Non-pharmacological therapy for neurodegenerative disease

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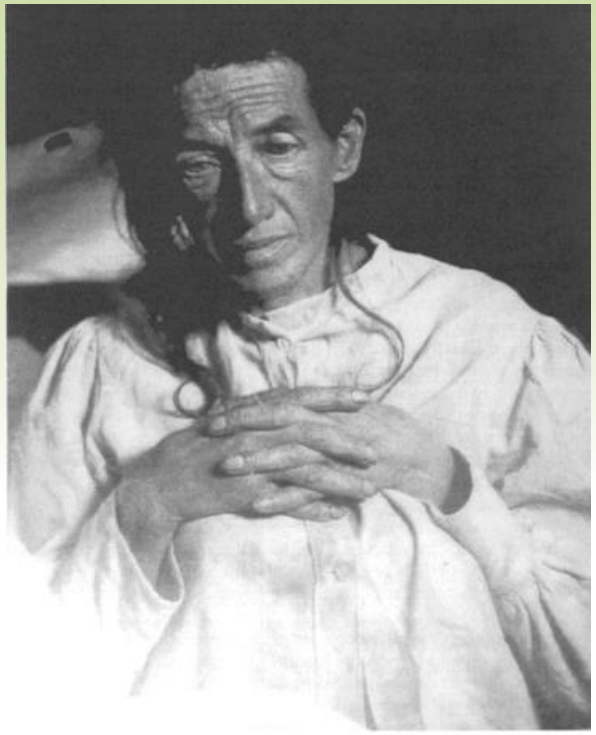
AD & PD: Commonest Neurodegenerative diseases

Dr. Alois Alzheimer



Alzheimer's original patient: Auguste D.

Dr. James Parkinson

Symptoms

Alzheimer' s Disease

Cognition

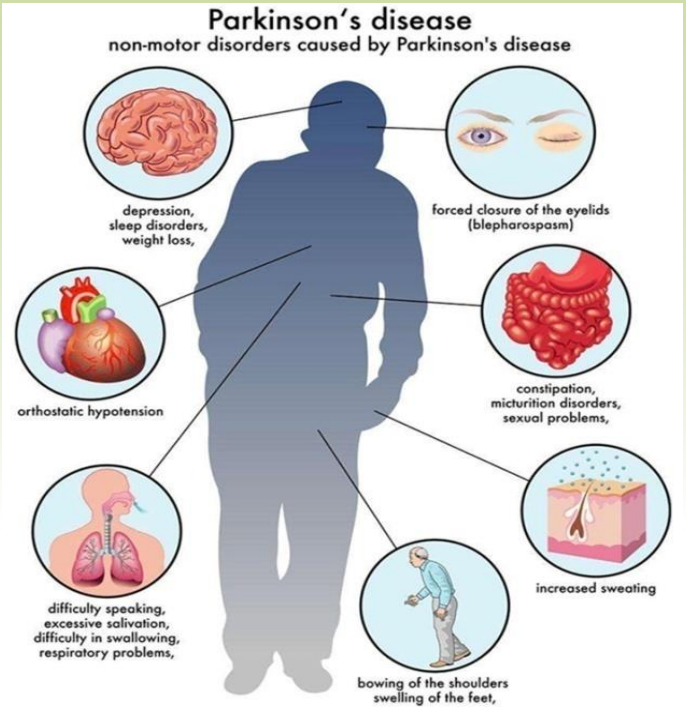
- memory
- language
- executive
- visuospatial

Non-Cog

- psychiatry
- depression
- anxiety
- apathy

Lancet. 2005 Dec 17;366(9503)

Parkinson' s Disease



Motor Symptoms:

- Resting tremor
- Rigidity
- Bradykinesia
- Gait and postural disturbance

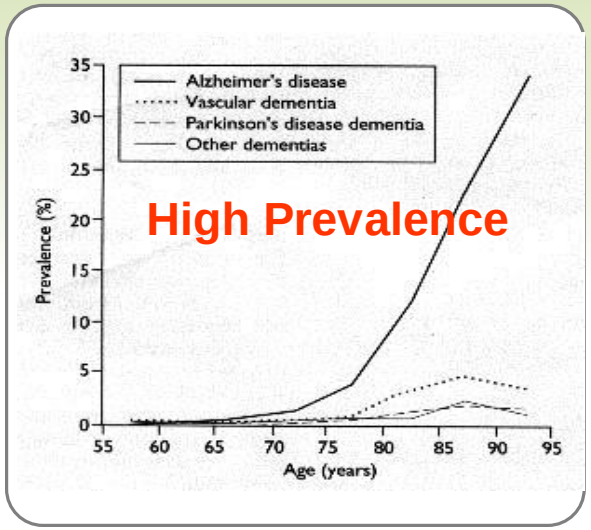
Non-motor Symptoms:

