

Mechanisms of Motor Symptom Improvement by Long-Term Tai Chi Training in Parkinson's Disease Patients

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Abstract

Background

Tai Chi has been shown to improve motor symptoms in Parkinson's disease (PD), but its long-term effects was not clear and the related mechanism was not elucidated. Therefore, we investigated the mechanism of long-term Tai Chi training on improving motor symptoms in PD.

Methods

95 early-stage PD patients were enrolled and randomly divided into Tai Chi (N = 32), brisk walking (N = 31) and no-exercise group (N = 32). All subjects were assessed at baseline, 6 months and 12 months after one-year intervention. Motor symptoms were evaluated by Berg balance scale (BBS), Unified PD rating scale (UPDRS), Timed Up and Go test (TUG) and 3D gait analysis. Functional MRI, plasma cytokine and metabolomics, blood Huntingtin interaction protein 2 (*HIP2*) mRNA levels were analyzed to investigate the mechanisms of Tai Chi training at macro and molecular level. The longitudinal effects of self-changes were calculated using repeated measures ANOVA. Generalized estimating equations (GEE) was used to assess the association of longitudinal data of rating scales. Switch rates were used into the fMRI analysis. False discovery rate (FDR) correction was used to perform multiple correction.

Results

Tai Chi group had better performance in BBS, UPDRS, TUG and step width. Besides, Tai Chi had more advantages in improving BBS, step width than brisk walking. Improved BBS was correlated with enhanced visual network function and downregulation of IL-1 β . Improvements in UPDRS were associated with enhanced default mode network function, decreased L-malic acid and 3-phosphoglyceric acid, increased adenosine and *HIP2* mRNA levels. In addition, arginine biosynthesis, urea cycle, TCA cycle and beta oxidation of very long chain fatty acids were also improved by Tai Chi.

Conclusions

Long-term Tai Chi training improved motor function, especially gait and balance, in PD. Enhanced brain network function, reduced inflammation, improved amino acid metabolism, energy metabolism and neurotransmitters metabolism, decreased vulnerability to dopaminergic degeneration might be the mechanisms of Tai Chi effects.

Trial registration:

This study is registered at Chinese Clinical Trial Registry (Registration number: ChiCTR-OPC-16008074; Registration date: March 8, 2016).

Background

Parkinson disease (PD) is the second most common neurodegenerative disease globally, characterized by bradykinesia, resting tremor and rigidity [1]. With the progression of disease, patients lose postural stability and have difficulty in gait and balance, causing frequent falls and disability in daily living [2]. Although some motor symptoms, such as tremor and rigidity, may be alleviated by drug therapy, some clinical features such as postural instability are less responsive to medication and need alternative treatments [3].

Physical exercises were shown to improve mobility, gait, balance and quality of life in PD [4, 5]. Tai Chi, brisk walking and tango dancing demonstrated the highest level of evidence of efficacy, especially in improving postural stability [6–8]. Tai Chi, a mind-body exercise that utilizes continuous, curved, and spiral body movements with breathing control [9], was shown to have improved aerobic capacity, muscle strength, balance, and motor control, as well as reduced stress and anxiety in older adults [10]. High quality of evidence from randomized controlled trials done by Fuzhong Li et al. found improvement of maximal excursion, direction control, gait velocity and quality of life after 6-month Tai Chi training in PD patients [6, 11]. However, previous studies focusing on Tai Chi training only showed the short-term (up to 6 months) benefits for PD patients. Owing to the progressive nature of PD, the long-term effects of such interventions should be concerned.

What's more important, the beneficial mechanisms of Tai Chi remain largely unclear. Evidence based on animal studies of neurodegenerative disease found that physical exercise might improve the production of neurotrophic factors, neurotransmitters, and hormones, promoting many processes such as synaptic plasticity, neurogenesis, angiogenesis, and autophagy [12]. Several studies focusing on the mechanisms of Tai Chi in older adults have shown improved brain metabolism and muscle energetics using brain ^1H MRS and a muscle ^{31}P MRS [13], enhanced default mode network (DMN) connectivity using resting-state functional MRI (rs-fMRI) [14]. However, the mechanisms of Tai Chi training on PD patients were not investigated. It is necessary to understand the inner physiological changes of the brain and body by Tai Chi training on PD patients.

Functional MRI and blood biomarkers tests probably will give us a deep insight into the mechanisms of Tai Chi in PD. Rs-fMRI was widely used to explore the brain function and neuroplasticity at macro level. In addition, molecular biomarkers in the blood of PD, which can reflect pathogenesis and disease progression, also provide us ways to study mechanisms of Tai Chi [15, 16]. Previous animal studies showed that exercise might bring benefits to PD through inhibiting oxidative stress, repairing mitochondrial damage, and promoting the production of growth factors [4]. To investigate the mechanisms of Tai Chi training in PD patients, cytokines and metabolomics analysis in blood were chosen. Huntingtin interaction protein 2 (HIP2) is an E2 ubiquitin-conjugating enzyme associated with

neurodegenerative diseases, decreased *HIP2* expression has been reported in the blood [17–19] and the substantia nigra of PD patients [20]. Reduction of *HIP2* expression could cause motor function impairment and increased vulnerability to dopaminergic degeneration in Parkinson's disease models [21]. Thus, *HIP2* could also be a genuine disease-relevant biomarker for PD. Thus, combined analysis of cytokines, metabolomics, and *HIP2* mRNA were used in order to discover the underlying mechanisms of long-term Tai Chi training in PD at molecular level.

