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Title: The effects of three months of aerobic dance on hippocampal volume and cognition in elderly people with amnestic mild cognitive impairment: a randomized controlled trial

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Word count of the text: 3529.

Number of tables: 2.

Number of figures: 1.

Type of article：original research

Abstract

Whether dancing could increases the hippocampal volume of seniors with amnestic mild cognitive impairment(aMCI) remains debatable. The aim of the present study was to investigate the influence of aerobic dance on hippocampal volume and cognition after three months' aerobic dance in older adults with aMCI. In this randomized controlled trial, 68 elderly people with aMCI were randomized to either aerobic dance group or the control group using 1:1 allocation ratio. Specially designed aerobic dance routine was performed by the dance group three times a week for three months, while all participants received monthly health care education after inclusion. MRI with a 3.0 T MRI scanner and cognitive assessments were performed before and after intervention. The high-resolution 3D T1-weighted anatomical images were acquired for the analysis of hippocampal volume. A total of 35 participants (mean age: 71.51 ± 6.62 years) were randomized into aerobic dance group and 33(mean age:69.82 ± 7.74 years) into control group, and all the data was analyzed based on the intention to treat (ITT) method. Patients in the treatment group showed increased volume in the right hippocampus (mean difference [MD] in right hippocampus volume over 3 months 0.13; 95% confidence interval [CI] 0.05, 0.21; $p<0.001$) and memory enhancement (MD in Memory Scale-Revised Logical Memory change over 3 months 2.12; 95% CI -0.06, 4.13; $p = 0.02$) compared to the control group. In conclusion, three months of aerobic dance could increase the volume of right hippocampus and improve episodic memory in elderly persons with aMCI.

This study was registered on the Chinese Clinical Trial Registry (www.chictr.org.cn). Registration number：ChiCTR-INR-15007420.

Keywords: cognitive dysfunction, dancing, hippocampus, cognition

Introduction

Mild cognitive impairment (MCI) is the initial stage of impaired cognitive function unlike normal age-related cognitive decline that is not severe enough to cause significant impairment in activities of daily life(Petersen et al. 1997). According to Alzheimer's Association International Conference (AAIC)(Jack et al. 2018), amnestic MCI (aMCI) is considered as a preclinical stage of Alzheimer's disease(AD) and its early diagnosis and intervention is the key to AD prevention.

Until now, there is no strong evidence of pharmaceutical treatment in reversing the progression of Alzheimer's disease (Fink et al. 2018, Wang et al. 2016). However, the role of non-pharmaceutical therapy in MCI prevention and treatment has been recognized, which includes change in lifestyle, Mediterranean diet (Radd-Vagenas et al. 2018), risk factors control (Sanford 2017, Ganguli et al. 2013), cognitive training (Hampstead et al. 2012), psychological intervention and exercise therapy (Verdelho et al. 2013, Zhu et al. 2018, Hsu et al. 2018). Furthermore, dual-task training is reported to be more effective in improving cognitive functions in elderly adults compared to physical or cognitive training alone (Joubert et al. 2018, Rahe et al. 2015) .

Dancing is a special type of dual-task training which combines physical activity with motor learning, attention, music and rhythm-motor integration(Rektorova et al. 2020). Our recent meta-analysis concluded that dancing could improve cognition in elderly with MCI(Zhu et al. 2020). Meanwhile, hippocampal atrophy /shape change is believed to be a typical MRI marker in AD and aMCI(Shi et al. 2009), and that hippocampal volume is a strong predictor of memory decline in MCI(Mak et al. 2017). In addition, studies showed that aerobic exercise could increase hippocampus volume in younger adults(Frodl et al. 2019) and MCI(ten Brinke et al. 2015), while another study revealed that dance-related cognitive improvement was not dependent on hippocampal atrophy in mixed seniors with normal cognition and MCI(Kropacova et al. 2019). Whether dancing could increase the hippocampal volume in MCI patients remains debatable, therefore, we aimed to explore the change of hippocampus volumes in patients with aMCI after aerobic dance intervention by single blinded, randomized trial.