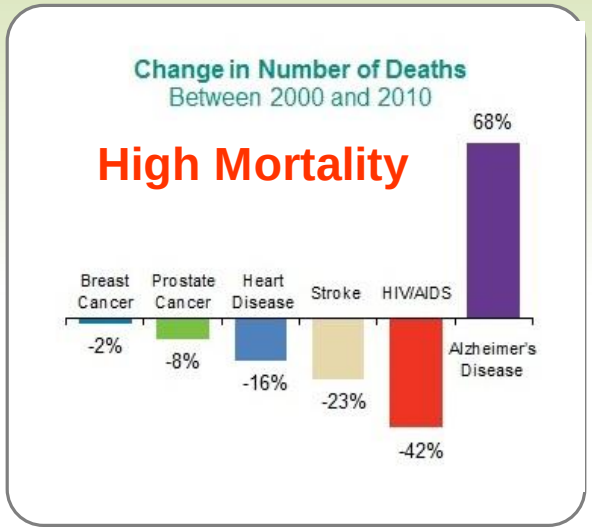
- RBD
- Depression
- Anxiety
- Constipation
- Hyposmia

Lancet. 2009; 373: 2055-66.

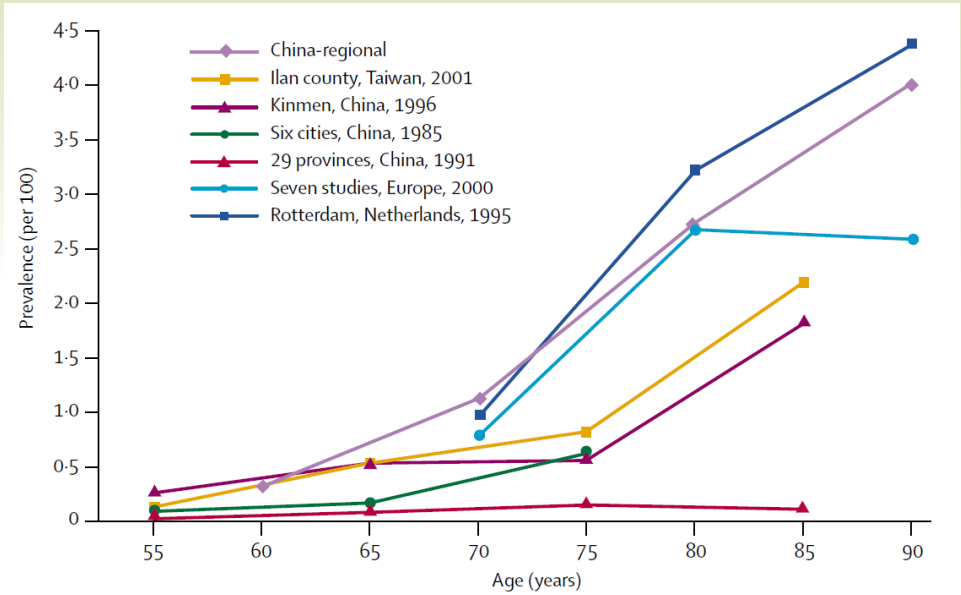
Prevalence

Alzheimer' s Disease
Prevalence 5.4% in China (>65 years)
Nearly ten million





Parkinson' s Disease
Prevalence 1.7% in China (>65 years)
More than 2.5 million



Ferri CP. Lancet. 2005 Dec 17;366(9503)

Zhang ZX.Lancet. 2005 Feb 12-18;365(9459):595-7.