Finally, our study is to discover the long-term effect of Tai Chi training on motor symptoms of PD. More importantly, fMRI and blood biomarkers (including cytokines, metabolomics and *HIP2* mRNA) were used to explore the underlying mechanisms of Tai Chi training.

Methods

We conducted a one-year RCT to evaluate the impact of long-term Tai Chi training on motor symptoms in PD patients and more importantly investigate the related mechanisms.

Subjects

95 early stage (Hoehn-Yahr 1-2.5) PD patients (50-80 years old) were recruited. The medication was stable at least 3 months before recruitment and not changed during follow-up unless necessary due to the disease progression. Our study was approved by Ruijin Hospital Ethic Committee of Shanghai Jiao Tong University School of Medicine at December 04, 2014. This study is registered at Chinese Clinical Trial Registry (Registration number: ChiCTR-OPC-16008074; Registration date: March 8, 2016). PD was diagnosed by two movement disorder specialists (SDC, YYT). All of the PD patients met both the PD diagnostic criteria of United Kingdom Brain Bank [22] and Movement Disorders Society [23]. All participants provided written informed consents.

Randomization

After recruitment, participants were randomly assigned to Tai Chi (N=32), brisk walking (N=31) and control group (N=32) without stratification. The randomization method is to draw lots. Then, 12-month exercise intervention (Tai Chi, brisk walking or non-exercise) with strict quality control was introduced. Details could be seen in **Additional File 1**.

Assessments

Berg Balance Scale (BBS), Unified PD rating scale (UPDRS), Time up and Go test (TUG) and Spatial 3D gait analysis were used to assess the motor symptoms, gait and balance of PD patients. Assessments were performed at baseline, 6 months and 12 months.

Investigation of mechanisms

Mechanisms were investigated by fMRI, plasma cytokines and metabolomics, and the blood *HIP2* mRNA levels. Assessments were done at baseline, 6 months and 12 months. Details could be seen in **Additional File 1**.

Statistical analysis

R (version 3.5.1), RStudio (version 1.1463) and related packages were introduced into statistical analysis. MATLAB R2018a (version 9.4.0.813654, MathWorks, Inc.) was used into the analysis of fMRI.

All analyses about clinical measurements were conducted on an intention-to-treat basis. Analysis of variance (ANOVA) was used to compare numerical demographic information. Pearson Chi-Square test or Fisher test was used into analysis at categorical demographic information. Shapiro-Wilk normality test was used to assess the normality of variables. Independent-sample t-tests (with 95% confidence intervals) were used to compare group means. Data were presented in the way of between-group differences. The longitudinal effects of self-changes were calculated using repeated measures ANOVA.

Switch rates were used into the fMRI analysis [24]. The least absolute shrinkage and selection operator (LASSO), linear regression and Bayesian belief network (BBN) were introduced to analyze fMRI.

Generalized estimating equations (GEE) was used to assess the association of longitudinal data of rating scales. Mixed effect regression using restricted maximum likelihood method was introduced to analyze cytokine levels, *HIP2* levels and metabolites. Bonferroni correction was used in performing multiple corrections. Pathway analysis was performed using MetaboAnalyst 4.0 platform. Enrichment analysis was performed using MetaboAnalyst 4.0 platform referenced with the small molecule pathway database (SMPDB). False discovery rate (FDR) correction was used to perform multiple correction. Detailed could be seen in **Additional File 1**.

Results

Baseline characteristics of participants

95 patients were recruited in this study at baseline (Tai Chi group 32, brisk walking group 31, control group 32). All of them were Han ethnicity. No patients presented either on-off phenomenon or dyskinesias. Three groups were matched in age, gender, disease duration and education. 66 patients finished 6-month and 12-month follow-up. Details were shown in **Table 1 and Figure 1**. There were no differences of levodopa equivalent daily dosage (LEDD) at baseline and 12-month visit between the groups.

Table 1 Demographic information of all the subjects

	Tai Chi Group (N = 32)	Brisk Walking Group (N = 31)	Control Group (N = 32)	<i>p</i> value
Gender, Female (N (%))	15 (46.88)	9 (29.41)	13 (41.18)	0.500
Age at baseline (mean ± SD)	62.7 (5.51)	61.9 (5.64)	61.9 (6.76)	0.400
Education, years (mean ± SD)	13.60 (2.71)	13.10 (2.57)	12.40 (2.83)	0.472
History of Hypertension (N (%))	7 (21.88)	3 (11.76)	5 (17.65)	0.800
History of Diabetes mellitus (N (%))	1 (3.13)	0 (0.00)	1 (3.13)	1.000
History of smoking (N (%))	2 (6.25)	2 (6.25)	2 (6.25)	0.600
Family History (N(%))	8 (25.00)	5 (17.65)	3 (11.76)	0.600
Tremor dominant (N (%))	22 (68.75)	22 (64.71)	17 (58.82)	0.800
Disease duration (mean ± SD)	5.91 (4.01)	3.82 (1.87)	4.32 (2.46)	0.082
Hoehn – Yahr staging (N (%))				0.097
1.0	9 (28.13)	8 (25.81)	1 (3.13)	
1.5	5 (15.63)	7 (22.58)	11 (34.38)	
2.0	13 (40.63)	13 (41.94)	13 (40.63)	
2.5	5 (15.63)	3 (9.68)	7 (21.88)	
LEDD at baseline (mean ± SD)	326 (197)	260 (174)	347 (109)	0.800
LEDD (mean ± SD)	56.33 (91.68)	39.71 (83.30)	57.21 (107.24)	0.939
LEDD, levodopa equivalent daily dosage; N, number; SD, standard deviation				
LEDD: LEDD at 12 months minus LEDD at baseline				