Methods

Study design

This is a single-blind, randomized controlled trial to investigate the effects of aerobic dance and health education program in older adults with aMCI. The ethics committee of the First Affiliated Hospital of Nanjing Medical University approved the study in January 2013(2012-SR-098). All participants signed the written informed consent.

Sample size calculation

Change in hippocampus volume on the right side after 3 months of intervention was considered as the primary outcome for sample size calculation. To detect a moderate effect size of 0.75 SD, a minimum sample size of 56 (28 per group) was required to achieve 80% statistical power at the significance level of 0.05 (two-sided). The sample size was calculated using PASS version 16, as a result considering 20% potential loss to follow up rate, a total of 68 samples are recruited for this trial.

Patients

All participants were recruited from memory clinic of the First Affiliated Hospital of Nanjing Medical University during June 2014 to December 2016. In addition, this trial was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital China). All participants signed the written informed consent.

The inclusion criteria: (1) age between 50 and 85 years (both inclusive); (2)

following the diagnostic criteria of amnestic mild cognitive impairment according to the National Institute of Aging and Alzheimer's Association(NIA-AA) guidelines(Petersen et al. 2014); (3) with memory loss for at least 3 months;(4) Mini-Mental State Examination(MMSE) score ≥25 and Montreal Cognitive Assessment(MoCA) score≤26; (5) Hachinski Ischemic Score(HIS)≤4; (6) above primary school education; and (7) signed written informed consent.

The exclusion criteria: (1) diagnose of vascular dementia based on the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherché et l'Enseignement; (2) Hachinski Ischemic Score (HIS)＞4; (3) could not take the cognitive assessments and MRI tests due to disorders, such as deafness, blindness or severe language disorders; (4) drug intake in the past months which may influence the cognitive performance; (5) current psychiatric problems including severe depression or anxiety; (6) medical contraindication of exercise such as unstable conditions(e.g. cerebrovascular disease, liver and kidney disease, falling sickness, disease of internal secretion); and (7) functional limitations caused by orthopedic diseases(e.g. fracture, osteoarthritis, joint replacement).

Randomization

Participants were randomized (1:1 ratio) and allocated to either the intervention(aerobic dance) or control group(health education program only) based on a computer-generated randomized sequence by an independent statistician. Thereafter, a clinician who was not involved in the enrollment or outcome measures opened the sequentially numbered, sealed envelopes that had the details of the participants and their allocation to the respective groups.

Interventions

The treatment group (aerobic dance group)

The treatment group participated in moderate intensity, group aerobic dance program for three months. The dance routine (https://www.youtube.com/watch?v=WuIv1enhtL0) was designed by an experienced physical therapist, that lasted for approximately 35 minutes and performed three times per week. The dance routine included a 5-minute warm-up, a 25-minute dancing with the target heart rate and a 5-minute cool-down period. The intensity of dancing was set to 60-80% of maximum heart rate to ensure the safety of participants. Two physical therapists(PT) with more than five years' experience of exercise intervention programed the dance routine. One PT led the group dance while the other was responsible for monitoring the heart rate and dancing performance. During the training, cardiotachometers(ONrhythm 50, GEONATURE) was used to monitor the heart rate of the participants. Each training session consisted of 11 to 16 participants and during the first two weeks, the PT demonstrated a sequence of dancing steps and taught the participants how to combine the steps and follow the music. This dance routine was composed of seven sub-sessions: knee bending, heel up, boxing, shoulder movement, kicking, square-stepping, and sculling exercises. All the participants had to be highly focused during the training, memorize all the steps involved and follow the movement sequence properly.

Both the experimental and control group received a lecture of health education program(120 minutes long) after inclusion in this study. This education program covered information about risk factors of dementia, healthy diet, healthy life-style and insomnia management. The participants were contacted by phone every month to remind them the main points of the education program.

The control group

The control group received health education only.