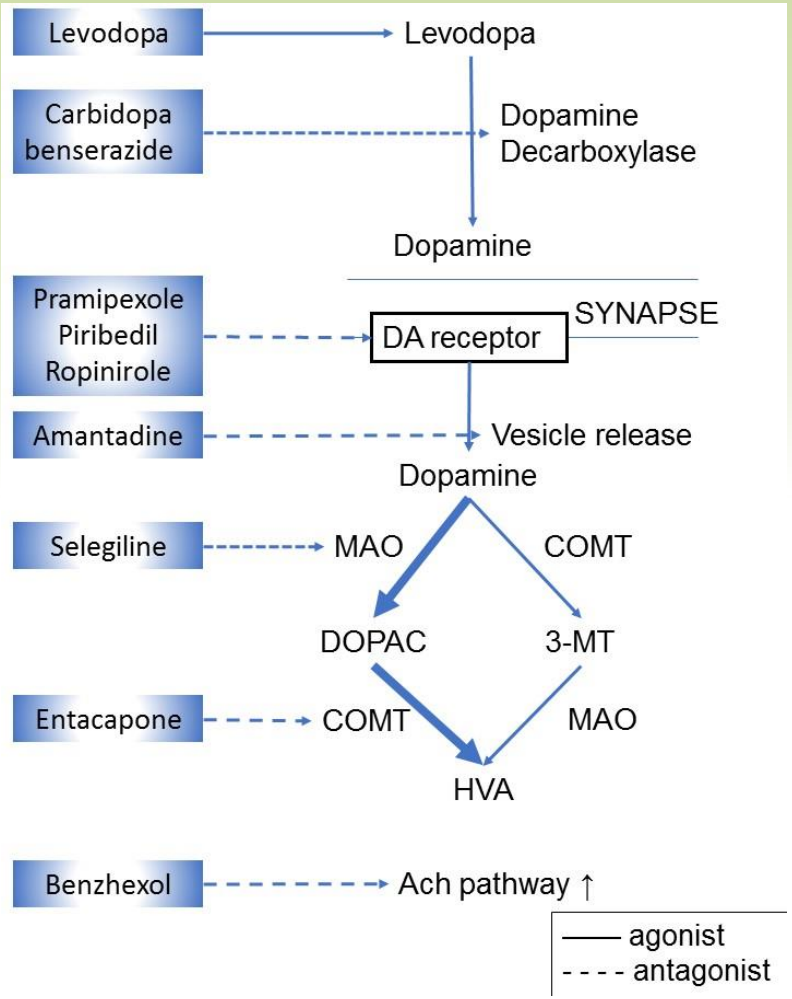
Current Medical Treatment

AD: only a few FDA approved medications with limited effect and some side effects

