006

Hawkes, T. D., Siu, K. C., Silsupadol, P., & Woollacott, M. H. (2012). Why does older adults' balance become less stable when walking and performing a secondary task? Examination of attentional switching abilities. *Gait Posture, 35*(1), 159-163. doi:10.1016/j.gaitpost.2011.09.001

Henry, L. A., & Bettenay, C. (2010). The Assessment of Executive Functioning in Children. *Child and Adolescent Mental Health, 15*(2), 110-119. doi:10.1111/j.1475-3588.2010.00557.x

Hikichi, H., Kondo, K., Takeda, T., & Kawachi, I. (2017). Social interaction and cognitive decline: Results of a 7-year community intervention. *Alzheimers Dement (N Y), 3*(1), 23-32. doi:10.1016/j.trci.2016.11.003

Hofer, S., & Frahm, J. (2006). Topography of the human corpus callosum revisited-comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage, 32*(3), 989-994. doi:10.1016/j.neuroimage.2006.05.044

Hofstetter, S., Tavor, I., Tzur Moryosef, S., & Assaf, Y. (2013). Short-term learning induces white matter plasticity in the fornix. *J Neurosci, 33*(31), 12844-12850. doi:10.1523/JNEUROSCI.4520-12.2013

Hsu, Y. C., Hsu, C. H., & Tseng, W. Y. (2012). A large deformation diffeomorphic metric mapping solution for diffusion spectrum imaging datasets. *Neuroimage, 63*(2), 818-834. doi:10.1016/j.neuroimage.2012.07.033

Hsu, Y. C., Lo, Y. C., Chen, Y. J., Wedeen, V. J., & Tseng, W. Y. (2015). NTU-DSI-122: A diffusion spectrum imaging template with high anatomical matching to the ICBM-152 space. *Hum Brain Mapp, 36*(9), 3528-3541. doi:10.1002/hbm.22860

Huang, C. M., Polk, T. A., Goh, J. O., & Park, D. C. (2012). Both left and right

doi:10.6342/NTU201900503

posterior parietal activations contribute to compensatory processes in normal aging. *Neuropsychologia, 50*(1), 55-66. doi:10.1016/j.neuropsychologia.2011.10.022

Huff, M. J., Balota, D. A., Minear, M., Aschenbrenner, A. J., & Duchek, J. M. (2015). Dissociative global and local task-switching costs across younger adults, middle-aged adults, older adults, and very mild Alzheimer's disease individuals. *Psychol Aging, 30*(4), 727-739. doi:10.1037/pag0000057

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *Br J Psychiatry, 140*, 566-572.

Jellison, B. J., Field, A. S., Medow, J., Lazar, M., Salamat, M. S., & Alexander, A. L. (2004). Diffusion tensor imaging of cerebral white matter: A pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. *American Journal of Neuroradiology, 25*(3), 356.

Jimura, K., & Braver, T. S. (2010). Age-related shifts in brain activity dynamics during task switching. *Cereb Cortex, 20*(6), 1420-1431. doi:10.1093/cercor/bhp206

Jimura, K., Cazalis, F., Stover, E. R., & Poldrack, R. A. (2014). The neural basis of task switching changes with skill acquisition. *Front Hum Neurosci, 8*, 339. doi:10.3389/fnhum.2014.00339

Johansen-Berg, H., & Rushworth, M. F. (2009). Using diffusion imaging to study human connectional anatomy. *Annu Rev Neurosci, 32*, 75-94. doi:10.1146/annurev.neuro.051508.135735

Jolly, T. A., Cooper, P. S., Rennie, J. L., Levi, C. R., Lenroot, R., Parsons, M. W., Michie, P. T., & Karayanidis, F. (2017). Age-related decline in task switching is linked to both global and tract-specific changes in white matter microstructure. *Hum Brain Mapp, 38*(3), 1588-1603. doi:10.1002/hbm.23473

Kennedy, K. M., Rodrigue, K. M., Bischof, G. N., Hebrank, A. C., Reuter-Lorenz, P. A., & Park, D. C. (2015). Age trajectories of functional activation under conditions of low and high processing demands: an adult lifespan fMRI study of the aging brain. *Neuroimage, 104*, 21-34. doi:10.1016/j.neuroimage.2014.09.056

Kim, C., Johnson, N. F., Cilles, S. E., & Gold, B. T. (2011). Common and distinct mechanisms of cognitive flexibility in prefrontal cortex. *J Neurosci, 31*(13), 4771-4779. doi:10.1523/JNEUROSCI.5923-10.2011

Kim, Cilles, S. E., Johnson, N. F., & Gold, B. T. (2012). Domain general and domain preferential brain regions associated with different types of task switching: a meta-analysis. *Hum Brain Mapp, 33*(1), 130-142. doi:10.1002/hbm.21199

Kim, H. S., An, Y. M., Kwon, J. S., & Shin, M. S. (2014). A preliminary validity study of the cambridge neuropsychological test automated battery for the assessment of executive function in schizophrenia and bipolar disorder. *Psychiatry Investig, 11*(4), 394-401. doi:10.4306/pi.2014.11.4.394

Kimberg, D. Y., Aguirre, G. K., & D'Esposito, M. (2000). Modulation of task-related neural activity in task-switching: an fMRI study. *Brain Res Cogn Brain Res, 10*(1-2), 189-196.

Klanker, M., Feenstra, M., & Denys, D. (2013). Dopaminergic control of cognitive flexibility in humans and animals. *Front Neurosci, 7*, 201. doi:10.3389/fnins.2013.00201

Kray, J., & Lindenberger, U. (2000). Adult age differences in task switching. *Psychol Aging, 15*(1), 126-147.

Kuo, L. W., Chen, J. H., Wedeen, V. J., & Tseng, W. Y. (2008). Optimization of diffusion spectrum imaging and q-ball imaging on clinical MRI system. *Neuroimage, 41*(1), 7-18. doi:10.1016/j.neuroimage.2008.02.016

doi:10.6342/NTU201900503

Kwon, Y. H., Nam, K. S., & Park, J. W. (2012). Identification of cortical activation and white matter architecture according to short-term motor learning in the human brain: Functional MRI and diffusion tensor tractography study. *Neurosci Lett, 520*(1), 11-15. doi:10.1016/j.neulet.2012.05.005

Lan, C., Chen, S. Y., & Lai, J. S. (2008). The exercise intensity of Tai Chi Chuan. *Med Sport Sci, 52,* 12-19. doi:10.1159/000134225

Lan, C., Chen, S. Y., Lai, J. S., & Wong, A. M. (2013). Tai chi chuan in medicine and health promotion. *Evid Based Complement Alternat Med, 2013,* 502131. doi:10.1155/2013/502131

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist, 9*(3), 179-186.

Le Bihan, D. (2003). Looking into the functional architecture of the brain with diffusion MRI. *Nat Rev Neurosci, 4*(6), 469-480. doi:10.1038/nrn1119

Leunissen, I., Coxon, J. P., Caeyenberghs, K., Michiels, K., Sunaert, S., & Swinnen, S. P. (2014). Task switching in traumatic brain injury relates to cortico-subcortical integrity. *Hum Brain Mapp, 35*(5), 2459-2469. doi:10.1002/hbm.22341

Li, J. X., Hong, Y., & Chan, K. M. (2001). Tai chi: Physiological characteristics and beneficial effects on health. *Br J Sports Med, 35*(3), 148-156.

Li, R., Zhu, X., Yin, S., Niu, Y., Zheng, Z., Huang, X., Wang, B., & Li, J. (2014). Multimodal intervention in older adults improves resting-state functional connectivity between the medial prefrontal cortex and medial temporal lobe. *Front Aging Neurosci, 6,* 39. doi:10.3389/fnagi.2014.00039

Liang, S. Y., & Wu, W. C. (1996). *Tai Chi Chuan: 24 And 48 Postures With Martial Applications.* Boston: Yang's Martial Arts Association Publication Center Press.

Liu-Ambrose, T., Nagamatsu, L. S., Graf, P., Beattie, B. L., Ashe, M. C., & Handy, T.

C. (2010). Resistance training and executive functions: A 12-month randomized controlled trial. *Arch Intern Med, 170*(2), 170-178. doi:10.1001/archinternmed.2009.494

Liu-Ambrose, T., Nagamatsu, L. S., Voss, M. W., Khan, K. M., & Handy, T. C. (2012). Resistance training and functional plasticity of the aging brain: A 12-month randomized controlled trial. *Neurobiol Aging, 33*(8), 1690-1698. doi:10.1016/j.neurobiolaging.2011.05.010

Luciana, M., & Nelson, C. A. (1998). The functional emergence of prefrontally-guided working memory systems in four- to eight-year-old children. *Neuropsychologia, 36*(3), 273-293.

Ma, C., Zhou, W., Tang, Q., & Huang, S. (2018). The impact of group-based Tai chi on health-status outcomes among community-dwelling older adults with hypertension. *Heart Lung*. doi:10.1016/j.hrtlng.2018.04.007

MacDonald, A. W., Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 288*(5472), 1835-1838.

Madden, D. J., Spaniol, J., Costello, M. C., Bucur, B., White, L. E., Cabeza, R., Davis, S. W., Dennis, N. A., Provenzale, J. M., & Huettel, S. A. (2009). Cerebral white matter integrity mediates adult age differences in cognitive performance. *J Cogn Neurosci, 21*(2), 289-302. doi:10.1162/jocn.2009.21047

Matthews, M. M., & Williams, H. G. (2008). Can Tai chi enhance cognitive vitality? A preliminary study of cognitive executive control in older adults after A Tai chi intervention. *J S C Med Assoc., 104*(8), 255-257.

Mayer, K. M., & Vuong, Q. C. (2014). TBSS and probabilistic tractography reveal white matter connections for attention to object features. *Brain Struct Funct,*

doi:10.6342/NTU201900503

219(6), 2159-2171. doi:10.1007/s00429-013-0631-6

Monchi, O., Petrides, M., Petre, V., Worsley, K., & Dagher, A. (2001). Wisconsin Card Sorting revisited: Distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *J Neurosci, 21*(19), 7733-7741.

Monsell, S. (2003). Task switching. *Trends Cogn Sci, 7*(3), 134-140.

Monsell, S., Sumner, P., & Waters, H. (2003). Task-set reconfiguration with predictable and unpredictable task switches. *Mem Cognit, 31*(3), 327-342.

Moreau, D., Morrison, A. B., & Conway, A. R. (2015). An ecological approach to cognitive enhancement: Complex motor training. *Acta Psychol (Amst), 157,* 44-55. doi:10.1016/j.actpsy.2015.02.007

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Hua, K., Faria, A. V., Mahmood, A., Woods, R., Toga, A. W., Pike, G. B., Neto, P. R., Evans, A., Zhang, J., Huang, H., Miller, M. I., van Zijl, P., & Mazziotta, J. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage, 40*(2), 570-582. doi:10.1016/j.neuroimage.2007.12.035

Mortimer, J. A., Ding, D., Borenstein, A. R., DeCarli, C., Guo, Q., Wu, Y., Zhao, Q., & Chu, S. (2012). Changes in brain volume and cognition in a randomized trial of exercise and social interaction in a community-based sample of non-demented Chinese elders. *J Alzheimers Dis, 30*(4), 757-766.