Outcome measurements

All the participants were assessed for the primary and secondary outcome measurements at baseline and after 3 months' intervention. The primary outcome measure was the hippocampal volume, while the secondary outcomes were clinical assessments.

MRI acquisition and Analysis

MRI scanning was performed on a 3.0T MRI System(Siemens AG, Erlangen, Germany) using a standard birdcage head transmit and receive coil at baseline and after the 3-months of intervention. The high-resolution 3D T1-weighted anatomical images were acquired in a sagittal plan using a magnetization-prepared rapid gradient-echo sequence (TR=1,900 msec; TE=2.52 msec; FA=90°; FOV=256x256 mm^2 ; matrix size=256x256; slice thickness=1 mm; inter-slice gap=0.5 mm; voxel size=1x1x1 mm^3 ; 176 slices), after that, axial fluid-attenuated inversion recovery images were obtained for diagnosis: inversion time(TI)=2,500 msec; TR=9,000 msec; TE=100 msec; slice thickness=5 mm.

All MRI images were collected by a single imaging technologist and evaluated by an experienced radiologist to exclude patients with obvious brain lesions, such as cerebral infraction, moderate to severe white matter lesions assessed by Fazekas scale(grades from 0 to 6), brain tumor and other brain damage.

Hippocampal volume calculation

T1-weighted structural images were analyzed for the measurement of hippocampal volume. The key to measuring hippocampal volume is to accurately demarcate by taking oblique coronal section perpendicular to the long axis of hippocampus and from the head to the tail of hippocampus as the main measurement section(Pruessner et al. 2000, Pruessner et al. 2001, Cendes et al. 1993). We used two methods to measure hippocampal volume. The first one was manual measurement. Initially, we identified the boundaries of hippocampus through the sagittal and coronal plane, and drew out an outline of the structure of hippocampus. Secondly we got the area of each layer, multiplied the area of the hippocampus by the thickness of each layer, and added up to get the whole volume of the hippocampus. The intracranial volume(ICV) was measured by multiplying its frontal and back, left and right, upper and lower diameters. The anterior-posterior diameter was the intersection of the extension line of the AC-PC line and the internal plate of the skull, while the transverse diameter was the vertical line passing through the central point of AC-PC on the axial image. Moreover, the upper and lower diameter was the intersection line between the vertical line passing through the central point of AC-PC on the sagittal image and the internal plate of the parietal bone(frontal bone) and the frontal edge of the foramen magnum. Finally, standardization was obtained through the division of the hippocampal volume by whole brain volume(Free, et al. 1995). The other method was using ITK-SNAP open program to calculate the volume, which provide semi-automatic segmentation as well as manual delineation to analyze medical images and obtain their three-dimensional model. We identified and labeled the borders of the left and right hippocampus separately for each image, and then volume was calculated using few tools of the ITK-SNAP software(Yushkevich et al. 2017).

One experienced investigator, who was blinded to the groups, measured hippocampal volumes of both sides at baseline and after three months' dance training of all the subjects in random order using the two methods described.

Clinical Assessments

Global cognition was assessed using MMSE and MoCA (Yu et al. 2012, Luis et al. 2009). Cognitive domains were assessed by various tests, including episodic memory (Wechsler Memory Scale-Revised Logical Memory, WMS-RLM)(Wang et al. 2015), executive function(Trail Making Test Part A&B, TMT A&B)(Perrochon et al. 2014), Symbol Digit Modalities Test(SDMT)(Cherbuin et al. 2010), and Forward and backward Digit Span Task(DST) Chinese version(Laures-Gore et al. 2011). Abilities of daily living were measured by Functional Activities Questionnaire(FAQ) and quality of life was measured by Short Form Health Survey(SF-36) (Hsiao et al. 2015, Lam et al. 1998). While depression was assessed using Geriatric Depression Scale(GDS-15) (de Paula et al. 2015). All these assessments were completed at baseline and after three months' dance training. The cognitive assessments were completed by an experienced speech therapist while, the all other measurements were taken by an experienced physiatrist. Both of them were blinded to the randomization.