Treatments-at-a-glance

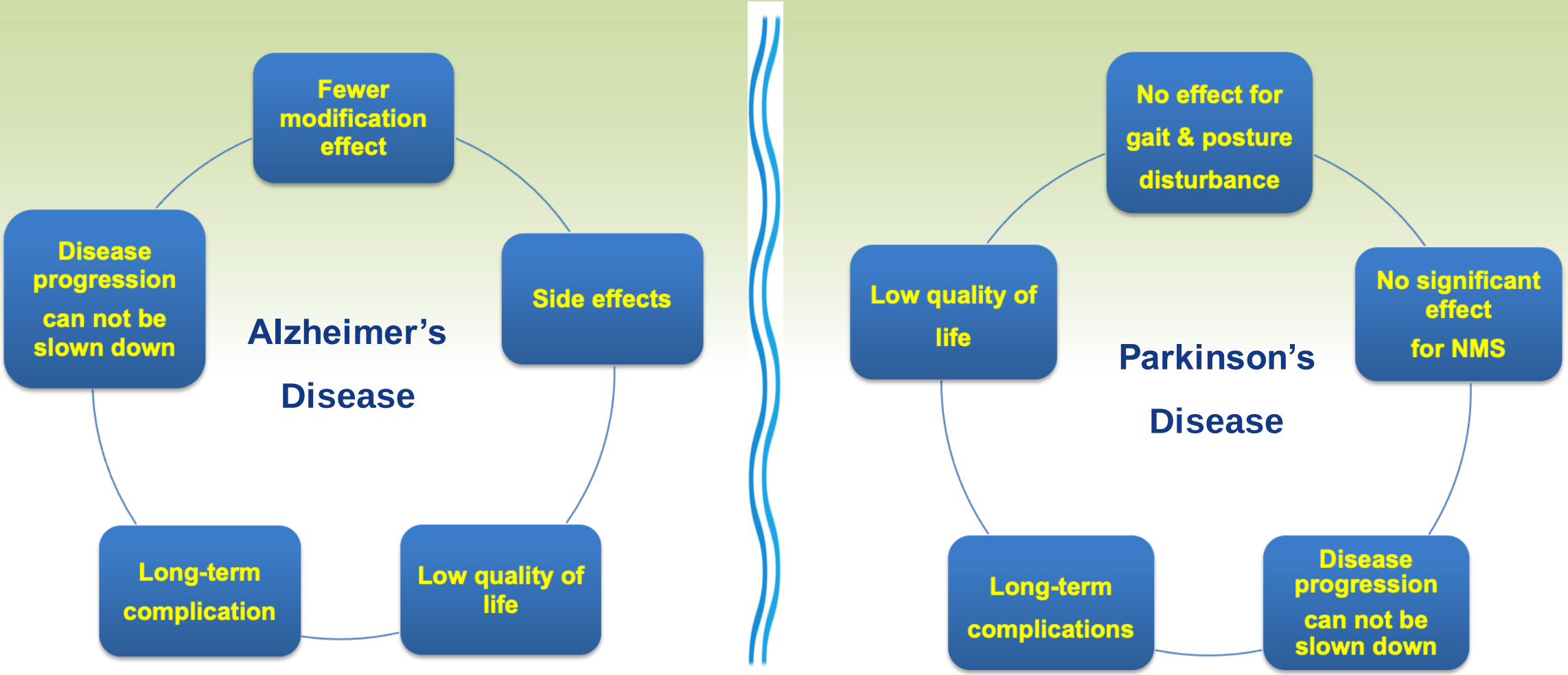
Generic	Brand	Approved For	Side Effects
donepezil	Aricept	All stages	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
galantamine	Razadyne	Mild to moderate	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
memantine	Namenda	Moderate to severe	Headache, constipation, confusion and dizziness.
rivastigmine	Exelon	Mild to moderate	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
memantine + donepezil	Namzaric	Moderate to severe	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, headache, constipation, confusion and dizziness.