Nagamatsu, L. S., Handy, T. C., Hsu, C. L., Voss, M., & Liu-Ambrose, T. (2012). Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment: A 6-month randomized controlled trial. *Archives of internal medicine, 172*(8), 666-668. doi:10.1001/archinternmed.2012.379

Nashiro, K., Qin, S., O'Connell, M. A., & Basak, C. (2018). Age-related differences in BOLD modulation to cognitive control costs in a multitasking paradigm: Global switch, local switch, and compatibility-switch costs. *Neuroimage, 172*, 146-161. doi:10.1016/j.neuroimage.2018.01.030

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc, 53*(4), 695-699. doi:10.1111/j.1532-5415.2005.53221.x

Neubert, F. X., Mars, R. B., Buch, E. R., Olivier, E., & Rushworth, M. F. (2010). Cortical and subcortical interactions during action reprogramming and their related white matter pathways. *Proc Natl Acad Sci U S A, 107*(30), 13240-13245. doi:10.1073/pnas.1000674107

Nguyen, M. H., & Kruse, A. (2012). A randomized controlled trial of Tai chi for balance, sleep quality and cognitive performance in elderly Vietnamese. *Clin Interv Aging, 7*, 185-190.

Nishiguchi, S., Yamada, M., Tanigawa, T., Sekiyama, K., Kawagoe, T., Suzuki, M., Yoshikawa, S., Abe, N., Otsuka, Y., Nakai, R., Aoyama, T., & Tsuboyama, T. (2015). A 12-week physical and cognitive exercise program can improve cognitive function and neural efficiency in community-dwelling older adults: A randomized controlled trial. *J Am Geriatr Soc, 63*(7), 1355-1363. doi:10.1111/jgs.13481

Nyunt, M. S., Fones, C., Niti, M., & Ng, T. P. (2009). Criterion-based validity and reliability of the Geriatric Depression Screening Scale (GDS-15) in a large validation sample of community-living Asian older adults. *Aging Ment Health, 13*(3), 376-382. doi:10.1080/13607860902861027

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Perry, A., Wen, W., Kochan, N. A., Thalamuthu, A., Sachdev, P. S., & Breakspear, M. (2017). The independent influences of age and education on functional brain networks and cognition in healthy older adults. *Hum Brain Mapp, 38*(10), 5094-5114. doi:10.1002/hbm.23717

Philipp, A. M., Weidner, R., Koch, I., & Fink, G. R. (2013). Differential roles of inferior frontal and inferior parietal cortex in task switching: Evidence from stimulus-categorization switching and response-modality switching. *Hum Brain Mapp, 34*(8), 1910-1920. doi:10.1002/hbm.22036

Ratcliff, R., & Frank, M. J. (2012). Reinforcement-based decision making in corticostriatal circuits: Mutual constraints by neurocomputational and diffusion models. *Neural Comput, 24*(5), 1186-1229. doi:10.1162/NECO_a_00270

Reese, T. G., Heid, O., Weisskoff, R. M., & Wedeen, V. J. (2003). Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. *Magn Reson Med, 49*(1), 177-182. doi:10.1002/mrm.10308

Reimers, S., & Maylor, E. A. (2005). Task switching across the life span: Effects of age on general and specific switch costs. *Dev Psychol, 41*(4), 661-671. doi:10.1037/0012-1649.41.4.661

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills, 8*, 271-276.

Rizio, A. A., & Diaz, M. T. (2016). Language, aging, and cognition: frontal aslant tract and superior longitudinal fasciculus contribute toward working memory performance in older adults. *Neuroreport, 27*(9), 689-693. doi:10.1097/wnr.0000000000000597

doi:10.6342/NTU201900503

Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., Lawrence, A. D., McInnes, L., & Rabbitt, P. M. (1998). A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: Implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. *J Int Neuropsychol Soc, 4*(5), 474-490. doi: 10.1017/s1355617798455073

Rodriguez-Herreros, B., Amengual, J. L., Gurtubay-Antolin, A., Richter, L., Jauer, P., Erdmann, C., Schweikard, A., Lopez-Moliner, J., Rodriguez-Fornells, A., & Munte, T. F. (2015). Microstructure of the superior longitudinal fasciculus predicts stimulation-induced interference with on-line motor control. *Neuroimage, 120*, 254-265. doi:10.1016/j.neuroimage.2015.06.070

Rypma, B., Berger, J. S., Genova, H. M., Rebbechi, D., & D'Esposito, M. (2005). Dissociating age-related changes in cognitive strategy and neural efficiency using event-related fMRI. *Cortex, 41*(4), 582-594.

Rypma, B., Berger, J. S., Prabhakaran, V., Bly, B. M., Kimberg, D. Y., Biswal, B. B., & D'Esposito, M. (2006). Neural correlates of cognitive efficiency. *Neuroimage, 33*(3), 969-979. doi:10.1016/j.neuroimage.2006.05.065

Sakai, K. (2008). Task set and prefrontal cortex. *Annu Rev Neurosci, 31*, 219-245. doi:10.1146/annurev.neuro.31.060407.125642

Sakai, K., & Passingham, R. E. (2003). Prefrontal interactions reflect future task operations. *Nat Neurosci, 6*(1), 75-81. doi:10.1038/nn987

Sanchez-Cubillo, I., Perianez, J. A., Adrover-Roig, D., Rodriguez-Sanchez, J. M., Rios-Lago, M., Tirapu, J., & Barcelo, F. (2009). Construct validity of the Trail Making Test: Role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *J Int Neuropsychol Soc, 15*, 438-450. doi:

10.1017/s1355617709090626

Scholz, J., Klein, M. C., Behrens, T. E., & Johansen-Berg, H. (2009). Training induces changes in white-matter architecture. *Nat Neurosci, 12*(11), 1370-1371. doi:10.1038/nn.2412

Seghete, K. L., Herting, M. M., & Nagel, B. J. (2013). White matter microstructure correlates of inhibition and task-switching in adolescents. *Brain Res, 1527*, 15-28. doi:10.1016/j.brainres.2013.06.003

Seghier, M. L. (2013). The angular gyrus: multiple functions and multiple subdivisions. *Neuroscientist, 19*(1), 43-61. doi:10.1177/1073858412440596

Serbruyns, L., Leunissen, I., van Ruitenbeek, P., Pauwels, L., Caeyenberghs, K., Solesio-Jofre, E., Geurts, M., Cuypers, K., Meesen, R. L., Sunaert, S., Leemans, A., & Swinnen, S. P. (2016). Alterations in brain white matter contributing to age-related slowing of task switching performance: The role of radial diffusivity and magnetization transfer ratio. *Hum Brain Mapp, 37*(11), 4084-4098. doi:10.1002/hbm.23297

Shang, C. Y., Wu, Y. H., Gau, S. S., & Tseng, W. Y. (2013). Disturbed microstructural integrity of the frontostriatal fiber pathways and executive dysfunction in children with attention deficit hyperactivity disorder. *Psychol Med, 43*(5), 1093-1107. doi:10.1017/S0033291712001869

Smith, J. C., Nielson, K. A., Antuono, P., Lyons, J. A., Hanson, R. J., Butts, A. M., Hantke, N. C., & Verber, M. D. (2013). Semantic memory functional MRI and cognitive function after exercise intervention in mild cognitive impairment. *J Alzheimers Dis, 37*(1), 197-215. doi:10.3233/jad-130467

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K., Browndyke, J. N., Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. *Psychosom Med, 72*(3), 239-252. doi:10.1097/PSY.0b013e3181d14633

Song, S. K., Sun, S. W., Ju, W. K., Lin, S. J., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage, 20*(3), 1714-1722.

Song, S., Sharma, N., Buch, E. R., & Cohen, L. G. (2012). White matter microstructural correlates of superior long-term skill gained implicitly under randomized practice. *Cereb Cortex, 22*(7), 1671-1677.

Starns, J. J., & Ratcliff, R. (2010). The effects of aging on the speed-accuracy compromise: Boundary optimality in the diffusion model. *Psychol Aging, 25*(2), 377-390. doi:10.1037/a0018022

Stefanova, E., Jecmenica Lukic, M., Ziropadja, L., Markovic, V., Stojkovic, T., Tomic, A., Dragasevic Miskovic, N., & Kostic, V. (2014). Attentional set-shifting in Parkinson's disease patients with freezing of gait-acquisition and discrimination set learning deficits at the background? *J Int Neuropsychol Soc, 20*(9), 929-936. doi:10.1017/s1355617714000769

Sugimoto, H., Demura, S., & Nagasawa, Y. (2014). Age-and gender-related differences in physical functions of the elderly following 1-year regular exercise therapy: Comparison with standard values. *American Journal of Sports Science and Medicine, 2*(4), 148-153. doi:10.12691/ajssm-2-4-6

Svatkova, A., Mandl, R. C., Scheewe, T. W., Cahn, W., Kahn, R. S., & Hulshoff Pol, H. E. (2015). Physical exercise keeps the brain connected: Biking increases white matter integrity in patients with Schizophrenia and healthy controls. *Schizophr*

Bull, 41(4), 869-878.

Tao, J., Chen, X., Liu, J., Egorova, N., Xue, X., Liu, W., Zheng, G., Li, M., Wu, J., Hu, K., Wang, Z., Chen, L., & Kong, J. (2017). Tai Chi Chuan and Baduanjin Mind-Body Training Changes Resting-State Low-Frequency Fluctuations in the Frontal Lobe of Older Adults: A Resting-State fMRI Study. *Front Hum Neurosci, 11,* 514. doi:10.3389/fnhum.2017.00514

Tao, J., Liu, J., Egorova, N., Chen, X., Sun, S., Xue, X., Huang, J., Zheng, G., Wang, Q., Chen, L., & Kong, J. (2016). Increased hippocampus-medial prefrontal cortex resting-state functional connectivity and memory function after Tai Chi Chuan practice in elder adults. *Front Aging Neurosci, 8*, 25.

Taylor-Piliae, R. E. (2008). The effectiveness of Tai Chi exercise in improving aerobic capacity: An updated meta-analysis. *Med Sport Sci, 52*, 40-53. doi:10.1159/000134283

Taylor-Piliae, R. E., Haskell, W. L., Stotts, N. A., & Froelicher, E. S. (2006). Improvement in balance, strength, and flexibility after 12 weeks of Tai chi exercise in ethnic Chinese adults with cardiovascular disease risk factors. *Altern Ther Health Med, 12*(2), 50-58. doi: 10.1016/j.ejcnurse.2005.10.008

Taylor-Piliae, R. E., Newell, K. A., Cherin, R., Lee, M. J., King, A. C., & Haskell, W. L. (2010). Effects of Tai Chi and western exercise on physical and cognitive functioning in healthy community-dwelling older adults. *J Aging Phys Act, 18*(3), 261-279. doi: 10.1123/japa.18.3.261

Toepper, M., Gebhardt, H., Bauer, E., Haberkamp, A., Beblo, T., Gallhofer, B., Driessen, M., & Sammer, G. (2014). The impact of age on load-related dorsolateral prefrontal cortex activation. *Front Aging Neurosci, 6*, 9. doi:10.3389/fnagi.2014.00009

Tsai, C. F., Lee, W. J., Wang, S. J., Shia, B. C., Nasreddine, Z., & Fuh, J. L. (2012). Psychometrics of the Montreal Cognitive Assessment (MoCA) and its subscales: Validation of the Taiwanese version of the MoCA and an item response theory analysis. *Int Psychogeriatr, 24*(4), 651-658. doi:10.1017/s1041610211002298

Tuch, D. S. (2004). Q-ball imaging. *Magn Reson Med, 52*(6), 1358-1372. doi:10.1002/mrm.20279

Vallesi, A., Arbula, S., Capizzi, M., Causin, F., & D'Avella, D. (2015). Domain-independent neural underpinning of task-switching: an fMRI investigation. *Cortex, 65,* 173-183. doi:10.1016/j.cortex.2015.01.016

van Schouwenburg, M. R., den Ouden, H. E., & Cools, R. (2015). Selective attentional enhancement and inhibition of fronto-posterior connectivity by the basal ganglia during attention switching. *Cereb Cortex, 25*(6), 1527-1534. doi:10.1093/cercor/bht345

Voelcker-Rehage, C., Godde, B., & Staudinger, U. M. (2011). Cardiovascular and coordination training differentially improve cognitive performance and neural processing in older adults. *Front Hum Neurosci, 5,* 26. doi:10.3389/fnhum.2011.00026

Voss, M. W., Heo, S., Prakash, R. S., Erickson, K. I., Alves, H., Chaddock, L., Szabo, A. N., Mailey, E. L., Wojcicki, T. R., White, S. M., Gothe, N., McAuley, E., Sutton, B. P., & Kramer, A. F. (2013). The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: Results of a one-year exercise intervention. *Hum Brain Mapp, 34*(11), 2972-2985. doi:10.1002/hbm.22119

Wakana, S., Jiang, H., Nagae-Poetscher, L. M., van Zijl, P. C., & Mori, S. (2004). Fiber tract-based atlas of human white matter anatomy. *Radiology, 230*(1), 77-87.

doi:10.6342/NTU201900503

doi:10.1148/radiol.2301021640

Wang, C. Y., Olson, S. L., & Protas, E. J. (2002). Test-retest strength reliability: Hand-held dynamometry in community-dwelling elderly fallers. *Arch Phys Med Rehabil, 83*(6), 811-815.