Statistical analysis

All the data was analyzed with SPSS software version 25.0(SPSS Inc. Chicago, IL, USA). The primary analysis was based on intent-to-treat method, while multiple imputation was used to treat missing data of outcome measurements at three months(Quan et al. 2018). The rate of missing data was 6.824%. Independent sample t-test was used to determine the between group difference of outcome measurements with pooled data. The results are reported as mean difference[MD], corresponding 95% confidence interval[CI], and associated p-value. All p-values are two-sided. The statistical significance was set at alpha = 0.05.

We compared hippocampal volume obtained from the automated segmentation with the volume from the manual segmentation at each time point. The results were obtained using intraclass correlations coefficient (ICC) (Shrout et al. 1979) which is a well-recognized tool for assessing the reliability parameters between segmentation methods (Worker et al. 2018).

Results

Participants

Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) highlighting the whole process from screening to the end of the study. We assessed 112 subjects who complained loss of memory and other cognitive decline. A number of 44 people were excluded according to inclusion and exclusion criteria. Thus, 68 subjects were included in this study and were randomly assigned to either intervention group(n=35) or control group(n=33).

Descriptive statistics about randomized participants at baseline are summarized in Table 1. The two groups were equally balanced for age, gender, height, weight, years of education, hypertension and HIS.

Sixty-two of the 68 participants completed the 3 months intervention and follow-up assessment. A total of 36 dance training sessions were carried out, with mean attendance rate of 88.9%. During the trial, two participants in the control group were dropped out because of loss of interest. In addition, four participants in the intervention group were also dropped out with the following reasons: one participant was diagnose with cancer and advised for surgery, one moved to another city and could not attend training; while the other two participants lost interest in the study. Luckily no adverse event was reported during the whole duration of this study.

Hippocampal volume

Data of hippocampal volume was collected from 29 individuals in the experimental group and 25 subjects in the control group at baseline and after intervention. Fourteen participants were excluded from hippocampal volume calculation due to low quality of image caused by excessive head movement during the MRI scanning. The right, left and total hippocampal volume is summarized in table 2. The volume of right hippocampus ($p<0.001$,95%CI:-0.21,-0.05) as well as total hippocampal volume($p<0.05$,95% CI:-0.32,-0.01) was increased significantly in the experimental group after 3-month aerobic dance compared to the control group. In addition, there was minimal shrinkage in the left hippocampus in the intervention group, however there was no in between group difference(p=0.46, 95%CI: -0.13,0.06).

All ICC scores calculated were greater than 0.75 of hippocampal volume measured by both methods. In addition, the results of automated segmentation method were significantly correlated with manual segmentations at each time point.

Cognition

Cognitive outcomes are summarized in table 2. Three months' aerobic dance showed a significant increase in WMS-RLM score in the experimental group compared to the control group(p<0.05, 95% CI: 0.46,6.49). While the other cognitive assessments showed a trend of improvement, however no significant in between group difference was found.

Other outcome measurements

Other outcomes including FAQ, SF-36 and GDS were summarized in table 2. There was no significant improvement in functional activities, quality of life and depression in the aerobic training participants compared to the control group.

Discussion

Aerobic dance and hippocampal volume

This randomized clinical trial contributes new findings about the effects of aerobic dance on hippocampal volume and cognition in older adults with aMCI. The key finding was that aerobic dance increased right hippocampal volume and improved episodic memory in aMCI participants.

Right hippocampal volume was increased by 11.8% while total hippocampus volume was increased by 4.5%, respectively, which is corroborate with ten Brinke LF's study(ten Brinke et al. 2015).Their study reported a 5.6% volume increase in the left hippocampus, a 2.5% increase in the right hippocampus, and a 4% increase in total hippocampus volume after 6 months' aerobic training in elderly women with probable MCI. Another study showed increased volume in both hippocampi after 6 months multicomponent exercise program in elderly people with MCI due to AD(Teixeira et al. 2018). However in our study, we found a decrease in volume of the left hippocampus by 2.61% in the intervention group while, 5.88% in the control group.