PD: many anti-symptom treatment without approved disease-modified therapy



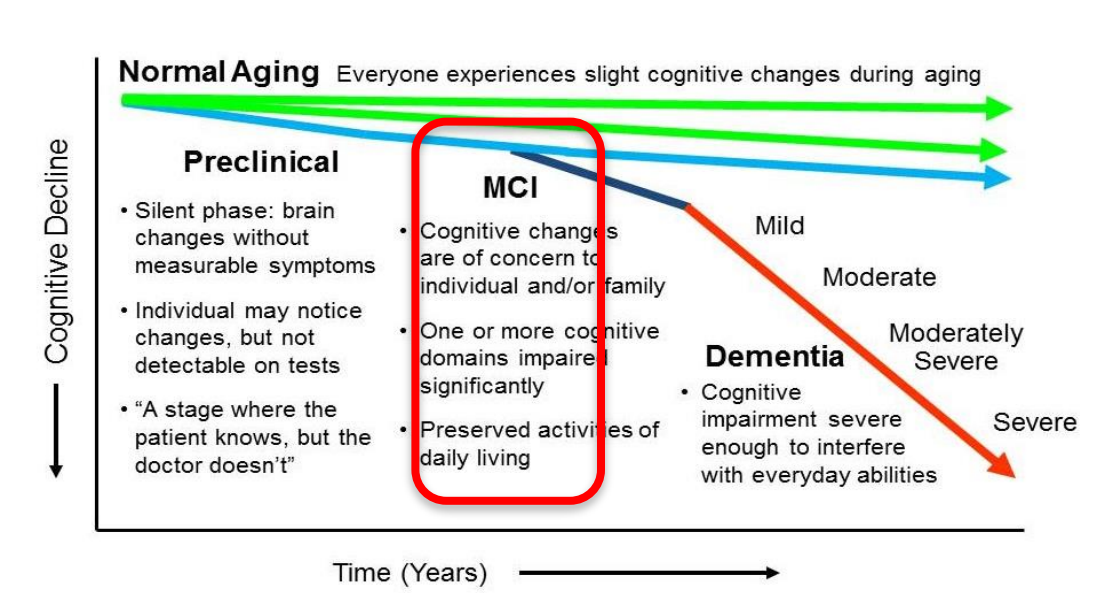
Treatment dilemmas

Drug therapy can improve symptoms, but has many limitations

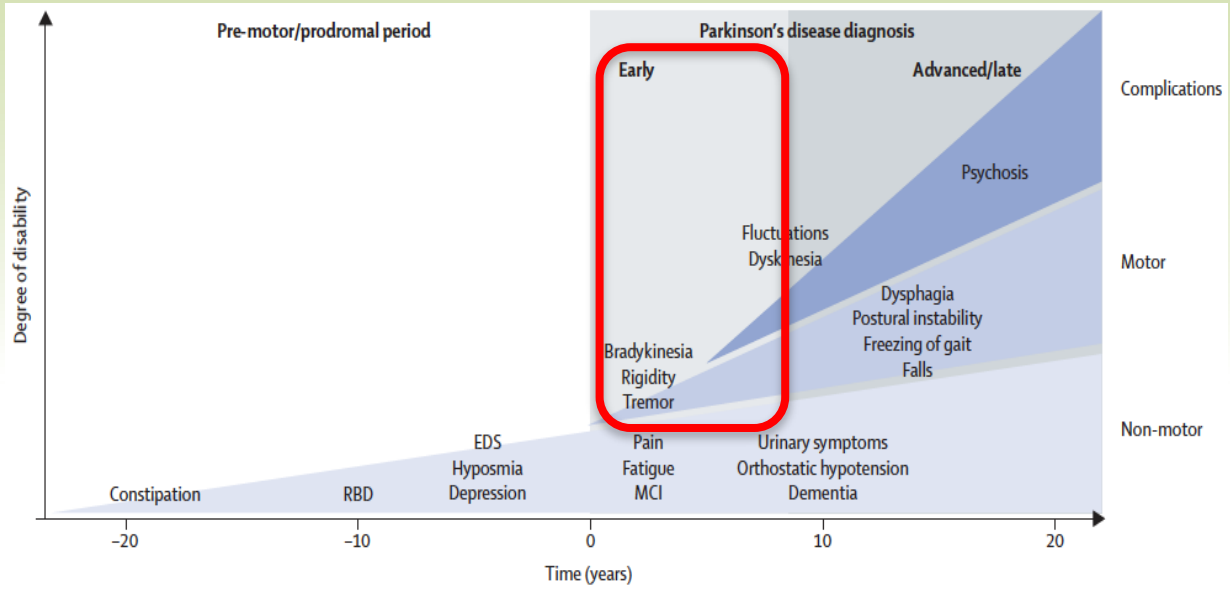


Non-pharmacological Therapy for Early AD & PD

Early intervention can improve symptoms and even delay disease progression



Alzheimer's disease



Parkinson's disease

Cognitive training for old people

Effects of Cognitive Training Interventions With Older Adults

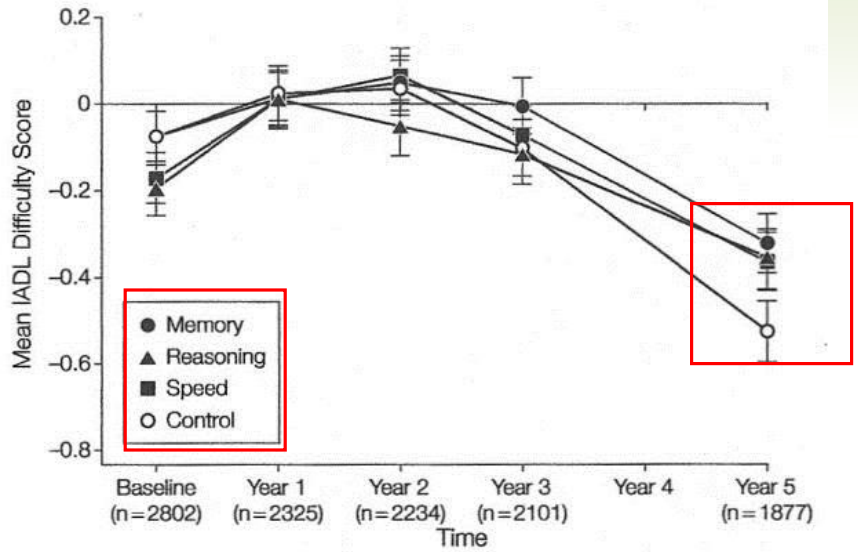
A Randomized Controlled Trial

Karlene Ball, PhD
Daniel B. Berch, PhD
Karin F. Helmers, PhD
Jared B. Jobe, PhD
Mary D. Leveck, PhD
Michael Marsiske, PhD

Context Cognitive function in older adults is related to independent living and need for care. However, few studies have addressed whether improving cognitive functions might have short- or long-term effects on activities related to living independently.