Clinical improvements

Patients showed better performance after Tai Chi training in BBS ($p \leq 0.035$). In addition, Tai Chi improved the performance in BBS (6 months: $p = 0.006$, 12 months: $p = 0.044$) since 6 months and lasted to 12 months. Compared to brisk walking, Tai Chi had more advantages in improving BBS scores (6 months: $p = 0.005$, 12 months: $p = 0.022$). **(Additional File 2-Table S1, Figure 2.A)**

Patients showed better changes after Tai Chi training in UPDRS and TUG ($p \leq 0.045$). Tai Chi group showed improvement in UPDRS at 12 months compared with controls (UPDRS: $p = 0.015$, UPDRS-III: p

<0.001). In addition, Tai Chi improved the performance in TUG (6 months: $p=0.017$, 12 months: $p=0.011$). Tai Chi improved patients' performance in step width (severer side: 6 months: $p=0.002$, 12 months: $p<0.001$; milder side: 6 months: $p<0.001$, 12 months: $p<0.001$) compared with controls since 6 months and lasted to 12 months. When compared to brisk walking, Tai Chi also showed advantages in improving step width (severer side: 6 months: $p=0.03$, 12 months: $p=0.03$; milder side: 6 months: $p=0.004$, 12 months: $p=0.111$). **(Additional File 2-Table S1, Figure 2. B-D)**

Mechanisms of Tai Chi effects

fMRI switch rates

Better performances of BBS ($p=0.044$) in Tai Chi group were associated with the changes of visual network (VN). Improvements in UPDRS ($p=0.023$) and UPDRS-III ($p=0.006$) of PD patients were associated with enhancements of default mode network (DMN) after Tai Chi training. **(Additional File 2-Table S2, Figure 2. E-H)**

Cytokines

The levels of IL-1 β (6 months: $p=0.013$, 12 months: $p=0.028$), IL-5 (6 months: $p=0.028$, 12 months: $p=0.248$), IL-7 (6 months: $p=0.032$, 12 months: $p=0.016$) and IL-9 (6 months: $p=0.037$, 12 months: $p=0.019$) were significantly downregulated in Tai Chi group compared with control group. **(Additional File 2-Table S3)**

Levels of IL-13 (6 months: $p=0.002$, 12 months: $p=0.005$), PDGF-BB (6 months: $p=0.022$, 12 months: $p=0.011$), MIP-1 β (6 months: $p=0.003$, 12 months: $p=0.008$) and MCP-1 (6 months: $p=0.032$, 12 months: $p=0.06$) were stable in Tai Chi group but significantly increased in controls. The relatively stable levels of IL-13 (6 months: $p=0.019$, 12 months: $p=0.021$) and MCP-1 (6 months: $p=0.0007$, 12 months: $p=0.022$) were seen in Tai Chi group compared with brisk walking group. **(Additional File 2-Table S3)** In addition, upregulation and downregulation of MIP-1 α were respectively seen in control group ($p=0.006$) and brisk walking group ($p=0.029$), while Tai Chi group had no changes at 6 months. But MIP-1 α returned to the baseline level in three groups at 12 months. **(Additional File 2-Table S3)**

Higher level of GM-CSF was found in Tai Chi group while no change was seen either in control group (6 months: $p=0.005$, 12 months: $p=0.011$) or in brisk walking group (6 months: $p=0.006$, 12 months: $p=0.014$). Those changes above could be observed since 6 months and lasted to 12 months. **(Additional File 2-Table S3)**

Furthermore, by analyzing the association between changes of cytokines and changes of clinical presentations, we found that downregulation of IL-1 β were positively related to improved BBS scores ($p\leq 0.031$). **(Additional File 2-Table S4)**

Metabolomics

We tested 123 metabolites, of which 27 metabolites showed statistically changes. After Bonferroni correction, 11 metabolites were left significant. Fumaric acid, L-aspartic acid and pyroglutamic acid were decreased after Tai Chi training only at 6 months ($p \leq 0.033$). Downregulation of homocysteine and methionine sulfoxide, and upregulation of azelaic acid were seen in Tai Chi group both at 6 months ($p \leq 0.005$) and 12 months ($p \leq 0.032$). L-malic acid, 3-phosphoglyceric acid were downregulated, while L-fucose, adenosine and pipercolic acid were upregulated after Tai Chi training at 12 months ($p \leq 0.028$). **(Additional File 2-S5)**