There are two possible reasons which might have caused the difference in results among our study and these two studies: firstly is the intervention time, in our study duration was 3 months, while the other two studies were for 6 months, which means that longer intervention time might cause significant changes in hippocampus volume. Secondly, we used a different exercise protocol compared to these studies, which could possibly lead to different effects on the hippocampus. In our study, the aerobic dance consisted of physical movements that require abundant spatial stimulation, leading to an increased activation of the hippocampus, which appears to be involved in memory consolidation while locomotion(Burgess et al. 2002). The hippocampal and entorhinal networks are activated, and the place cells in hippocampus fire in response to a unique, specific position in the environment(Foster et al. 2013). Therefore, dancing may provide a benefit by input-stimulation following a simple exploration in motion of the surrounding environment.

We observed difference in appearance between the two hippocampus (right and left), which may be caused by functional differences between the two sides of hippocampus. The right hippocampus is especially involved in encoding spatial memory, while the left hippocampus is involved more in context-dependent episodic or autobiographical memory as well as episodic verbal memory(Burgess et al. 2002; Ezzati et al. 2016).Which might mean that the aerobic dance we used require more learning and memory process of spatial information, which require the involvement of the right hippocampus, leading to significant increase in its volume.

Aerobic dance and cognition

A number of clinical trials have provided evidence that aerobic dance training can enhance cognition including global cognition(Song et al. 2018), memory and executive function in older adults with MCI(Nuzum et al. 2020). Our study demonstrated that 3 months' aerobic dance training could improve episodic memory, but not executive function and global cognition in aMCI patients. This is because the population sample in our study was consisted of amnestic MCI patients, where the first and core clinical symptom is memory loss, especially episodic memory(Bruno et al. 2007). In addition the dance routine in our study had of a variety of movements in a specific order that require a lot of cognitive efforts such as initiation, orientation and concentration that particularly challenges episodic memory. This might have caused improvement in the episodic memory in our dance group compared to those in the control group. Furthermore as the improvement in episodic memory was the key benefit to aMCI participants in our study, such aerobic dance might be better intervention for these patients.

Benefits of aerobic dance on cognition and its possible mechanism in elderly

Recently, different types of aerobic dance training have been used as their intervention for elderly people in multiple studies. In addition, our recent meta analysis concluded that aerobic dance significantly improves global cognitive function and memory in older adults with MCI.[15] Furthermore, this specially designed aerobic dance combines physical exercise with cognitive tasks, which could be considered, as a type of dual-task training should be focused in the future studies(Murillo-Garcia et al. 2020). Several studies suggested that dual-task training has superior effects on cognition in older adults compared to single aerobic training or cognitive training alone(Joubert et al. 2018, Rahe et al. 2015, Tait et al. 2017) . The combination of aerobic exercise and cognitive efforts in the dancing program, may improve cognition in the following ways. Chronic aerobic exercise may cause cardiovascular fitness improvements, which promote long-term angiogenesis and cerebral circulation. This adaptation is related to increased delivery and upregulation of neurotrophins and supporting factors to the brain, particularly to the hippocampal neurogenic niche. And with the combination of cognitive training, the dual-task training could provide long-term cognitive benefits and protection against age-related cognitive decline(Stimpson et al. 2018).

Limitations

Few limitations have been recognized in the present study. Firstly, the participants in the present study were highly educated people(the average education years of intervention group and control group is 10.49 ±3.94,9.49±4.14 respectively), which could cause a selection bias from the main population of aMCI. Secondly, one of the method of hippocampal volume calculation in our study was manual, which might not be as convenient as a newly designed measuring software(Ahdidan et al. 2016; Frisoni et al. 2015), which developed an automatica segmentation algorithm for hippocampal volume calculation. Therefore for future studies, we strongly recommend the use of professional software for measuring hippocampal volume based on the consensus standard of hippocampus segmentation, and measuring the volume by referring to the standard database.