Wang, C., Bannuru, R., Ramel, J., Kupelnick, B., Scott, T., & Schmid, C. H. (2010). Tai Chi on psychological well-being: Systematic review and meta-analysis. *BMC Complement Altern Med, 10*, 23. doi:10.1186/1472-6882-10-23

Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The Physical Activity Scale for the Elderly (PASE): Development and evaluation. *J Clin Epidemiol, 46*(2), 153-162. doi: 10.1016/0895-4356(93)90053-4

Wasylyshyn, C., Verhaeghen, P., & Sliwinski, M. J. (2011). Aging and task switching: A meta-analysis. *Psychol Aging, 26*(1), 15-20. doi:10.1037/a0020912

Wayne, P. M., Walsh, J. N., Taylor-Piliae, R. E., Wells, R. E., Papp, K. V., Donovan, N. J., & Yeh, G. Y. (2014). Effect of tai chi on cognitive performance in older adults: systematic review and meta-analysis. *J Am Geriatr Soc, 62*(1), 25-39. doi:10.1111/jgs.12611

Wedeen, V. J., Wang, R. P., Schmahmann, J. D., Benner, T., Tseng, W. Y., Dai, G., Pandya, D. N., Hagmann, P., D'Arceuil, H., & de Crespigny, A. J. (2008). Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *Neuroimage, 41*(4), 1267-1277. doi:10.1016/j.neuroimage.2008.03.036

Wei, G. X., Dong, H. M., Yang, Z., Luo, J., & Zuo, X. N. (2014). Tai Chi Chuan optimizes the functional organization of the intrinsic human brain architecture in older adults. *Front Aging Neurosci, 6*, 74. doi:10.3389/fnagi.2014.00074

Wei, G. X., Gong, Z. Q., Yang, Z., & Zuo, X. N. (2017). Mind-body practice changes fractional amplitude of low frequency fluctuations in intrinsic control networks.

Front Psychol, 8, 1049. doi:10.3389/fpsyg.2017.01049

Wei, G. X., Xu, T., Fan, F. M., Dong, H. M., Jiang, L. L., Li, H. J., Yang, Z., Luo, J., & Zuo, X. N. (2013). Can Taichi reshape the brain? A brain morphometry study. *PLoS One, 8*(4), e61038. doi:10.1371/journal.pone.0061038

Wichmann, T., & DeLong, M. R. (2006). Deep brain stimulation for neurologic and neuropsychiatric disorders. *Neuron, 52*(1), 197-204. doi:10.1016/j.neuron.2006.09.022

Wichmann, T., & DeLong, M. R. (2013). The Basal Gnaglia. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), *Principles of Neural Science* (5th Edition ed., pp. 982-998): McGraw-Hill Companies, Inc.

Wollesen, B., & Voelcker-Rehage, C. (2013). Training effects on motor–cognitive dual-task performance in older adults. *European Review of Aging and Physical Activity, 11*(1), 5-24. doi:10.1007/s11556-013-0122-z

Wu, M. T., Tang, P. F., Goh, J. O. S., Chou, T. L., Chang, Y. K., Hsu, Y. C., Chen, Y. J., Chen, N. C., Tseng, W. Y., Gau, S. S., Chiu, M. J., & Lan, C. (2018). Task-switching performance improvements after Tai Chi Chuan training are associated with greater prefrontal activation in older adults. *Front Aging Neurosci, 10*(280). doi:10.3389/fnagi.2018.00280

Yeh, G. Y., Chan, C. W., Wayne, P. M., & Conboy, L. (2016). The impact of Tai Chi exercise on self-efficacy, social support, and empowerment in heart failure: Insights from a qualitative sub-study from a randomized controlled trial. *PLoS One, 11*(5), e0154678. doi:10.1371/journal.pone.0154678

Yin, S., Zhu, X., Li, R., Niu, Y., Wang, B., Zheng, Z., Huang, Z., Huo, L., & Li, J. (2014). Intervention-induced enhancement in intrinsic brain activity in healthy older adults. *Sci Rep, 4,* 7309. doi: 10.1038/srep07309

doi:10.6342/NTU201900503

Ystad, M., Hodneland, E., Adolfsdottir, S., Haasz, J., Lundervold, A. J., Eichele, T., & Lundervold, A. (2011). Cortico-striatal connectivity and cognition in normal aging: A combined DTI and resting state fMRI study. *Neuroimage, 55*(1), 24-31. doi:10.1016/j.neuroimage.2010.11.016

Yu, A. P., Tam, B. T., Lai, C. W., Yu, D. S., Woo, J., Chung, K. F., Hui, S. S., Liu, J. Y., Wei, G. X., & Siu, P. M. (2018). Revealing the neural mechanisms underlying the beneficial effects of Tai Chi: A neuroimaging perspective. *Am J Chin Med, 46*(2), 231-259. doi:10.1142/s0192415x18500131

Zahodne, L. B., Nowinski, C. J., Gershon, R. C., & Manly, J. J. (2014). Which psychosocial factors best predict cognitive performance in older adults? *J Int Neuropsychol Soc, 20*(5), 487-495. doi:10.1017/s1355617714000186

Zheng, G., Liu, F., Li, S., Huang, M., Tao, J., & Chen, L. (2015). Tai Chi and the protection of cognitive ability: A systematic review of prospective studies in healthy adults. *Am J Prev Med, 49*(1), 89-97. doi:10.1016/j.amepre.2015.01.002

Zhu, Z., Hakun, J. G., Johnson, N. F., & Gold, B. T. (2014). Age-related increases in right frontal activation during task switching are mediated by reaction time and white matter microstructure. *Neuroscience, 278*, 51-61. doi:10.1016/j.neuroscience.2014.07.076

Zhu, Z., Johnson, N. F., Kim, C., & Gold, B. T. (2015). Reduced frontal cortex efficiency is associated with lower white matter integrity in aging. *Cereb Cortex, 25*(1), 138-146. doi:10.1093/cercor/bht212

APPENDICES

Appendix 1. IRB Approval

國立台灣大學醫學院附設醫院D研究倫理委員會

Research Ethics Committee D
National Taiwan University Hospital
7, Chung-Shan South Road, Taipei, Taiwan, 100,R.O.C
Phone: 2312-3456 Fax: 23951950

臨床試驗/研究許可書

許可日期：2013 年 5 月 9 日

倫委會案號：201212161RIND
計畫名稱：比較太極拳與西方有氧運動改善健康老年人與輕度認知功能障礙老年人認知功能之成效與療效之神經機制：神經認知與神經影像研究。
部門/計畫主持人：國立台灣大學醫學院物理治療學系暨研究所／湯佩芳副教授
計畫文件版本日期：【*計畫書：2013/04/18、中摘：2013/04/18、同意書：2013/4/18、廣告文宣：2013/4/18*】
上述計畫業經 2013 年 3 月 29 日本院 D 研究倫理委員會第 10 次會議審查同意，符合研究倫理規範。本委員會的運作符合優良臨床試驗準則及政府相關法律規章。
本臨床試驗許可書之有效期限為 1 年(自 2013 年 5 月 9 日起至 2014 年 5 月 8 日止)，計畫主持人須依國內相關法令及本院規定通報嚴重不良反應事件及非預期問題，並應於到期日至少 6 週前提出持續審查申請表，本案需經持續審查，方可繼續執行。

主任委員

何弘能

Clinical Trial/Research Approval
National Taiwan University Hospital

Date of approval: May 09, 2013

NTUH-REC No.：201212161RIND
Title of protocol：Comparisons of Cognitive Effect and Its Neural mechanisms of Tai Chi Chuan and Western-style Aerobic Exercises in Healthy Older Adults and Older Adults with Mild Cognitive Impairment: Neurocognitive and Neuroimaging Studies.
Department/ Principle Investigator：National Taiwan University College of Medicine School of Physical Therapy / Dr. Tang, Pei-Fang
Version date of documents：【***Protocol: 2013/04/18 ; Chinese Summary: 2013/04/18 ; ICF: 2013/4/18 ; Advertisement: 2013/4/18***】

The protocol has been approved by the 10th meeting of Research Ethics Committee D of the National Taiwan University Hospital on Mar. 29, 2013. The committee is organized under, and operates in accordance with, the Good Clinical Practice guidelines and governmental laws and regulations.

The duration of this approval is one year (from May 09, 2013 to May 08, 2014). The investigator is required to report Serious Adverse Events and Unanticipated Problems in accordance with the governmental laws and regulations and NTUH requirements, and apply for a continuing review not less than six weeks prior to the approval expiration date.

Hong-Nerng Ho, M.D.
Chairman
Research Ethics Committee D

Hong-Nerng H

doi:10.6342/NTU201900503

Appendix 2. Subject’s Informed Consent Form

國立臺灣大學醫學院附設醫院
National Taiwan University Hospital

臨床試驗/研究受試者說明暨同意書

研究倫理委員會案號：201212161RIND

臨床試驗/研究受試者說明書

您被邀請參與此臨床試驗/研究，這份表格提供您本試驗/研究之相關資訊，本試驗/研究已取得研究倫理委員會審查通過，研究主持人或其授權人員將會為您說明試驗/研究內容並回答您的任何疑問，請您經過慎重考慮後方予簽名。您須簽署同意書後才能參與本試驗/研究。

中文計畫名稱: 比較太極拳與西方有氧運動改善健康老年人與輕度知能障礙老年人認知功能之療效與療效之神經機制:神經認知與神經影像研究

英文計畫名稱: Comparisons of Cognitive Effect and the Underlying Neural Mechanisms of Tai Chi Chuan and Western-style Aerobic Exercises in Healthy Older Adults and Older Adults with Mild Cognitive Impairment: Neurocognitive and Neuroimaging Studies

執行單位：國立臺灣大學物理治療學系暨研究所　　委託單位/藥廠：無
經費來源：國家科學委員會
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※二十四小時緊急聯絡人：湯佩芳　　電話：02-33668128；0919553092

受試者姓名：
性別：　　　出生日期：
病歷號碼：
通訊地址：
聯絡電話：
法定代理人、輔助人或有同意權人之姓名：
與受試者關係：
性別：　　　出生日期：
身分證字號：
通訊地址：
聯絡電話：

doi:10.6342/NTU201900503

一、藥品、醫療技術、醫療器材全球上市現況簡介：

本研究不涉及藥品或醫療技術/器材。

二、試驗/研究目的：

1. 比較 12 週的太極拳與西方有氧運動訓練對健康老年人之認知功能、大腦神經纖維結構完整性、及執行工作記憶任務時腦部活化區域與程度之影響，以了解此兩種運動療效之異同。(研究一)
2. 探討健康老年人在太極拳運動訓練前後與西方有氧運動訓練前後之認知功能的改變與訓練前後大腦神經纖維結構完整性及執行工作記憶任務時腦部活化區域與程度的改變間之相關性，以了解此兩種運動療效之神經機制異同。(研究一)
3. 比較 16 週的太極拳與西方有氧運動訓練對輕度知能障礙老年人之認知功能、大腦神經纖維結構完整性、及執行工作記憶任務時腦部活化區域與程度之影響，以了解此兩種運動之療效異同。(研究二)
4. 探討輕度知能障礙老年人在太極拳運動訓練前後與西方有氧運動訓練前後之認知功能的改變與訓練前後大腦神經纖維結構完整性及執行工作記憶任務時腦部活化區域與程度的改變間之相關性，以了解此兩種運動療效之神經機制異同。(研究二)