We also found several associations between metabolites and clinical presentations. The L-malic acid, 3-phosphoglyceric acid, and adenosine were associated with changes of UPDRS ($p \leq 0.043$). The L-malic acid, L-fucose, and pipercolic acid were associated with the changes of UPDRS-III ($p \leq 0.041$). **(Additional File 2-Table S6)**

Pathway analysis showed group differences in arginine biosynthesis both at 6 months (Tai Chi v.s. Control: $p=0.007$; Tai Chi v.s. Brisk Walking: $p=0.006$) and 12 months (Tai Chi v.s. Brisk Walking: $p < 0.001$). **(Additional File 2-Table S7, Additional File 3-Figure S1-3)** In enrichment analysis, significant group difference was found in urea cycle both at 6 months (Tai Chi v.s. Control: $p=0.009$; Tai Chi v.s. Brisk Walking: $p=0.05$) and 12 months (Tai Chi v.s. Brisk Walking: $p < 0.001$). **(Additional File 2-Table S8, Additional File 3-Figure S4-6)**

In association analysis, TCA cycle was correlated with BBS ($p=0.037$), UPDRS ($p=0.002$), UPDRS-III ($p=0.014$). Beta oxidation of very long chain fatty acids was relevant to UPDRS ($p=0.033$), UPDRS-III ($p=0.033$). **(Additional File 2-Table S9)**

***HIP2* mRNA levels**

The control group showed tendency of downregulation of *HIP2* mRNA ($p = 0.697$). Compared with controls, the *HIP2* mRNA level was elevated after Tai Chi training since 6 months ($p < 0.001$) and lasted to 12 months ($p < 0.001$). Tai Chi training seemed to be better in upregulating *HIP2* mRNA level than brisk walking ($p=0.277$). **(Additional File 3-Figure S7)**

We found that the difference of UPDRS and UPDRS-III was associated with the change of *HIP2* mRNA level after Bonferroni correction ($p < 0.005$). Association between the difference of BBS and the change of *HIP2* mRNA level was also detected, but it did not survive after Bonferroni correction. **(Additional File 2-Table S10)**

Discussion

Long-term beneficial effects of Tai Chi on improving balance, and other motor symptoms in PD were found in our study. Tai Chi improved BBS, UPDRS, TUG, step width, indicating its beneficial effects on motor symptoms (including gait and balance). Tai Chi had more advantages in improving BBS, step width than brisk walking.

More importantly, we want to explore the mechanisms of Tai Chi in improving the motor symptoms of PD. By using fMRI testing, we found the association between changes of BBS and the switch of VN. Relationship between improvement of UPDRS and the function of DMN was also positive. Plasma cytokines IL-1 β , IL-5, IL-7, IL-9, IL-13, MCP-1, MIP-1a, MIP-1 β were relatively downregulated and GM-CSF were upregulated after Tai Chi training. Among them, downregulation of IL-1 β were positively related to improved BBS scores. Decreased L-malic acid and 3-phosphoglyceric acid, and increased adenosine were associated with changes of UPDRS in PD after Tai Chi training, while downregulation of L-malic acid, upregulation of L-fucose and pipercolic acid were related to changes of UPDRS-III. Arginine biosynthesis, urea cycle, TCA cycle and beta oxidation of very long chain fatty acids were also affected by Tai Chi. The *HIP2* mRNA levels were significantly elevated after Tai Chi training, and its change was correlated with the changes of UPDRS and UPDRS-III in PD by Tai Chi.

Our study found significant improvement of motor function (especially gait and balance) in PD patients after Tai Chi training, which was consistent with the results of previous studies [6, 11]. The mechanism of Tai Chi's beneficial effects might be associated with the improved brain networks function in PD patients. Our results indicated association between enhanced VN function and improved BBS scores. The VN was composed by bilateral striate and extrastriate visual areas [25]. Visual-proprioceptive sensory conflict could influence gait and balance [26]. The visual cue lessens the vestibular noise and improves personal balance in environment [26]. PD patients with freezing of gait displayed reduced network connections in VN [27, 28]. Thus, improved VN function might explain for the better performance of BBS in PD after Tai Chi training. We also observed change of DMN was related to improvement in UPDRS and UPDRS-III. The DMN included the hippocampus, parahippocampal, fusiform and angular gyrus, the precuneus and the middle temporal gyrus [25]. Precuneus is one of the functional hub regions of DMN, and its interactions with sensorimotor network were positively associated with motor performances [29]. Thus, improvement of DMN could explain the improved motor function in PD after Tai Chi training since connection of precuneus to motor areas might be associated to processes of motor mental imagery and planning [29].

Proinflammatory cytokines were downregulated after Tai Chi training. Among them, decreased IL-1 β was correlated with improved BBS score. Inflammation plays an important role in the pathogenesis and disease progression of PD [15]. Meta-analysis of inflammatory cytokines in PD demonstrated significantly higher blood levels of IL-1 β compared with healthy controls [30]. IL-1 β plays an important role in different neurobiological processes, such as neuroinflammation, neurotoxicity, and host defense. Therefore, this cytokine has been linked to both acute and chronic neurodegenerative conditions [31]. PD symptoms were observed in IL-1 β wild-type animals, IL-1 β may contribute to the initiation or progression of PD [31]. Decreased IL-1 β , indicating reduced inflammation, might explain for the improved BBS in PD patients after Tai Chi training.