Conclusions

This study shows that three months of aerobic dance can not only increase the volume of hapocampus(right) but also improves episodic memory in aMCI patients. This means that such dance have great potential for enhancing cognitive function by increasing hypocampus volume(neurogenesis). However further studies using functional MRI and positron emission tomography(PET) scan are needed to explore the mechanism of cognitive improvement by aerobic dance.

Acknowledgement The authors thank Miss Wang Shiyan and Miss Zhang Kathryn Chu, who helped us designing the dance routine and dubbing the dance video.

Funding This work was supported by the National Natural Science Foundation of China (NSFC)[Grant Number 81802244, 81971237, 81772454]; Science and Technology Department of Jiangsu Province, China [Grant Number BE2013724, BE2017734];and the National Key R&D Program of China [Grant Number 2018YFC2001600].

Compliance with ethical standards

Competing interest The Authors declare that there is no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethic standards of the ethics committee of the First Affiliated Hospital of Nanjing Medical University(2012-SR-098).

Consent to participate All participants signed the written informed consent.

Consent to publish All authors agree to publish in this journal.

Authors contribution **Yi Zhu:**Funding application, study management and coordination, and initial manuscript draft.**Tong Wang:** Research ideas providing and manuscript revision. **Ling Zhang:** Hippocampal volume calculation, manuscript revision.**Yaxin Gao:** Patient screening and inclusion, manuscript draft.**Ming Qi:**MRI scanning protocol design, manuscript revision.**Han Wu:**Ethical application, assessments of participants and manuscript draft.**Jinhui Ma,Lehana Thabane**：Study design, statistical analysis and revision of the manuscript.**Qian Zhong,Cuiyun Sun**：Intervention for the participants and manuscript draft.**Hongyuan Ding**:Completed the MRI scanning and manuscript revision.**Nawab Ali**：Data analysis and manuscript draft. **Qiumin Zhou** ：Cognitive assessments,data analysis and manuscript revision.**Li Zhou,Qin Zhang:** Data collection of baseline characteristics and follow-up,and manuscript revision.**Ting Wu,Wei Wang:** Study design, inclusion and exclusion criteria, patient diagnosis and manuscript revision.

Availability of the data and materials

Contact the corresponding author if there is any need of the relevant data or materials.

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Table

Table 1. Patient characteristics at baseline

Characteristics	Treatment Group (n=35)	Control Group (n=33)
Age (years), mean (SD)	71.51 (6.62)	69.82 (7.74)
Female, n (%)	18(51.42%)	23(65.71%)
Height (cm), mean (SD)	157.17(8.50)	156.02(8.57)
Weight (kg), mean (SD)	57.78(8.50)	57.47(10.61)
High Blood pressure+, n (%)	3(8.57%)	6(18.18%)
Hachinski Ischemia Score		
0	13(37.14%)	7(21.21%)
1	15 (42.86%)	13 (31.14%)
2	2(5.71%)	8 (24.24%)
3	4(11.43%)	5(15.15%)
4	1(2.86%)	0(0.00%)
Education years, mean (SD)	10.49(3.94)	9.49(4.14)

Abbreviation: SD = Standard deviation

Note: + High blood pressure is defined as systolic blood pressure > 140mmHg or diastolic blood pressure > 90mmHg.