三、試驗/研究之主要納入與排除條件：

本研究的研究人員會幫您做評估，並與您討論參加本研究之相關條件。若您符合條件且有意願參加，請您在加入研究前簽署本受試者說明及同意書。以下之研究一適用於沒有從事規律運動且未有認知障礙之社區老年人，研究二適用於輕度知能障礙老年人。

研究一

符合下列條件者適合參加研究一：

1. 年齡在 50 歲-85 歲之間
2. 教育程度 6 年以上或可讀寫中文
3. 認知功能正常(中文(台灣)版蒙特利爾認知評估量表評估分數≥ 26 分及臨床失智評分量表評估分數為 0 分)
4. 無失智症病史
5. 慣用手腳為右手及右腳
6. 無規律運動習慣
7. 良好之視力與聽力(含矯正後)，無色盲

若有下列狀況者，不能參加研究一：

1. 有任何會影響身體活動的神經系統(如中風、巴金森氏症、頭部外傷等)、嚴重肌肉骨骼系統 (如無法獨立行走者)、心肺系統(如心絞痛、心衰竭、心肌梗塞、未控制高血壓)等疾病者
2. 日常生活功能無法完全獨立者(巴氏量表分數< 100 分)
3. 有衰弱傾向者(簡短身體功能量表分數≤ 9 分)
4. 有精神疾病、酒精性腦病變病史等影響認知功能之疾病者
5. 如有以下情形者，可以進行運動訓練，但無法進行磁振造影檢查：有任何無法進行磁振造影評估之禁忌症，包括體內有任何金屬植入(如心律調節器、動脈瘤夾、金屬支架、氣管切開金屬管、骨釘或金屬片等)、癲癇病史、幽閉恐懼症，或不願意接受磁振造影檢查者

研究二

符合下列條件者，適合參加研究二：

1. 年齡在 50 歲-85 歲之間
2. 確診為輕度知能障礙患者，且未被診斷為失智症
3. 教育程度 6 年以上或可讀寫中文
4. 慣用手腳為右手及右腳
5. 無規律運動習慣
6. 良好之視力與聽力(含矯正後)，無色盲

若有下列狀況者，不能參加研究二：

1. 有任何影響身體活動的其他神經系統(如中風、巴金森氏症、頭部外傷等)、嚴重肌肉骨骼系統(如無法獨立行走者)、心肺系統(如心臟病、心肌哽塞、心絞痛及未控制的高血壓等)等疾病者
2. 日常生活功能無法完全獨立者(巴氏量表分數<100 分)
3. 有衰弱傾向者(簡短身體功能量表分數≤9 分)
4. 有精神疾病、酒精性腦病變病史等影響記憶功能之疾病者
5. 如有以下情形者，可以進行運動訓練，但無法進行磁振造影檢查：有任何無法進行磁振造影評估之禁忌症，包括體內無任何金屬植入(如心律調節器、動脈瘤夾、金屬支架、氣管切開金屬管、骨釘或金屬片等)、癲癇病史、幽閉恐懼症，或不願意接受磁振造影檢查者

若您有意願參加本研究，我們將先為您作電話或面試篩選，以確定您符合上述條件。面試篩選將依您的方便在台大醫學院物理治療學系、台大醫院、或耕莘醫院永和分院進行。若您符合上述之條件，我們將邀請您成為本研究計畫之受試者，並簽署此受試者同意書。

四、試驗/研究方法及相關檢驗：

我們將以抽籤方式將您隨機分配至太極拳運動組、西方有氧運動組及控制組。各組詳細的訓練方式如下：

1. 太極拳運動組：
   (1) 研究一：接受為期 12 週，每週 3 次，每次 60 分鐘的太極拳運動訓練，訓練前 6 週以 12 式短版太極拳練習；訓練後 6 週則增加太極拳運動招式，以 24 式長版太極拳練習。每次運動內容包含 10 分鐘的暖身及伸展運動、40 分鐘的太極拳運動、10 分鐘的緩和運動及 10 分鐘休息。訓練時將同時監測心跳、血壓、呼吸速率及血氧濃度。休息後請您完全恢復後再離開運動場所。
   (2) 研究二：接受為期 16 週，每週 3 次，每次 60 分鐘的太極拳運動訓練，訓練前 8 週以 12 式短版太極拳練習；訓練後 8 週則增加太極拳運動招式，以 24 式長版太極拳練習。每次運動內容包含 10 分鐘的暖身及伸展運動、40 分鐘的太極拳運動、10 分鐘的緩和運動及 10 分鐘休息。訓練時將同時監測心跳、血壓、呼吸速率及血氧濃度。休息後請您完全恢復後再離開運動場所。
2. 西方有氧運動組：
   (1) 研究一：接受為期 12 週，每週 3 次，每次 60 分鐘的西方有氧運動訓練。每次運動內容包含 10 分鐘的暖身及伸展運動、40 分鐘的有氧運動(以固定式健身車或跑步機進行訓練)、10 分鐘的緩和運動及 10 分鐘休息。訓練時將同時監測心跳、血壓、呼吸速率及血氧濃度。休息後請您完全恢復後再離開運動場所。
   (2) 研究二：接受為期 16 週，每週 3 次，每次 60 分鐘的西方有氧運動訓練。每次運動內容包含 10 分鐘的暖身及伸展運動、40 分鐘的有氧運動(以固定式健身車或跑步機進行訓練)、10 分鐘的緩和運動及 10 分鐘休息。訓練時將同時監測心跳、血壓、呼吸速率及血氧濃度。休息後請您完全恢復後再離開運動場所。
3. 控制組：
   (1) 研究一：接受為期 12 週，每週 1 次，每次 60 分鐘的靜態衛教課程 (包

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括健康老化相關知識，如疾病管理、情緒紓壓、營養保健等)，不進行任何有關動態活動課程，並於研究期間盡量維持原本的日常生活作息。

(2) 研究二：接受為期 16 週，每週 1 次，每次 60 分鐘的靜態衛教課程 (包括健康老化相關知識，如疾病管理、情緒紓壓、營養保健等)，不進行任何有關動態活動課程，並於研究期間盡量維持原本的日常生活作息。

您會在開始訓練前、12 週或 16 週訓練後，共接受兩次的評估測試，每次測試均包括(1)基本健康狀況調查、(2)認知功能測試、(3)體能測試以及(4)功能性和擴散頻譜磁振造影檢查，前三項測試共需約 2-3 小時，將依您的方便在台大醫學院物理治療學系、台大醫院、或耕莘醫院永和分院進行。而功能性和擴散頻譜磁振造影檢查則會另約一天於台大醫院或政大台灣心智科學腦造影中心進行，耗時大概需要 1 至 1.5 小時。功能性磁振造影檢查時請您平躺在磁振造影(MRI)掃描儀器中，保持清醒與以手按鍵回答問題。磁振造影檢查結果可提供您的大腦構造與活化之資訊。

五、剩餘檢體處理情形：

本研究不採集任何檢體。

六、可能產生之副作用、發生率及處理方法：

1. 於運動訓練介入的過程中，若覺得運動量或運動強度過大無法負荷，請直接與運動指導員反應，我們將依照您的體能狀況做適當的調整；若運動的過程中有感到疲勞或任何身體不適的現象，也請立即與在場的運動指導員報備，並做適度的休息或停止訓練計畫介入，待您完全恢復後再離開運動場所。
2. 磁振造影術(MRI)是一個非常安全、非侵入性的影像技術。不像 X 光，磁振造影術不使用電離輻射，且不具放射線傷害。磁振造影目前已廣泛運用於臨床檢查及健康檢查，是相當安全之臨床常規檢查項目。當掃描器噪音非常大時，將在實驗中提供您適當的聽覺保護用具。
3. 磁振造影掃描當中您若有任何不適，請您隨時用掃描儀內的按鍵或對講機與掃描室外的研究人員聯絡，研究人員會馬上停止掃描，讓您離開掃描儀與掃描室，並等您恢復後再離開臺大醫院。

七、其他替代療法及說明：

本研究不涉及醫療處置。

八、試驗/研究預期效益：

1. 您可以獲得自己的認知與體能狀況，並得知您腦部結構與活化之間相互

關聯之訊息。

2. 在研究過程中，您可隨時撤回同意書，退出實驗，絕不影響醫病關係；計畫主持人和研究人員亦有權中止此研究，屆時您將失去參加研究所附帶之好處。

九、試驗/研究進行中受試者之禁忌、限制與應配合之事項：

當您參與這個研究計畫後，請您不要同時參加其他的訓練計畫或更改服用藥物、以免影響研究結果。若有任何生活作息或藥物更動時，請隨時告訴研究醫師或研究人員。另外，若您是輕度認知功能障礙之患者，麻煩請配合下列之事項：

1. 當您適合也願意參加這個研究計畫時，我們會知會您的主治醫師或家庭醫師，以確認您的身體狀況確實適合參加這個研究計劃。
2. 請您遵照研究醫師及研究人員的指示，並且配合依照規定時間回到門診追蹤及接受訓練、檢查。

在試驗期間發生嚴重疾病或意外事件時，若無法立即聯絡到計畫相關人員，儘可能先至本院急診室就醫，並主動告知醫護人員有加入臨床試驗，亦可請本院總機同仁利用公務手機協尋計畫主持醫師或協同主持醫師。

提醒您，於磁振掃瞄檢查時必須（1）保持頭部不動；（2）不配戴任何金屬物件（如：髮飾、髮夾），磁性物質（如：金融卡、磁碟片）皆請勿配帶；（3）勿化妝（女）、勿用髮油（男），以免檢查中有癢感及干擾影像。

十、機密性：

臺大醫院將依法把任何可辨識您的身分之記錄與您的個人隱私資料視為機密來處理，不會公開。如果發表試驗/研究結果，您的身分仍將保密。您亦瞭解若簽署同意書即同意您的原始醫療紀錄可直接受監測者、稽核者、研究倫理委員會及主管機關(若試驗受美國食品藥物管理局管轄，則主管機關包含美國食品藥物管理局)檢閱，以確保臨床試驗/研究過程與數據符合相關法律及法規要求；若試驗受美國食品藥物管理局管轄，則試驗結果將公佈於一個公開的臨床試驗資訊網站：Clinicaltrials.gov.，但您的個人資料仍將保密。上述人員並承諾絕不違反您的身分之機密性。

十一、損害補償與保險：

(一) 如依本研究所訂臨床試驗/研究計畫，因而發生不良反應造成損傷，由研究主持人負補償責任。但本受試者同意書上所記載之可預期不良反應，不予補償。

(二) 如依本研究所訂臨床試驗/研究計畫，因而發生不良反應或損害，本醫院願意提供專業醫療照顧及醫療諮詢。您不必負擔治療不良反應或傷害之必要醫療費用。

(三) 除前二項補償及醫療照顧外，本研究不提供其他形式之補償。若您不願意接

受這樣的風險，請勿參加試驗/研究。

(四) 您不會因為簽署本同意書，而喪失在法律上的任何權利。

十二、受試者權利：

(一) 試驗/研究過程中，與您的健康或是疾病有關，可能影響您繼續接受臨床試驗/研究意願的任何重大發現，都將即時提供給您。

(二) 本試驗/研究已經過本院研究倫理委員會審查，並已獲得核准。本院研究倫理委員會委員由醫事專業人員、法律專家、社會工作人員及其他社會公正人士所組成，每月開會一次，審查內容包含試驗/研究之利益及風險評估、受試者照護及隱私保護等。如果您在試驗/研究過程中對試驗/研究工作性質產生疑問，對身為患者之權利有意見或懷疑因參與研究而受害時，可與本院之研究倫理委員會聯絡請求諮詢，其電話號碼為： (02)2312-3456 轉 63155。