Objective To evaluate whether 3 cognitive training interventions improve mental abilities and daily functioning in older, independent-living adults.

Design Randomized, controlled, single-blind trial with recruitment conducted from March 1998 to October 1999 and 2-year follow-up through December 2001.



Training

- **Memory**
- **Reasoning**
- **Speed of Process**

Results in 5-year after training

- **Training effect lasted for 3 years**
- **Training group ability of daily activity**

Cognitive training slowed down declined ADL

Ball K. JAMA, 2002, 288(18): 2271-2281.

Multitasking training for old people

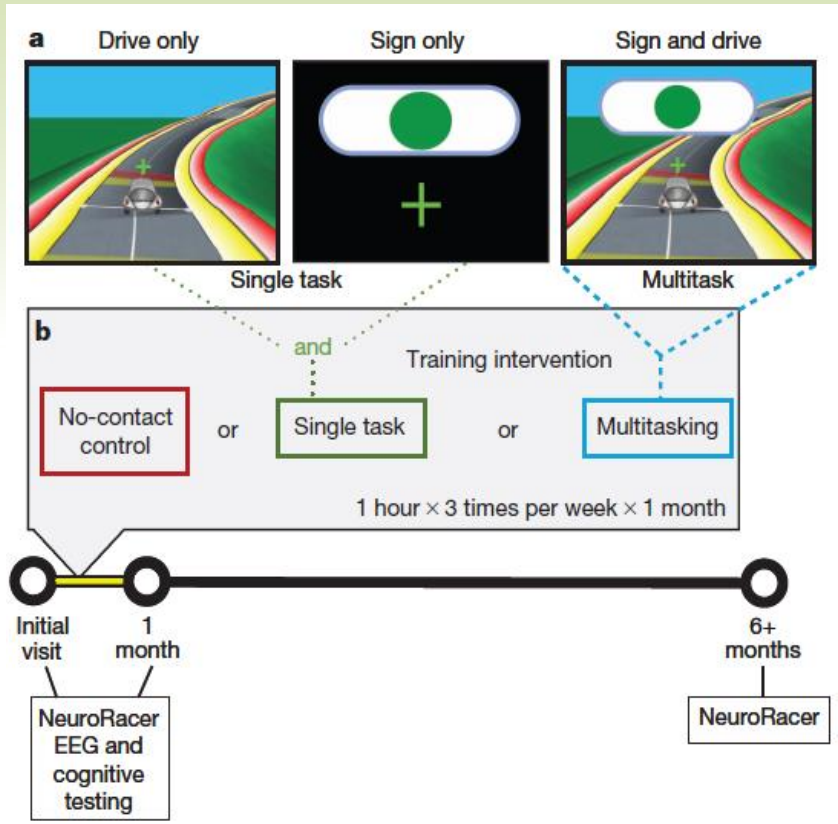
LETTER

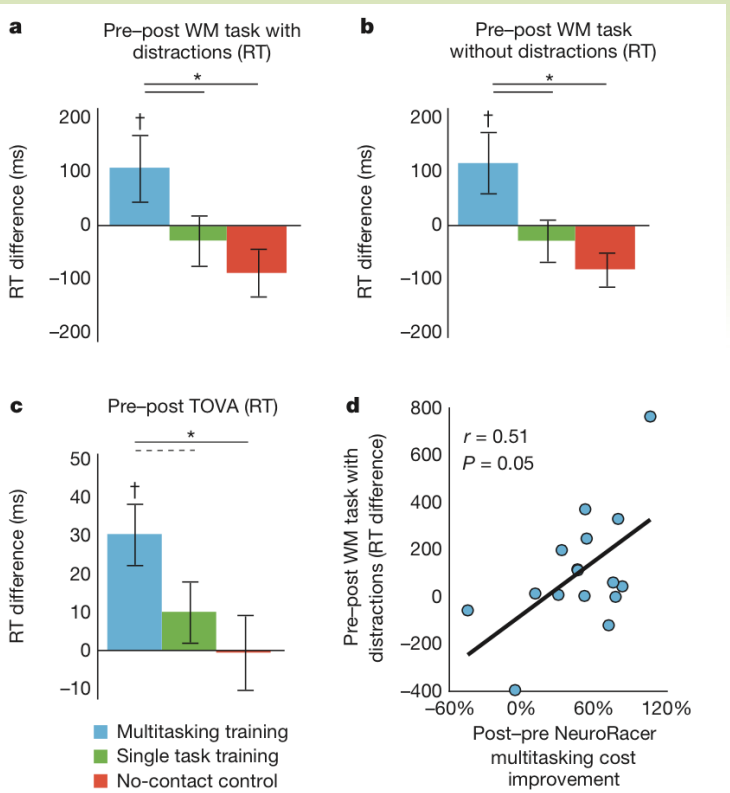
doi:10.1038/nature12486

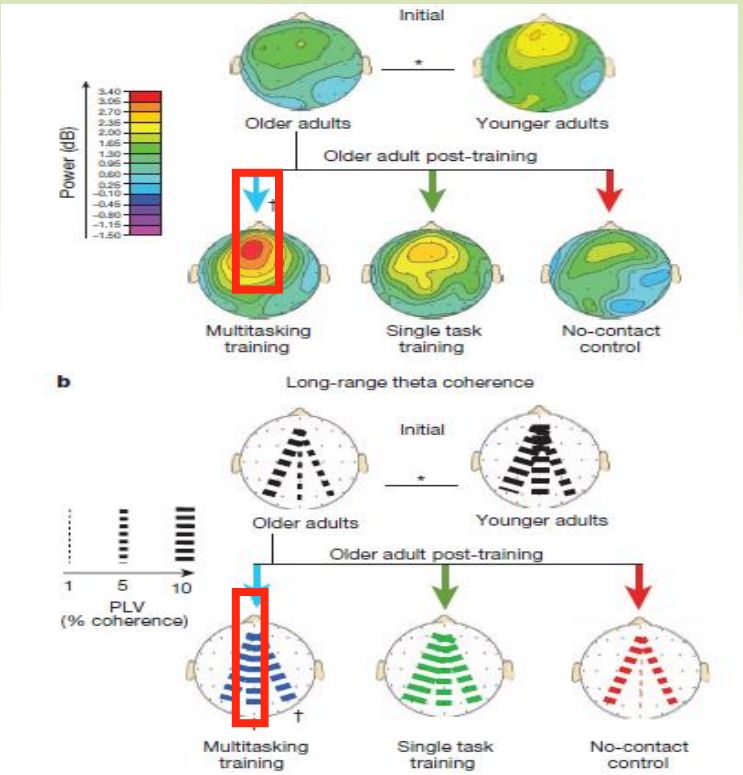
Video game training enhances cognitive control in older adults

J. A. Anguera[1,2,3], J. Boccanfuso[1,3], J. L. Rintoul[1,3], O. Al-Hashimi[1,2,3], F. Faraji[1,3], J. Janowich[1,3], E. Kong[1,3], Y. Larraburo[1,3], C. Rolle[1,3], E. Johnston[1] & A. Gazzaley[1,2,3,4]