As for the results of metabolomics analysis, dysregulation of metabolites and metabolic pathways in PD were revealed, which were mainly associated with amino acid metabolism (pipercolic acid, L-fucose, arginine biosynthesis), energy metabolism (L-malic, 3-phosphoglyceric acid, urea cycle, TCA cycle and beta oxidation of very long chain fatty acids) and neurotransmitters metabolism (adenosine) [32]. L-

arginine, which participated in the synthesis of nitric oxide, could affect oxidative stress and energy metabolism playing a key role in the pathogenesis of PD [33]. Deficiency of TCA cycle enzymes and dysfunction of mitochondria, which regulated neuroinflammation and neurodegeneration, were also observed in PD [34]. The coupling of adenosine with its specific receptors acts as an upstream neuromodulator for neurotransmitters such as acetylcholine, glutamate, g-amino-butyric acid (GABA), and dopamine that is implicated in the modulation of multiple body functions [35]. Our results indicated improved amino acid metabolism, energy metabolism and neurotransmitters metabolism in PD patients after Tai Chi training.

HIP2 is an E2 ubiquitin-conjugating enzyme via UPS pathway related to protein cleavage [36]. Impaired UPS system is related with protein aggregation, causing inflammation and abnormal oxidation [37]. Reduction of the *HIP2* expression led to spontaneous motor function impairment and increased vulnerability to dopaminergic degeneration in PD models [21]. In our previous study, the *HIP2* mRNA level was found downregulated in 20 PD patients and then elevated after one-year Tai Chi training accompanying improved motor function [21]. Our present study further confirmed that Tai Chi could reverse the downregulation of *HIP2* mRNA in a larger PD cohort, and linked its change with the improvement of motor function in PD patients after Tai Chi training, indicating Tai Chi's role in decreasing the vulnerability to dopaminergic degeneration in PD.

Based on the above evidence from fMRI and blood biomarkers, we found enhanced brain network function, reduced inflammation, improved amino acid metabolism, energy metabolism and neurotransmitters metabolism, decreased vulnerability to dopaminergic degeneration in PD after Tai Chi training.

Limitations

There were some limitations in our study. First, the number of subjects in our study is not enough. Because of the small sample, validity might be lost, therefore, larger sized cohort studies are warranted. The dropout is inevitable in the long-time visit, causing the relatively small sample amount. Second, the dropout rate of brisk walking and control could not be ignored. Since Tai Chi was monitored in fixed Tai Chi class, it was much easier to keep training than brisk walking. Besides, patients in the Tai Chi class were willing to stick to Tai Chi training since they had benefited from it.

Conclusions

Our study revealed that long-term Tai Chi training improves PD patients with motor function, especially in gait and balance. Enhanced brain network function, reduced inflammation, improved amino acid metabolism, energy metabolism and neurotransmitters metabolism, decreased vulnerability to dopaminergic degeneration might be the mechanisms of Tai Chi effects.

List Of Abbreviations

ANOVA, analysis of variance; BBN, Bayesian belief network; BBS, Berg Balance scale; DMN, default mode network; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; GEE, generalized estimating equations; GM-CSF, granulocyte-macrophage colony stimulating factor; *HIP2*, Huntingtin interaction protein 2; IL, interleukin; LASSO, least absolute shrinkage and selection operator; LEDD, levodopa equivalent daily dosage; MCP1, monocyte chemotactic protein 1; MIP, macrophage inflammatory protein; PD, Parkinson's disease; PDGF, platelet derived growth factor; TCA, tricarboxylic acid cycle; TUG, Timed Up and Go test; UPDRS, Unified Parkinson's Disease Rating Scale; UPS, ubiquitin proteasome; VN, visual network.

Declarations

Ethics approval and consent to participate

This study was approved by Ruijin Hospital Ethic Committee of Shanghai Jiao Tong University School, and all participants have given written informed consents.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GL and PH performed clinical assessment, run the statistical analysis and drafted the manuscript. SSC, YCH and XS performed clinical assessment. QYJ performed fMRI scan. PH performed gait assessment. GYH and BYL made fMRI analysis. YXL made fMRI data management. JX and ZW joined the study design. SDC and YYT performed patient recruitment and diagnosis. SDCn designed the study, supervised the study, double-checked the statistical analysis and revised the manuscript.