(三) 為進行試驗/研究工作，在試驗事項上您必須接受計畫主持人或協同主持人：湯佩芳 副教授/ 邱銘章 副教授/ 曾文毅 教授/ 方識欽 醫師 的照顧。如果您現在或於試驗/研究期間有任何問題或狀況，請不必客氣，可與 湯佩芳 副教授 聯絡(24 小時聯繫電話：0919-553-092 或 (02)33668128)。

本同意書一式 2 份，醫師已將同意書副本交給您，並已完整說明本研究之性質與目的。計畫主持人或協同主持人： 湯佩芳 已回答您有關試驗/研究的問題。

(五) 本研究預期不會衍生專利權或其他商業利益。

十三、試驗/研究之退出與中止：

您可自由決定是否參加本研究；研究過程中也可隨時撤銷同意，退出研究，不需任何理由，且不會引起任何不愉快或影響日後醫師對您的醫療照顧。計畫主持人亦可能於必要時中止該研究之進行。

若您在研究過程中途選擇退出，其之前被收集的資料仍將繼續保留且維護您的隱私及個人資料機密性，並不再繼續研究訓練及測試；若研究仍需持續收集資料，則當您退出後我們會先徵詢您的同意才會繼續向您收集資料。

主要主持人、協同主持人已詳細解釋有關本研究計畫中上述研究方法的性質與目的，及可能產生的危險與利益。

主要主持人/協同主持人簽名：____________________________

日期：西元 ________年 _______月 _______日

臨床試驗/研究受試者同意書

受試者：______________，已詳細瞭解上述研究方法及其所可能產生的危險與利益，有關本試驗/研究計畫的疑問，業經計畫主持人詳細予以解釋。本人同意接受為臨床試驗/研究計畫的自願受試者。

受試者簽名：____________________

日期：西元 _______年 ______月 ______日

法定代理人簽名：____________________

日期：西元 _______年 ______月 ______日

* 受試者為無行為能力(未滿七歲之未成年人者或受監護宣告之人)，由法定代理人為之；受監護宣告之人，由監護人擔任其法定代理人。

* 受試者為限制行為能力者(滿七歲以上之未成年人)，應得其本人及法定代理人之同意。

輔助人或有同意權人簽名：______________________

與受試者之關係（請圈選）：本人、配偶、父、母、兒、女、其他：_________

日期：西元 _______年 ______月 ______日

* 受試者因精神障礙或其他心智缺陷，致其為意思表示或受意思表示，或辨識其意思表示效果之能力，顯有不足，而受法院之輔助宣告者，應得輔助人之同意。

* 受試者雖非無行為能力或限制行為能力者，但因意識混亂或有精神與智能障礙，而無法進行有效溝通和判斷時，由有同意權之人為之。前項有同意權人為配偶及同居之親屬。

見證人 1： ___________________（簽名） **見證人 2：**______________________（簽名）

見證人 1 身分證字號：_______________ **見證人 2 身分證字號：**_______________

聯絡電話： 聯絡電話：

通訊地址： 通訊地址：

日期：西元 _______年 ______月 ______日 日期：西元 _______年 ______月 日

*受試者、法定代理人、輔助人或有同意權之人皆無法閱讀時，應由見證人在場參與所有有關受試者同意之討論。並確定受試者、法定代理人、輔助人或有同意權之人之同意完全出於其自由意願後，應於受試者同意書簽名並載明日期。試驗/研究相關人員不得為見證人。

*若意識清楚，但無法親自簽具者且無親屬或關係人在場，得以按指印代替簽名，惟應有二名見證人。

Appendix 3. Subject’s Basic Information Survey

基本資料調查

受試者姓名：_________
受試者編號：_____________ 性別：男／女　出生日期：
年齡：__歲　身高：__公分　體重：__公斤　BMI：______
慣用手：__慣用腳：________
血壓：Rest__/ mmHg; 心跳：Rest/exercise________bpm;
呼吸速率：Rest_______/min.
地址：___________________________　電話：__
居住環境：社區／安養院；獨棟式／大廈／公寓：_____樓；電梯：有／無
居住狀況：□自己家□親戚朋友家□宿舍　　□安養中心□其他_________
共同居住者：□獨居□配偶□兒女□朋友□看護□其他_ ___
心肺耐力：□可連續行走60分鐘以上□可連續行走30~60分鐘□可連續行走10~30分鐘□只可連續行走5~10分鐘□其他
每週運動量：□無□有；運動頻率：____(次/週)；運動期間：_____(分鐘/次)太極氣功18式
教育程度：□不識字□識字□小學□國中□高中□大學/學院□碩士以上
職業：□沒有□退休□勞工□公務員□農□商□其他_________________
醫療病史(含住院及急診)：□高血壓□糖尿病□心房震顫□心臟疾病□其他____________
就診醫院：________________________________ 醫師：___________________________
病歷號碼/身分證字號：________________________/_____
最近是否因任何疾病接受醫療或手術？（有／[✓ 無]）_____
A.　請問您是否有下述各項情形，並且請填寫空格：

有　無
01. □　□　您曾經認為自己有幽閉恐懼症嗎?
02. □　□　您曾經有失去意識、暈昏、癲癇、痙攣、抽蓄或周期性偏頭痛嗎？
如果有，何時(起始)__________何地____________，為什麼/處理與現況
03. □　□　您有出現神經系統疾病嗎？例如：中風、痲痹、帕金森氏症。
如果有，何時(起始)______，是什麼/處理與現況__________________
04. □　□　您曾經有因頭部受傷而失去意識或感染(腦炎)而造成顱內壓力上升嗎?
如果有，何時(起始)__________何地____________，為什麼/處理與現況
05. □　□　您有出現骨科系統疾病嗎？例如：關節炎、腰背痛、骨折。
如果有，何時(起始)______，是什麼/處理與現況__________________
06. □　□　您有出現心臟問題嗎？例如：高血壓、心律不整。
如果有，何時(起始)______，是什麼/處理與現況__________________
07. □　□　您有癲癇的家族史嗎?
08. □　□　您有糖尿病嗎？如果有，何時(起始)________，控制情形如何________
09. □　□　您曾經有在心臟中置入過任何東西嗎?
如果有，何時(起始)______，是什麼/處理與現況__________________
10. □　□　您有任何金屬在您的身體中嗎?(心臟起搏器、匙形植入管、植入的醫療泵浦、金屬板、金屬夾、別針、金屬尺、人工關節、彈丸、等等…。)
如果有，何時(起始)______，是什麼/處理與現況__________________

doi:10.6342/NTU201900503

11. □　□ 您有佩帶假牙、牙齒校正器、或不可移動的正牙保留器嗎?
(補牙沒關係)。
如果有，何時(起始)______，是什麼/處理與現況__________________

12. □　□ 您有出現呼吸系統問題嗎？例如：氣喘、呼吸困難。
如果有，何時(起始)______，是什麼/處理與現況__________________

13. □　□ 您曾經被診斷有心理方面的疾病嗎?
如果有，何時(起始)______，是什麼/處理與現況__________________

14. □　□ 您曾經有過(或認為您需要) 酒精或濫用毒品的治療嗎?
如果有，何時(起始)______，是什麼/處理與現況__________________

15. □　□ 您有抽香菸或雪茄? 如果有，您已經抽幾年菸了? __________
每天平均抽多少根香菸? ________ 每天抽多少根雪茄? _______

16. □　□ 您喝酒嗎? 如果有，每星期平均喝多少酒?______________

17. □　□ 您有視覺問題嗎？如果有，何時(起始)_____是什麼/處理與現況_____

18. □　□ 您有戴眼鏡或隱形眼鏡嗎？
請選一個或兩者均有: ___眼鏡 ____ 隱形眼鏡
如果有，您是: ____近視 __遠視 ____老花；度數：____

19. □　□ 您有其他不能用眼鏡校正的視覺問題嗎，如色盲或散光? ____

20. □　□ 您有聽覺問題嗎？如果有，何時(起始)_____是什麼/處理與現況_____

21. □　□ 您有出現暈眩、耳鳴的症狀嗎？
如果有，何時(起始)______，是什麼/處理與現況__________________

22. □　□ 有出現無法控制之動作嗎？如果有，何時(起始)_________

23. □　□ 您有出現平衡困難，例如滑倒、絆倒、跌倒嗎？
如果有，在何種情況____________。在過去一年中出現的次數______

24. □　□ 請問您是否容易注意力不集中？

25. □　□ 請問您是否對最近的事情時常記不起來？

26. □　□ 請問您目前是否有規律服用藥物？包含哪些？
□降血壓藥物□降血糖藥物□心臟血管用藥□利尿劑□感冒藥
□口服避孕藥□鎮定劑□安眠藥□抗精神藥物□抗痙攣藥物
□抗過敏藥□維他命□健康食品□中藥__________________________
□其他_______________
□服用之藥物劑量多少？____________________

27. □　□請問這些藥對您是否有副作用？為何__________________________

28. □　□有無睡眠問題?___________小時/天_______是/否易醒?_________

29. □　□是陌生環境是否易緊張?

Appendix 4. Edinburgh Handedness Inventory

愛丁堡慣用手量表

	左	右	無慣用	不清楚
什麼是您的慣用手?				
母親的慣用手:				
父親的慣用手:				

	左	右	無慣用	不清楚
外婆:				
外公:				
祖母:				
祖父:				

您的兄弟和姐妹有多少是慣用左手的?_____ 多少是慣用右手的? ______

您的孩子有多少是慣用左手的? _____________ 多少是慣用右手的? _________

以下活動，請在最適當的格子中勾選您最常用的情況。有些活動需要兩隻手。在這些情況下活動的哪部份，或對象，或慣用哪隻手要表明在格子裡。"從未用右" 和"從未用左" 是您在強迫的情況下才會去使用的。請回答下列所有問題。

活動	只用左從未用右 (-2)	喜歡用左 (-1)	無慣用 (0)	喜歡用右 (1)	只用右從未用左 (2)
寫字					
繪畫					
投球					
拿剪刀					
拿牙刷					
拿菜刀					
拿湯匙					
拿帚把（上面的那隻手）					
點火柴					
開盒子（蓋子）					

以下不納入計分：

踢球用的腳					
單眼看東西（如:照相機，望遠鏡）					

計分方式 (只加前 10 題) **總分 LQ = ____________**

laterality quotient (LQ) = (sum of |R|- sum of |L|)/(sum of |R| + sum of |L|)x 100%

LQ ≥ 60: 右手慣用手；LQ ≤ - 60: 左手慣用手

-60 < LQ < 60: 雙手皆可

出處：Oldfield RC. (1971). *Neuropsychologia, 9*(1), 97-113.
Isaacs K. L. et al. (2006). *Neurology*, 66, 1855-1858.