Table 2. Comparison of clinical parameters between two study groups

Outcome by group	**Summary at Different Time Point mean (95% CI)**		**From Baseline to 3 months mean (95% CI)**
	Baseline	**3 Months**	**Between-Group Difference in Change (intervention versus control)**
Hippocampus volume(right)[a]			
Exercise	0.90(0.83,0.97)	1.01(0.93,1.08)	0.00**(-0.21,-0.05)
Control	1.01(0.93,1.08)	0.98(0.92,1.04)	
Hippocampus volume(left) [a]			
Exercise	0.91(0.86,0.96)	0.88(0.84,0.93)	0.46(-0.13,0.06)[b]
Control	0.99(0.90,1.10)	0.94(0.88,1.00)	
Hippocampus volume(total) [a]			
Exercise	1.81(1.70,1.93)	1.89(1.78,2.01)	0.03* (-0.32,-0.01)[b]
Control	2.01(1.83,2.18)	1.92(1.81,2.02)	
Wechsler Memory Scale-Revised Logical Memory(WMS-RLM)			
Exercise	14.10(12.29,15.91)	16.67(14.92,18.42) [c]	0.02*(0.46,6.49)
Control	15.93(13.97,17.89)	14.38(12.95,15.81) [c]	
Montreal Cognitive Assessment(MoCA)			
Exercise	22.80(22.09,23.51)	24.43(23.63,25.23) [c]	0.26(-0.51,1.91)
Control	23.17(22.47,23.87)	23.59(22.91,24.27) [c]	
Mini-Mental State Examination(MMSE)			
Exercise	27.53(27.04,28.03)	28.03(27.53,29.53) [c]	0.84(-0.83,1.02)
Control	26.86(26.40,27.32)	27.62(27.03,28.20) [c]	

Abbreviation: SD = standard deviation; CI = confidence interval

Note: *0.001 ≤ p < 0.05; ** p <0.001; [a] This data of hippocampus volume included 29 cases in exercise group and 25 cases in control group; [b] Data with unequal variance; [c] Multiple imputation was used to deal with missing data to complete an Intention-To-Treat(ITT) analysis

Table 2. Comparison of clinical parameters between two study groups (continued)

Outcome by group	Summary at Different Time Point mean (SD)		From Baseline to 3 months mean (95% CI)
	Baseline	**3 Months**	**Between-Group Difference in Change (intervention versus control)**
Digit Span			
Exercise	16.50(15.46,17.54)	16.79(15.88,17.70) [c]	0.46(-1.06,2.37)
Control	17.38(16.31,18.45)	16.72(15.63,17.81) [c]	
Trail Making Test Part A(TMT-A)			
Exercise	75.43(64.57,86.30)	67.25(58.99,75.51) [c]	0.53(-15.56,7.97)
Control	68.45(60.40,76.49)	68.54(61.62,75.46) [c]	
Trail Making Test Part B(TMT-B)			
Exercise	210.33(182.02,238.64)	164.11(147.14,181.07) [c]	0.12(-57.55,6.31)
Control	185.62(160.02,211.22)	174.46(156.57,192.35) [c]	
Symbol Digit Modalities Test			
Exercise	31.57(28.15,34.98)	35.08(31.96,38.21) [c]	0.28(-2.04,7.14)
Control	32.90(28.90,36.89)	32.88(29.34,36.42) [c]	
Functional Activities Questionnaire(FAQ)			
Exercise	1.27(0.49,2.04)	0.61(0.06,1.16) [c]	0.47(-0.82,1.75）
Control	2.45(1.36,3.54)	1.22(0.59,1.84) [c]	
Short Form Health Survey - 36(SF-36)			
Exercise	108.00(101.72,114.28)	114.65(107.98,121.32) [c]	0.20(-2.74,13.08)
Control	109.48(104.21,114.75)	110.99(1106.06,115.91) [c]	
Geriatric Depression Scale(GDS)			
Exercise	11.17(8.36,13.98)	9.08(6.20,11.96)) [c]	0.36(-2.09,5.71)
Control	14.17(11.47,16.88)	10.88(8.81,12.96) [c]	

Abbreviation: SD = standard deviation; CI = confidence interval

Note: *0.001 ≤ p < 0.05; ** p <0.001; [c] Multiple imputation was used to deal with missing data to complete an Intention-To-Treat(ITT) analysis

Figure legends

Fig. 1. The flow diagram of the research.

Figure 1 shows the experimental process of this paper, including recruitment process, grouping process, and subsequent data analysis.