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References

1. Kalia LV, Lang AE. Parkinson's disease. *Lancet*. 2015;386:896–912.
2. Ashburn A, Stack E, Pickering RM, Ward CD. A community-dwelling sample of people with Parkinson's disease: characteristics of fallers and non-fallers. *Age Ageing*. 2001;30:47–52.
3. Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. *JAMA*. 2020;323:548–60.
4. Earhart GM, Falvo MJ. Parkinson disease and exercise. *Compr Physiol*. 2013;3:833–48.
5. Van Der Kolk NM, King LA. Effects of exercise on mobility in people with Parkinson's disease. *Mov Disord*. 2013;28:1587–96.
6. Li F, Harmer P, Fitzgerald K, Eckstrom E, Stock R, Galver J, et al. Tai chi and postural stability in patients with Parkinson's disease. *N Engl J Med*. 2012;366:511–9.
7. Mak MKY, Wong-Yu ISK. Six-Month Community-Based Brisk Walking and Balance Exercise Alleviates Motor Symptoms and Promotes Functions in People with Parkinson's Disease: A Randomized Controlled Trial. *J Parkinsons Dis*. 2021;11:1431–41.
8. Rios Romenets S, Anang J, Fereshtehnejad SM, Pelletier A, Postuma R. Tango for treatment of motor and non-motor manifestations in Parkinson's disease: a randomized control study. *Complement Ther Med*. 2015;23:175–84.
9. Lan C, Chen SY, Lai JS, Wong AM. Tai chi chuan in medicine and health promotion. *Evid Based Complement Alternat Med*. 2013;2013:502131.
10. Field T. Tai Chi research review. *Complement Ther Clin Pract*. 2011;17:141–6.
11. Li F, Harmer P. Economic Evaluation of a Tai Ji Quan Intervention to Reduce Falls in People With Parkinson Disease, Oregon, 2008–2011. *Prev Chronic Dis*. 2015;12:E120.
12. Mahalakshmi B, Maurya N, Lee SD, Bharath Kumar V. Possible Neuroprotective Mechanisms of Physical Exercise in Neurodegeneration. *Int J Mol Sci*. 2020;21.
13. Zhou M, Liao H, Sreepada LP, Ladner JR, Balschi JA, Lin AP. Tai Chi Improves Brain Metabolism and Muscle Energetics in Older Adults. *J Neuroimaging*. 2018;28:359–64.
14. Liu J, Tao J, Liu W, Huang J, Xue X, Li M, et al. Different modulation effects of Tai Chi Chuan and Baduanjin on resting-state functional connectivity of the default mode network in older adults. *Soc Cogn Affect Neurosci*. 2019;14:217–24.
15. Jiang T, Li G, Xu J, Gao S, Chen X. The Challenge of the Pathogenesis of Parkinson's Disease: Is Autoimmunity the Culprit? *Front Immunol*. 2018;9:2047.
16. Hatano T, Saiki S, Okuzumi A, Mohny RP, Hattori N. Identification of novel biomarkers for Parkinson's disease by metabolomic technologies. *J Neurol Neurosurg Psychiatry*. 2016;87:295–301.

17. Scherzer CR, Eklund AC, Morse LJ, Liao Z, Locascio JJ, Fefer D, et al. Molecular markers of early Parkinson's disease based on gene expression in blood. *Proc Natl Acad Sci U S A*. 2007;104:955–60.
18. Karlsson MK, Sharma P, Aasly J, Toft M, Skogar O, Sæbø S, et al. Found in transcription: accurate Parkinson's disease classification in peripheral blood. *J Parkinsons Dis*. 2013;3:19–29.
19. Calligaris R, Banica M, Roncaglia P, Robotti E, Finaurini S, Vlachouli C, et al. Blood transcriptomics of drug-naïve sporadic Parkinson's disease patients. *BMC Genom*. 2015;16:876.
20. Grünblatt E, Mandel S, Jacob-Hirsch J, Zeligson S, Amariglo N, Rechavi G, et al. Gene expression profiling of parkinsonian substantia nigra pars compacta; alterations in ubiquitin-proteasome, heat shock protein, iron and oxidative stress regulated proteins, cell adhesion/cellular matrix and vesicle trafficking genes. *J Neural Transm (Vienna)*. 2004;111:1543–73.
21. Su J, Huang P, Qin M, Lu Q, Sang X, Cai Y, et al. Reduction of HIP2 expression causes motor function impairment and increased vulnerability to dopaminergic degeneration in Parkinson's disease models. *Cell Death Dis*. 2018;9:1020.
22. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. 1992;55:181–4.
23. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015;30:1591–601.
24. Pedersen M, Zalesky A, Omidvarnia A, Jackson GD. Multilayer network switching rate predicts brain performance. *Proc Natl Acad Sci U S A*. 2018;115:13376–81.
25. Pedersini CA, Guàrdia-Olmos J, Montalà-Flaquer M, Cardobi N, Sanchez-Lopez J, Parisi G, et al. Functional interactions in patients with hemianopia: A graph theory-based connectivity study of resting fMRI signal. *PLoS One*. 2020;15:e0226816.
26. Assländer L, Hettich G, Mergner T. Visual contribution to human standing balance during support surface tilts. *Hum Mov Sci*. 2015;41:147–64.
27. Ruan X, Li Y, Li E, Xie F, Zhang G, Luo Z, et al. Impaired Topographical Organization of Functional Brain Networks in Parkinson's Disease Patients With Freezing of Gait. *Front Aging Neurosci*. 2020;12:580564.
28. Rogge AK, Röder B, Zech A, Hötting K. Exercise-induced neuroplasticity: Balance training increases cortical thickness in visual and vestibular cortical regions. *Neuroimage*. 2018;179:471–79.
29. Thibes RB, Novaes NP, Lucato LT, Campanholo KR, Melo LM, Leite CC, et al. Altered Functional Connectivity Between Precuneus and Motor Systems in Parkinson's Disease Patients. *Brain Connect*. 2017;7:643–47.
30. Qin XY, Zhang SP, Cao C, Loh YP, Cheng Y. Aberrations in Peripheral Inflammatory Cytokine Levels in Parkinson Disease: A Systematic Review and Meta-analysis. *JAMA Neurol*. 2016;73:1316–24.
31. Saghazadeh A, Ferrari CC, Rezaei N. Deciphering variability in the role of interleukin-1 β in Parkinson's disease. *Rev Neurosci*. 2016;27:635–50.