Appendix 5. Waterloo Footedness Questionnaire-revised

滑鐵盧慣用腳問卷修正版

問卷說明：請盡量選取最適合的選項回答下列問題。若您總是使用某側腳執行此活動，請選擇“總是左腳”或“總是右腳”。若您較經常使用某側腳執行此活動，請選擇“經常是左腳”或“經常是右腳”。若您使用兩腳執行此活動的機會相同，請選擇“兩腳機會相同”。請想像執行每一個活動時的情況來選擇最適合的答案，避免以同一個答案回答所有問題。若有需要可以暫停作答並試著執行該活動。

	總是左腳	經常是左腳	兩腳機會相同	經常是右腳	總是右腳
1. 您會用哪側腳踢您前方一顆靜止不動的球？	□	□	□	□	□
2. 若要單腳站，您會用哪側腳站立？	□	□	□	□	□
3. 若在沙灘上，您會用哪側腳推沙？	□	□	□	□	□
4. 若要站到一張椅子上，您會將哪側腳先放到椅子上？	□	□	□	□	□
5. 您會用哪側腳踩一個快速移動的蟲子？	□	□	□	□	□
6. 您會用哪側腳站在火車鐵軌上並保持平衡？	□	□	□	□	□
7. 若要用腳趾撿起一顆彈珠，您會用哪側腳？	□	□	□	□	□
8. 若要單腳跳，您會用哪側腳？	□	□	□	□	□
9. 你會用哪側腳幫忙將鐵鏟插入地面？	□	□	□	□	□
10. 當放鬆站立時，通常會以一側腳支撐大部分的重量，而讓另一側腳放鬆微彎，您會先以哪側腳來支撐大部分的重量？	□	□	□	□	□
11. 是否有任何原因(例如: 受傷)造成您在執行以上活動時改變用腳的習慣？	有	無	(請圈選)		
12. 您是否曾接受特別的訓練或鼓勵而使用特定腳來執行某個活動？	有	無	(請圈選)		
13. 如果您11或12題的答案為“有”，請解釋: ________					
總分 = ________					

計分方式

總是左腳	經常是左腳	兩腳機會相同	經常是右腳	總是右腳
-2	**-1**	**0**	**1**	**2**

共有 10 項題目。總分為正分表慣用腳為右腳；負分表慣用腳為左腳；0 分表兩腳使用機會相同

出處：Elias LJ et al. (1998) Neuropsychologia, 36:37-43

Appendix 6. Color Trails Tests-Parts 1 and 2

彩色路徑描繪測驗

方法：請受試者依照指導語完成測驗，紀錄所花費總時間、提示次數、錯誤次數

Part A：“這個測試是要請您做數字連連看，從 1 開始，請按照數字的順序連接，連線要連在框框中，速度越快越好，筆不要離開紙面。”

練習：①→②→③→④→⑤→⑥→⑦→⑧

Part B：先讓受試者看圖面上有兩種顏色的圓圈，上面有數字，之後請受試者“請從紅色的數字①開始，連接到黃色的數字②，再連到紅色的③，之後連到黃色的數字④，依此類推。連線要連在框框中，速度越快越好，筆不要離開紙面。”

練習：①（紅）→②（黃）→③（紅）→④（黃）→⑤（紅）→⑥（黃）→⑦（紅）→⑧（黃）

注意事項：

1. 測試開始時，先將起始與終點的數字位置指給受試者看。
2. 記錄時間自受試者準備好，將筆放在測驗紙上開始計時。
3. 當順序連接錯誤時，請受試者回到上一個正確的數字框中，重新開始連接
4. 當連接數字與數字間，受試者停頓超過 10 秒鐘，測試者可給予提示，指出正確位置，請受試者連接

評估工具：測驗紙、筆、碼錶

	Part 1		**Part 2**	
		備註		備註
總時間	___ min __ sec		___ min __ sec	
提示次數	_______次		_______次	
錯誤次數	_______次		_______次	

說明：

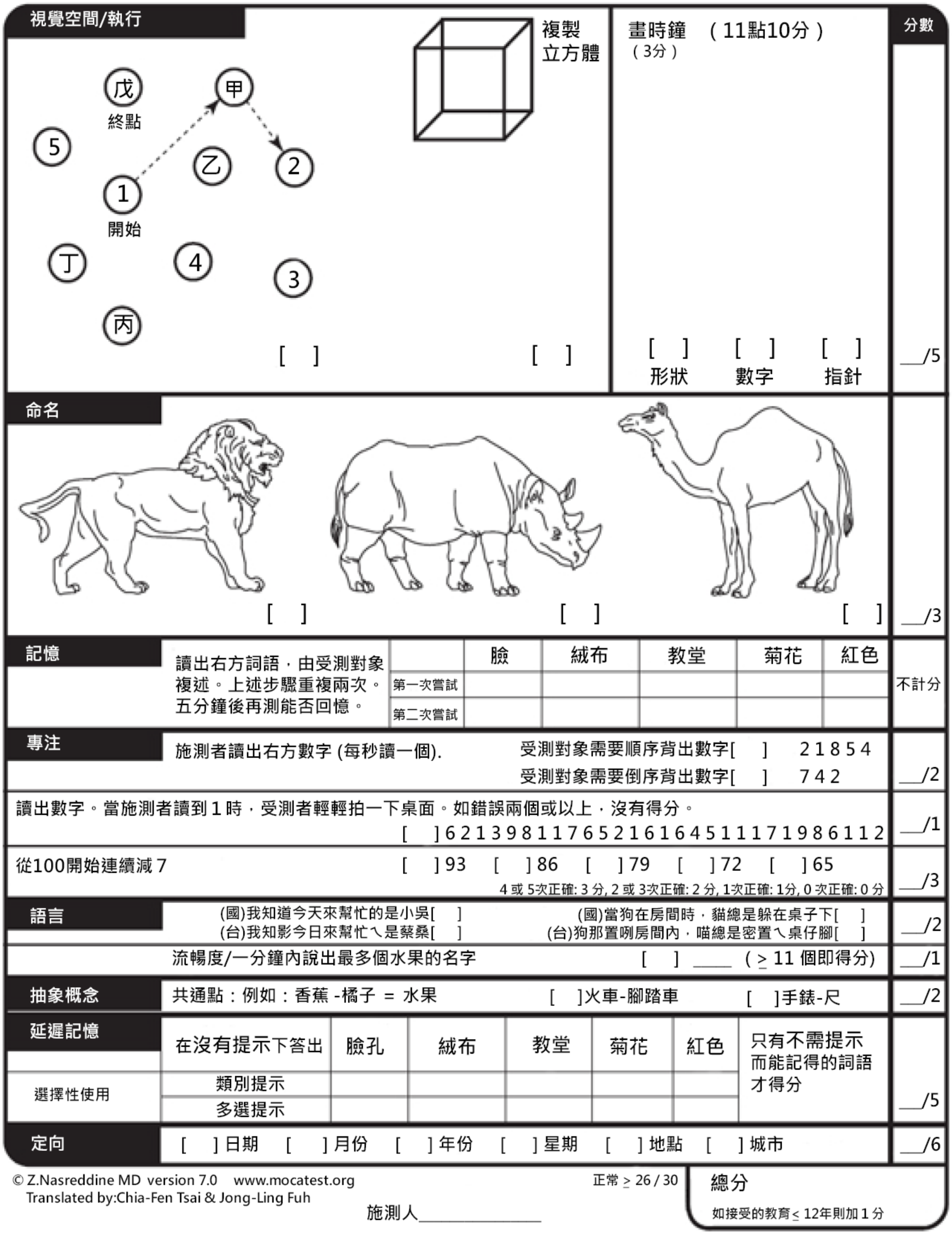
1. 次數記錄可先以正字標記，之後再總結次數

2. 備註欄中可記錄提示時或錯誤時的數字

（參照 D'Elia LF et al. (1996) Color Trails Test. USA: Psychological Assessment Resources）

Appendix 7. Montreal Cognitive Assessment

中文(台灣)版蒙特利爾認知評估量表 MoCA



視覺空間/執行

[ ] [ ]

複製立方體

畫時鐘 （11點10分）（3分）

[ ] 形狀 [ ] 數字 [ ] 指針

分數 __/5

命名

[ ] [ ] [ ] __/3

記憶

讀出右方詞語，由受測對象複述。上述步驟重複兩次。五分鐘後再測能否回憶。

	臉	絨布	教堂	菊花	紅色
第一次嘗試					
第二次嘗試					

不計分

專注

施測者讀出右方數字 (每秒讀一個).

受測對象需要順序背出數字[ ] 2 1 8 5 4

受測對象需要倒序背出數字[ ] 7 4 2 __/2

讀出數字。當施測者讀到 1 時，受測者輕輕拍一下桌面。如錯誤兩個或以上，沒有得分。

[ ] 6 2 1 3 9 8 1 1 7 6 5 2 1 6 1 6 4 5 1 1 1 7 1 9 8 6 1 1 2 __/1

從100開始連續減 7 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 或 5次正確: 3 分, 2 或 3次正確: 2 分, 1次正確: 1分, 0 次正確: 0 分 __/3

語言

(國)我知道今天來幫忙的是小吳[ ]

(台)我知影今日來幫忙ㄟ是蔡桑[ ]

(國)當狗在房間時，貓總是躲在桌子下[ ]

(台)狗那置咧房間內，喵總是密置ㄟ桌仔腳[ ] __/2

流暢度/一分鐘內說出最多個水果的名字 [ ] ____ (≥ 11 個即得分) __/1

抽象概念

共通點：例如：香蕉 -橘子 = 水果 [ ]火車-腳踏車 [ ]手錶-尺 __/2

延遲記憶

	在沒有提示下答出	臉孔	絨布	教堂	菊花	紅色	只有不需提示而能記得的詞語才得分
選擇性使用	類別提示						
	多選提示						

__/5

定向

[ ] 日期 [ ] 月份 [ ] 年份 [ ] 星期 [ ] 地點 [ ] 城市 __/6

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Translated by:Chia-Fen Tsai & Jong-Ling Fuh

正常 ≥ 26 / 30

總分

如接受的教育 ≤ 12年則加 1 分

施測人______________

出處：蔡佳芬、傅中玲 (2010)。蒙特利爾認知評估(台灣版)，取自 http://www.mocatest.org/

doi:10.6342/NTU201900503

Appendix 8. Mini-Mental State Examination

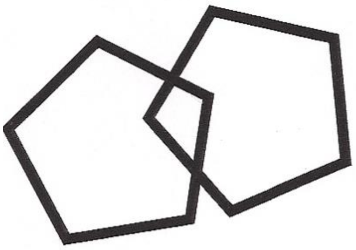
簡易心智量表(MMSE)

(準備項目: 手錶.鉛筆.白紙.)，或由於__________無法施測

項目	問題	得分
I、 定向感(共 10 分) 1. 時間（5 分）：____年____月____日，星期____，____季節 2. 地方（5 分）：____市_____大學_____路______大樓____樓		I-1. /5 I-2. /5
II、 注意力(共 8 分) 1. 訊息登錄（3 分）：腳踏車 快樂 紅色 2. 系列減七（5 分）：100-7 93 86 79 72 65		II-1. /3 II-2. /5
III、記憶(共 3 分)：腳踏車 快樂 紅色		III. /3
IV、 語言(共 5 分) 1. 命名（2 分）：錶 筆 2. 覆誦（1 分）：白紙真正寫黑字 3. 閱讀理解（1 分）：請閉上眼睛 4. 書寫造句（1 分）：（含文意，多於三個字）		IV-1. /2 IV-2. /1 IV-3. /1 IV-4. /1
V、 口語理解及行用能力(共 3 分)： 用左（右）手拿紙 折成一半 再交給我		V-1. /3
VI、 建構力（1 分）：圖形抄繪 請受試者看此圖，並在隔壁空位劃下這個圖形		VI-1. /1
	總分	/30

(譯自 Folstein et al. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*, *12*(3), 189-198.)

請閉上眼睛



Appendix 9. Instrumental Activities of Daily Living

工具性日常生活活動能力量表(IADL)

1. 上街購物【□ 不適用 (勾選“不適用”者，此項分數視為滿分)】 □3.獨立完成所有購物需求 □2.獨立購買日常生活用品 □1.每一次上街購物都需要有人陪 □0.完全不會上街購物	**勾選 1.或 0.者，列為失能項目。**
2. 外出活動【□ 不適用 (勾選“不適用”者，此項分數視為滿分)】 □4.能夠自己開車、騎車 □3.能夠自己搭乘大眾運輸工具 □2.能夠自己搭乘計程車但不會搭乘大眾運輸工具 □1.當有人陪同可搭計程車或大眾運輸工具 □0.完全不能出門	**勾選 1.或 0.者，列為失能項目。**
3. 食物烹調【□ 不適用 (勾選“不適用”者，此項分數視為滿分)】 □3.能獨立計畫、烹煮和擺設一頓適當的飯菜 □2.如果準備好一切佐料，會做一頓適當的飯菜 □1.會將已做好的飯菜加熱 □0.需要別人把飯菜煮好、擺好	**勾選 0.者，列為失能項目。**
4. 家務維持【□ 不適用 (勾選“不適用”者，此項分數視為滿分)】 □4.能做較繁重的家事或需偶爾家事協助（如搬動沙發、擦地板、洗窗戶） □3.能做較簡單的家事，如洗碗、鋪床、疊被 □2.能做家事，但不能達到可被接受的整潔程度 □1.所有的家事都需要別人協助 □0.完全不會做家事	**勾選 1.或 0.者，列為失能項目。**
5. 洗衣服【□ 不適用 (勾選“不適用”者，此項分數視為滿分)】 □2.自己清洗所有衣物 □1.只清洗小件衣物 □0.完全依賴他人	**勾選 0.者，列為失能項目。**
6. 使用電話的能力【□ 不適用 (勾選“不適用”者，此項分數視為滿分)】 □3.獨立使用電話，含查電話簿、撥號等 □2.僅可撥熟悉的電話號碼 □1.僅會接電話，不會撥電話 □0.完全不會使用電話	**勾選 1.或 0.者，列為失能項目。**
7.服用藥物【□ 不適用 (勾選“不適用”者，此項分數視為滿分)】 □3.能自己負責在正確的時間用正確的藥物 □2.需要提醒或少許協助 □1.如果事先準備好服用的藥物份量，可自行服用 □0.不能自己服用藥物	**勾選 1.或 0.者，列為失能項目。**

doi:10.6342/NTU201900503

8.處理財務能力【□ 不適用 (勾選“不適用”者，此項分數視為滿分)】 □2.可以獨立處理財務 □1.可以處理日常的購買，但需要別人協助與銀行往來或大宗買賣 □0.不能處理錢財	**勾選 0.者，列為失能項目。**
（註：上街購物、外出活動、食物烹調、家務維持、洗衣服等五項中有三項以上需要協助者即為輕度失能）	

出處：Lawton, M. P.,and Brody, E. (1969) Gerontologist , 9(3),179-186.
中文版：衛生福利部(2013)。服務個案評估量表及申請書

doi:10.6342/NTU201900503

Appendix 10. Clinical Dementia Rating

臨床失智評量表 CDR

總分：__________
給分邏輯：___________

	0	0.5	1	2	3
M					
O					
JPS					
CA					
HH					
PC					

一、在不熟悉的地方會迷路
二、工作表現或家事能力變差
三、使用字或命名上有困難
四、對讀過或看過的書報或電視內容記得很少
五、對剛介紹過的人記不起名字
六、遺失或找不到貴重東西（錢、重要證件）
七、在檢查時顯得注意力無法集中
八、不能記住幾天前的談話
九、財物處理能力減退

	Health CDR 0	Questionable CDR 0.5	Mild CDR 1	Moderate CDR 2	Severe CDR 3
Memory	*無記憶喪失 *偶爾遺忘	*輕微的遺忘 *回憶片段 *良性的遺忘	*對最近事物時常遺忘 *影響日常活動	*嚴重記憶喪失 *只記得很熟的事物 *無法記得新事物	*嚴重記憶喪失 *只有片段記憶
Orientation	*人、事、地定位正常	*除了對時間順序稍微有困難外，均正常	*時間順序有問題 *對人地定位正常 *有時會找不到路	*對時、地定位經常有問題	*只有人的定位正常
Judgment & Problem solving	*處理日常事物合宜 *判斷合宜	*對解決問題和事物之異同似乎有障礙	*處理複雜事物有困難 *社交判斷仍合宜	*解決問題和事物之異同有明顯困難 *社交判斷障礙	*無法做判斷或解決問題
Community affairs	*獨立處理工作，購物，生意，財務，正常生活	*對上述活動有疑似或輕度障礙	*雖參與上述活動但無法獨立，偶而仍有正常表現	*無法獨立勝任家庭外的事物 但外表看來正常	但外表看來即有病態
Home & hobbies	*家庭生活，嗜好及智力興趣仍維持	*對上述活動偶而有障礙	*家中功能有輕微但確實障礙 *放棄複雜外務，嗜好，興趣	*只保留簡單外務 *侷限的興趣勉強維持	*整天在自己房間
Personal care	*有自我照顧的能力		*需要時常的提醒	*在穿衣，個人衛生及個人情緒需要協助	*個人衛生失禁需要專人協助
CDR 4 Profound	說話無法理解或不相關；無法理解或遵照簡單指示；偶爾認得配偶或照顧者。 用手而較少使用器具進食，須人幫忙；大小便經常失禁，在扶助下可走幾步； 大部分時間無法行動；甚少外出；常有無目的的動作。				
CDR 5 Terminal	無法理解或沒有反應。無法辨認家人，需人餵食，可能會有吞嚥困難而需使用鼻管餵食。大小便失禁。臥床，無法坐立，站立，肢體收縮。				

註：如於兩格中無法決定選哪一格，請圈嚴重者

(出處：林克能、劉秀枝(2003)。臨床失智評量表. [Clinical Dementia Rating (CDR), Chinese Version]. *Acta Neurol Taiwan, 12*(3), 154-165.)

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Appendix 11. Geriatric Depression Scale-15

老人憂鬱短版量表

(Geriatric Depression Scale 15-item short-form)

以下的問題是人們對一些事物的感受，答案沒有對與不對。在過去一星期內，你是否曾有以下的感受。如有的話，請√「是」，若無的話，請√「否」。

	是	否
1. 你基本上對自己的生活感到滿意嗎?		▨
2. 你是否已放棄了很多以往的活動和嗜好?	▨	
3. 你是否覺得生活空虛?	▨	
4. 你是否常常感到煩悶?	▨	
5. 你是否常常感到心情愉快呢?		▨
6. 你是否害怕將會有不好的事情發生在你身上呢?	▨	
7. 你是否大部份時間感到快樂呢?		▨
8. 你是否常常感到無助? (即是沒有人能幫自己)	▨	
9. 你是否寧願晚上留在家，而不愛出外做些有新意的事情? (如：和家人到一間新開張餐館吃晚飯)	▨	
10.你是否覺得你比大多數人有多些記憶的問題呢?	▨	
11.你認為現在活著是一件好事嗎?		▨
12.你是否覺得自己現在是一無是處呢?	▨	
13.你是否感到精力充足?		▨
14.你是否覺得自己的處境無望?	▨	
15.你覺得大部份人的境況比自己好嗎?	▨	
總分		

給予一分如以下題目，√「是」: 2, 3, 4, 6, 8, 9, 10, 12, 14, 15
給予一分如以下題目，√「否」: 1, 5, 7, 11, 13
(給予一分題目皆以灰階標記)

得分越高顯示受訪者的抑鬱狀況越明顯。
總分達 8 分或以上，顯示受訪者可能有抑鬱症，須轉介老人精神科做進一步診斷及評估。

(譯自 Sheikh and Yesavage (1986), Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. Clinical Gerontologist; 5: 165-173.)

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Appendix 12. Physical Activity Scale for the Elderly

高齡者身體活動評量表(PASE)

本問卷是關於您目前身體活動及運動的程度，沒有對或錯的答案。只是評估您目前的活動程度。

休閒時間活動

1. 過去7天，你並非特別為了運動而走路到戶外的頻率？如工作、上課、溜狗或其他目的。每週幾天？
   1. 從不 (往第2題)
   2. 很少 (1-2天)
   3. 有時 (3-4天)
   4. 常常 (5-7天)

   平均而言，你每天花多少時間走路到戶外？幾小時？
   1. 低於1小時
   2. 1小時但低於2小時
   3. 2-4小時
   4. 超過4小時

2. 過去7天，你從事輕度運動或休閒活動的頻率？如保齡球、高爾夫、釣魚或其他感覺輕鬆的休閒活動。每週幾天？
   1. 從不 (往第3題)
   2. 很少 (1-2天)
   3. 有時 (3-4天)
   4. 常常 (5-7天)

   這些活動為何?________________

   平均而言，你每天花多少時間在輕度運動或休閒活動上？幾小時？
   1. 低於1小時
   2. 1小時低於2小時
   3. 2-4小時
   4. 超過4小時

3. 過去 7 天，你從事中度運動或休閒活動？如網球、跳舞或其他感覺中度費力的休閒活動。每週幾天？
    1. 從不 (往第 4 題)
    2. 很少 (1-2 天)
    3. 有時 (3-4 天)
    4. 常常 (5-7 天)

    這些活動為何？________________

    平均而言，你每天花多少時間從事中度運動或休閒活動？幾小時？
    1. 低於 1 小時
    2. 1 小時但低於 2 小時
    3. 2-4 小時
    4. 超過 4 小時

4. 過去 7 天，你從事劇烈的運動或休閒活動的頻率？如慢跑、游泳、有氧舞蹈、腳踏車、籃球或其他感覺非常費力的休閒活動。每週幾天？
    1. 從不 (往第 5 題)
    2. 很少 (1-2 天)
    3. 有時 (3-4 天)
    4. 常常 (5-7 天)

    這些活動為何？________________
    (註：若是外出輕鬆騎腳踏車代步、水中走路輕鬆游泳等，不算此類運動；詢問長者的費力狀況是否感到該活動「非常費力」才視為此類運動)

    平均而言，你每天花多少時間從事劇烈運動或休閒活動？幾小時？
    1. 低於 1 小時
    2. 1 小時但低於 2 小時
    3. 2-4 小時
    4. 超過 4 小時

5. 過去 7 天，你從事爲了增加肌力或肌耐力運動的頻率？如提重物、伏地挺身、拉單槓或其他運動。每週幾天？
    1. 從不 (往第 6 題)
    2. 很少 (1-2 天)
    3. 有時 (3-4 天)
    4. 常常 (5-7 天)

    這些活動為何？________________

    平均而言，你每天花多少時間從事增加肌力或肌耐力的運動？幾小時？
    1. 低於 1 小時
    2. 1 小時但低於 2 小時
    3. 2-4 小時
    4. 超過 4 小時

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工作相關活動

6. 過去7天，你工作賺錢或是做義工的頻率？(除了以坐姿及些微手部動作為主，如輕鬆的辦公室職務、電腦職務、開車等的工作之外) 每週幾天？
   1. 從不 (往第7題)
   2. 很少 (1-2天)
   3. 有時 (3-4天)
   4. 常常 (5-7天)

   你一星期總共花多少時間工作賺錢或是做義工？__________小時

家庭活動

7. 過去7天，你是否有執行輕度的家事？如掃地、洗碗。
   0. 沒有
   1. 有

8. 過去7天，你是否有執行吃力的家事或雜務？如吸地板、擦地板、洗窗戶、牆壁或其他活動。
   0. 沒有
   1. 有

9. 過去7天，你是否有執行家庭修理的工作？如木工、油漆、修傢俱、修電器或其他工作。
   0. 沒有
   1. 有

10. 過去7天，你是否有執行庭院、草坪或栽種盆栽的工作？如鋤草、除落葉、修剪樹枝或其他工作。(注意：室內種植少數量盆栽的澆水活動不列入此類活動)
    0. 沒有
    1. 有

11. 過去7天，你是否有執行戶外園藝的工作？
    0. 沒有
    1. 有

12. 過去7天，你是否有照顧其他人？如小孩、老年人、或其他身體功能不便的人。
    0. 沒有
    1. 有

譯自：Washburn et al. (1993) J Clin Epidemiol, 46: 153-162.