32. Shao Y, Le W. Recent advances and perspectives of metabolomics-based investigations in Parkinson's disease. *Mol Neurodegener.* 2019;14:3.
33. Virarkar M, Alappat L, Bradford PG, Awad AB. L-arginine and nitric oxide in CNS function and neurodegenerative diseases. *Crit Rev Food Sci Nutr.* 2013;53:1157–67.
34. Bose A, Beal MF. Mitochondrial dysfunction in Parkinson's disease. *J Neurochem.* 2016;139(Suppl 1):216–31.
35. Soliman AM, Fathalla AM, Moustafa AA. Adenosine role in brain functions: Pathophysiological influence on Parkinson's disease and other brain disorders. *Pharmacol Rep.* 2018;70:661–67.
36. Chen ZJ, Niles EG, Pickart CM. Isolation of a cDNA encoding a mammalian multiubiquitinating enzyme (E225K) and overexpression of the functional enzyme in *Escherichia coli*. *J Biol Chem.* 1991;266:15698–704.
37. Bence NF, Sampat RM, Kopito RR. Impairment of the ubiquitin-proteasome system by protein aggregation. *Science.* 2001;292:1552–5.

Figures

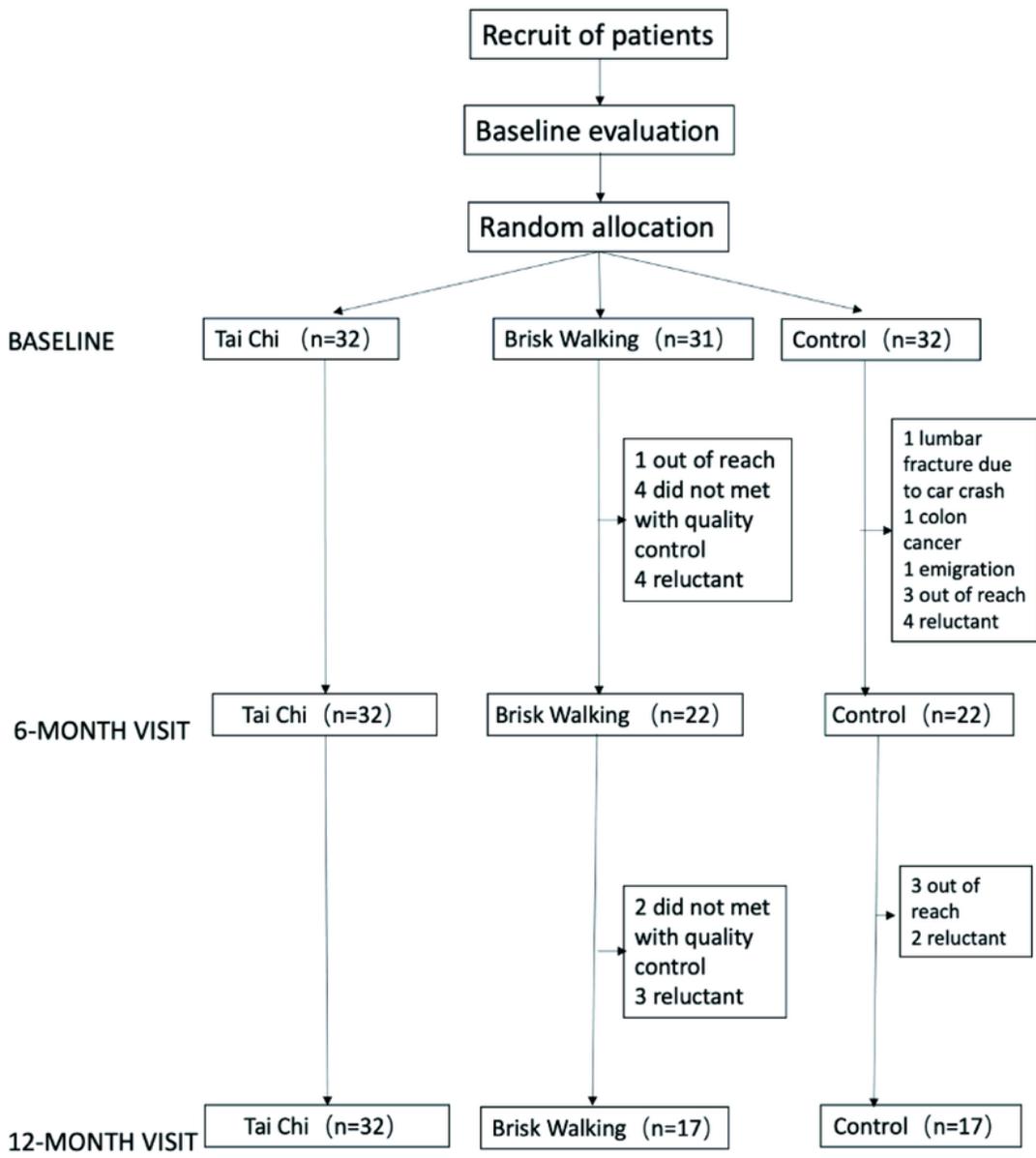


Figure 1

The flow chart of the patient recruitment and follow up

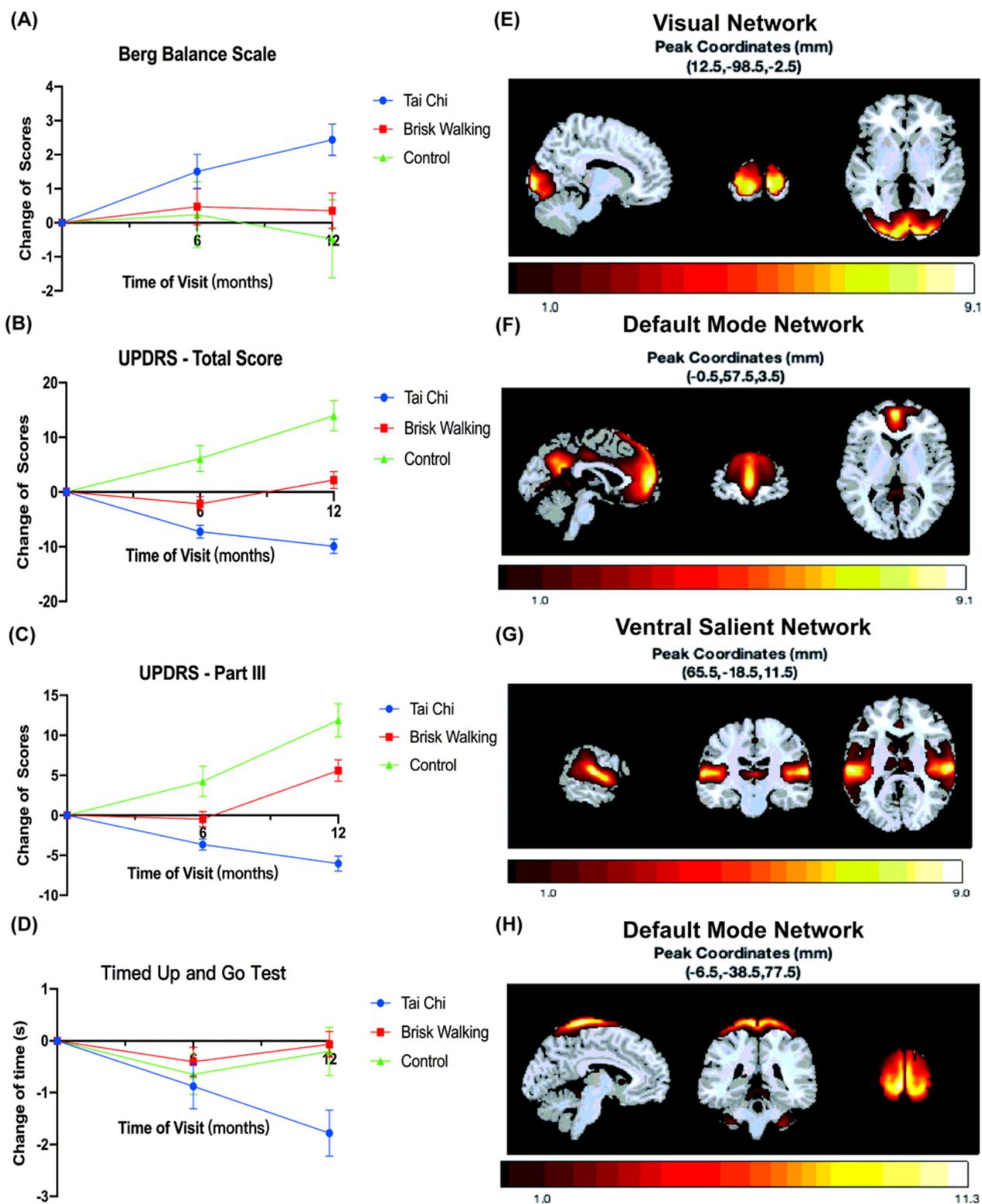


Figure 2

Changes of motor symptoms between groups and related fMRI changes. (A-D) The changes of rating scales between 3 groups. Data are shown as mean \pm SEM. (A) Berg Balance Scale, (B) UPDRS – Total Score, (C) UPDRS – Part III, (D) Timed Up and Go Test. (E-H) Neural networks associated with the changes of rating scales: (E) Visual network associated with Berg Balance scale; (F) Default mode

network associated with UPDRS – Total score; (G) Ventral salient network associated with UPDRS – Total score, but not significant; (H) Default mode network associated with UPDRS – Part III.

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