Appendix 13. Eyes Opened One-Leg Stance Test

睜眼單腳站立測試

方法：赤腳，雙手自然垂掛，以慣用腳站立，另一腳離地，眼睛張開站立。

紀錄：

1. 記錄可以維持站立平衡的時間，計時開始是以腳離地開始，當站立腳開始位移、或彎曲腳著地、或以彎曲腳支撐（靠著）站立腳時，計時終止。
2. 測試 5 次，5 次內可以達到 30 秒，則紀錄為 30 秒；若不到 30 秒，則在 5 次測試中選擇最好的成績。最長紀錄 30 秒。

評估工具：碼錶

注意事項：需注意受試者的安全，必要時使用保護帶

	前測	**後測**
日期(20YY/MM/DD) / 施測者		
站立腳	右腳 / 左腳	右腳 / 左腳
測試 1 (sec)		
測試 2 (sec)		
測試 3 (sec)		
測試 4 (sec)		
測試 5 (sec)		
備註		

（譯自 Bohannon et al.,Phys Ther 1984;64:1067-1070.）

【紀錄提醒】：取 5 次測試中最佳的成績；若其中 1 次已達 30 秒最佳成績，即測試結束，無需再重複測試。

Appendix 14. Four Square Step Test

四方踏步測試

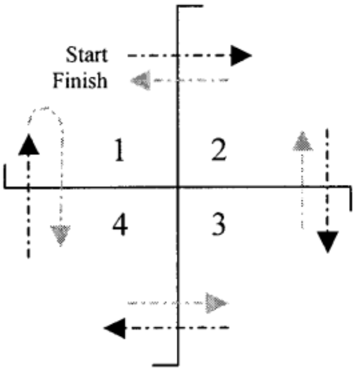
方法：

1. 使用四支拐杖，如圖示擺設
2. 讓受試者站在「1」的位置，面對「2」，請受試者依照 1→2→3→4→1→4→3→2→1 順序移動
3. 請受試者移動時，動作越快越好，但不可以碰到拐杖，兩隻腳均需踏到同一格後再繼續移動，踏步時眼睛盡量看前面不要低頭
4. 先示範一次給受試者看，再請受試者練習一次
5. 測試兩次，取最好的成績，若過程中有碰到枴杖或失去平衡等狀況，則再重複測試一次

口令：「當我說”開始”，請您依照 1→2→3→4→1→4→3→2→1 順序移動，動作越快越好，但不可以碰到拐杖，兩隻腳均需踏到同一格再繼續移動，踏步時臉盡量看前面不要低頭。」

紀錄：紀錄受試者的第一隻腳一開始踏入「2」至最後第二隻腳再次踏入「1」時所需的時間

評估工具：四支拐杖、碼錶



		前測	後測
日期(20YY/MM/DD) / 施測者			
測試	第一次	sec	Sec
	第二次	sec	Sec
備註			

(譯自 Dite et al., Arch Phys Med Rehabil 2002; 83: 1566-1571.)

【提醒】：盡個人最快速度，取 2 次測試中最佳的成績。

Appendix 15. Muscle Strength of Knee Extensors

下肢肌力測試

方法：使用手持測力器測試下肢膝關節伸直肌群的肌肉力量。

姿勢：

下肢肌力：坐姿，請受試者坐床緣，雙腳垂掛不得碰到地面，膝彎曲成 90 度角

下肢肌力測試口令：

“**等一下我要測量您的肌肉力量，請您依照我跟您說動作做出來，然後你要抵抗我的力量，不可以被我的手壓下去**”，然後示範要進行的測試動作與姿勢，待受試者準備好動作，“**準備好囉，現在用力頂住，不可以被我壓下去**”。測試者採用半跪姿，請受試者用力抵抗 5 秒，然後放鬆，紀錄測力器上的數值，然後換邊測試（或休息 15 秒再進行第二次測試）。

紀錄：紀錄公斤數，每個肌群測試 2 次，以平均值計算。

評估工具：握力器、手持測力器、固定式椅子

		前測		**後測**	
日期(20YY/MM/DD) /施測者					
	肌群	左	右	左	右
下肢 (公斤)	膝關節伸直肌群 (knee extension)-trial 1				
	膝關節伸直肌群 - trial 2				

【提醒】：取 2 次測試之平均值計分。

參照：Wang, C. Y. (2002), *Arch Phys Med Rehabil, 83*(6), 811-815.

Appendix 16. Six-Minute Walk Test

六分鐘行走測試

口令：我們要測試在六分鐘內，你最遠可以走的距離。你會在這個走廊上來回走六分鐘。而六分鐘是很長的時間，所以你要很努力。你很可能會感覺很喘或是疲憊，所以在六分鐘走路的過程當中，如果感覺到不舒服，你可以慢下來或者是停下來休息，當狀況比較減緩的時候，就盡可能繼續走。你要在兩個錐筒間來回的走，當你走到對面的錐筒，要準備折回去時，必須繞過錐筒。繞過錐筒的時候，請不要駐足。現在我示範一次。

準備開始了嗎？我等一下會用計數器去計算你走了幾趟。當你返回起點的時候，我會按計數器一次，這樣算一趟。記住!在六分鐘內，儘可能走多遠就走多遠，但是過程中不可以用跑的或是用跳的。好，現在要開始了，或是你準備好的時候我們再開始。

第一分鐘過後時，用不要太高的音調告訴病人【你做的很好，還有五分鐘】
剩下四分鐘的時候，則告訴病人【做的很好，繼續保持，還有四分鐘】
剩下三分鐘的時候，則告訴病人【做的很好，你已經走了一半了】
剩下兩分鐘的時候，則告訴病人【繼續保持下去，只剩下兩分鐘了】
剩下一分鐘的時候，則告訴病人【你做的相當好，只剩下一分鐘了】
剩下 15 秒的時候，則告訴病人 【再過一下我就會叫你停下來，那時候你就直接停在原地，然後我就會過去】

當時間到的時候，就喊【停】，然後走向病人，如果他看起來很疲憊，則要考慮拿一張椅子過去給他坐著休息。

如果有任何不正常的生理反應，就應該終止測試。

注意事項：

1. 如果病人在中途需停下來休息，測試者應告訴病人【你可以靠著牆休息，當你覺得可以走的時候再走】此時，不要將計時器按暫停。如果病人在六分鐘之前就停下來，且拒絕繼續走(或是你認為他不該繼續走)，就拉張椅子給病人坐著休息，不要再繼續走路。同時在備註欄記下當時走的距離、所花的時間和提早結束的原因。
2. 病人測試的時候要穿著舒適寬鬆的衣物、鞋子。
3. 測試前不可以有暖身期。
4. 在開始測試之前，請病人坐在椅子上休息至少十分鐘。
5. 站立時，同時確認禁忌症、測量脈搏、血壓、Borg’s of dyspnea。
6. 測試當中，測試者與受測者盡量不要與其他人做無謂的交談。
7. 測試終點記得做記號（如沙包或是膠布做記號）。

六分鐘行走測試

	前測	後測
日期(20YY/MM/DD)/施測者		
來回趟數(以正字計）		
休息次數(以正字計）		
行走總距離（一趟為 30 公尺）	____（趟）×30 m＋____m = ____m	____（趟）×30 m＋_____m = ____m
Borg's scale of dyspnea		

Borg's scale of dyspnea

5		13	有些吃力(累)
6		14	
7	非常非常輕鬆	15	吃力(累)
8		16	
9	非常輕鬆	17	非常吃力
10		18	
11	輕鬆	19	非常非常吃力(累)
12		20	

【提醒】：

1. 過程中，盡量不與受試者聊天，以免影響耐力表現。
2. 檢測人員站在受試者右後方跟著行走，以免擋住受試者路線。
3. 請受試者以一般走路速度或快走速度行走，切勿跑步。
4. 測試終點記得以膠布做記號。

Appendix 17. List of Abbreviations

6MWT	Six-Minute Walk Test
AD	axial diffusivity
ADHD	attention deficit hyperactive disorder
AG	angular gyrus
ALFF	amplitude of low frequency fluctuations
Ant	anterior
BMI	body mass index
BOLD	blood-oxygen-level dependent
CANTAB	Cambridge Neuropsychological Test Automated Battery
CF	callosal fibers
CF_{DLPFC}	callosal fibers connecting dorsolateral prefrontal cortices
CF_{IPL}	callosal fibers connecting inferior parietal lobules
CF_{OFG}	callosal fibers connecting orbitofrontal gyri
CF_{SPL}	callosal fibers connecting superior parietal lobules
CF_{VLPFC}	callosal fibers connecting ventrolateral prefrontal cortices
CON	control
CTT-1	Color Trails Test-part 1
CTT-2	Color Trails Test-part 2
DLPFC	dorsolateral prefrontal cortex
DSI	diffusion spectrum imaging
DTI	diffusion tensor imaging
EPI	echo planar images
Error	error rate
FA	fractional anisotropy

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fALFF	fractional amplitude of low frequency fluctuations
fMRI	functional magnetic resonance imaging
FOV	field of view
FSST	Four Square Step Test
FWE	family-wise error
GDS-15	Geriatric Depression Scale 15-item short-form
GFA	generalized fractional anisotropy
GLM	general linear model
HAROLD	Hemispheric Asymmetry Reduction in Older Adults
HRF	hemodynamic responses function
HR_{max}	maximal heart rate
IED	Intra/Extra-dimensional set shift
IED_{errors}	the number of total errors of IED test
IFG_o	inferior frontal gyrus pars opercularis
IFG_t	inferior frontal gyrus pars triangularis
IFOF	inferior fronto-occipital fasciculus
ILF	inferior longitudinal fasciculus
IPG	inferior parietal gyrus
ITI	inter-trial interval
ITT	intention-to-treat
L	left
MA	middle-aged adults
MD	mean diffusivity
MFG	middle frontal gyrus
MNI	Montreal Neurological Institute

MoCA	Montreal Cognitive Assessment
MOFG	middle orbital frontal gyrus
MPRAGE	Magnetization-Prepared Rapid Acquisition Gradient Echo
MRI	magnetic resonance imaging
MTR	magnetization transfer ratio
OA	older adults
ODF	orientation distribution function
OLST	one-legged stance test
PASE	Physical Activity Scale for the Elderly
PDF	probability density function
PFC	prefrontal cortex
$\text{PFS}_{\text{DLPFC}}$	prefronto-striatal tracts connecting DLPFC-striatum
$\text{PFS}_{\text{VLPFC}}$	prefronto-striatal tracts connecting VLPFC-striatum
R	right
RCT	randomized controlled trial
RD	radial diffusivity
RM ANCOVA	repeated measures analysis of covariance
RM ANOVA	repeated measures analysis of variance
RO	rolandic operculum
ROIs	regions of interest
rs-fMRI	resting-state functional magnetic resonance imaging
RT	reaction time
SD	standard deviation
SFG	superior frontal gyrus
SLF	superior longitudinal fasciculus

SMA	supplementary motor area
SMFG	superiomedial frontal gyrus
SMG	supramarginal gyrus
SPL	superior parietal lobule
SPM	Statistical Parametric Mapping
SST	study-specific template
TBAA	tract-based automatic analysis
TCC	Tai Chi Chuan
TE	echo time
TMT	Trail Making Test
TMT-B	Trail Making Test-B
TR	repetition time
WM	white matter
YA	young adults

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