multitasking training enhances cognitive control in older adults





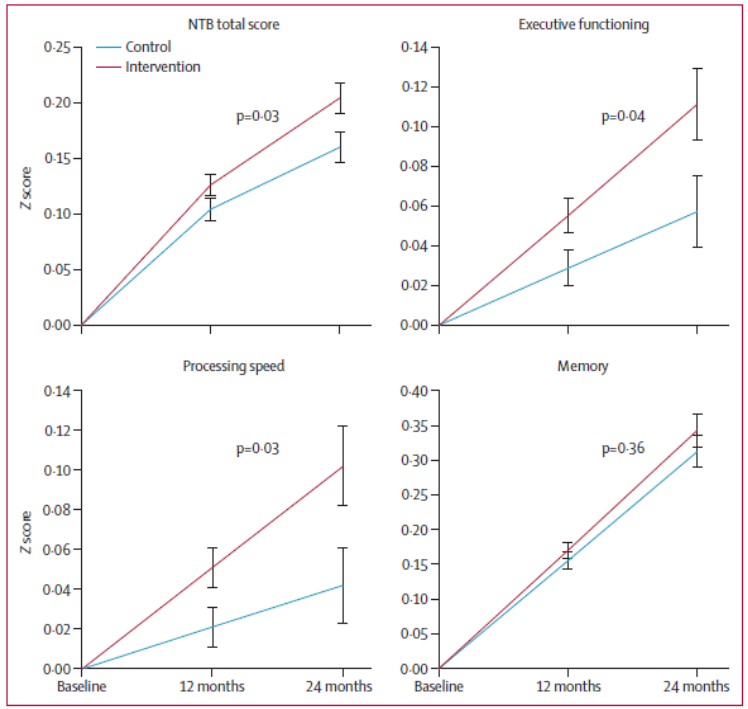


J. A. Anguera. Nature, 2013

Combined diet, exercise and cognitive training for old people

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto



FINGER study：

- **Combined intervention lasted for 2 years**
- **Training group showed advantages in global cognitive ability, executive function and processing speed after two-year intervention**

Ngandu T. Lancet, 2015

Cognitive training for MCI

Original Paper

Neurodegenerative Diseases

Neurodegenerative Dis 2011;8:138–145
DOI: 10.1159/000320575

Received: September 4, 2009
Accepted after revision: August 20, 2010
Published online: December 3, 2010

Effectiveness of Nonpharmacological Approaches in Patients with Mild Cognitive Impairment

Method :

- ➢Attention training
- ➢Executive functioning training
- ➢Memory training : episodic and semantic
- ➢Training for 6 months

Table 3. Participants' performance in measures where significant between-group differences were observed 6 months after the first assessment

Ability	Therapeutic condition		
	NoTh (n = 72)	nPhTh (n = 104)	p
General cognitive performance (MMSE)	27.06 (2.34)	29.00 (6.18)	0.000
General cognitive performance (MoCA)	22.45 (4.78)	24.71 (3.05)	0.005
Executive function			
Planning (FUCAS)	6.18 (0.56)	6.04 (0.25)	0.004
Verbal memory			
Delayed recall (MoCA)	2.38 (1.76)	3.19 (1.61)	0.003
Visual-constructive abilities			
Complex figure copying (ROCFT)	29.18 (7.19)	31.53 (5.30)	0.010
Clock drawing (MoCA)	2.29 (0.85)	2.58 (0.74)	0.012
Daily functioning			
Total daily functioning (FRSSD)	3.91 (2.49)	2.67 (1.70)	0.001

Table 4. Experimental patient performance with nPhTh (n = 104) in measures where significant changes were observed between the first and second assessments

Ability	1st assessment	2nd assessment	p
General cognitive performance (MoCA)	22.98 (3.36)	24.71 (3.05)	0.000
Attention			
Switching of visual selective attention (TEA)	14.11 (59.63)	6.23 (3.35)	0.001
Visual selective attention (TEA)	5.17 (1.81)	4.62 (1.38)	0.001
Digit symbol (WAIS-R)	32.21 (14.19)	34.45 (13.17)	0.000
Language			
Phrase comprehension (BDAE)	8.36 (1.33)	8.68 (1.25)	0.006
Verbal memory			
Delayed recall (RAVLT)	−2.62 (2.60)	−1.89 (2.56)	0.000
Delayed recall (MoCA)	2.26 (1.63)	3.19 (1.61)	0.000
Executive function			
Verbal fluency (FAS)	9.80 (3.00)	11.26 (3.18)	0.000
Visuoperceptual abilities			
Complex figure copying (ROCFT)	29.85 (5.89)	31.53 (5.30)	0.000
Daily functioning			
Total daily functioning (FRSSD)	3.04 (1.61)	2.67 (1.70)	0.013

Result A:

Better cognitive score of training group than control group

Result B:

Better cognitive score in post-training than pre-training state in the training group

Tsolaki M, et al. Neurodegener Dis 2010;8(3):138-145.

Our Studies: Cognitive and Tai Chi training for MCI

Year	Intervention	Participant	Follow-up
2012	Cognitive training in nursing home	MCI/Dementia	6-month
2016-2018	Cognitive training in community	MCI	18-month
2018-2021	Cognitive + Tai Chi training	MCI	24-month

Our study: 6-month cognitive training for cognitive impairment

Journal of Alzheimer's Disease 36 (2013) 245–251
DOI 10.3233/JAD-130158
IOS Press

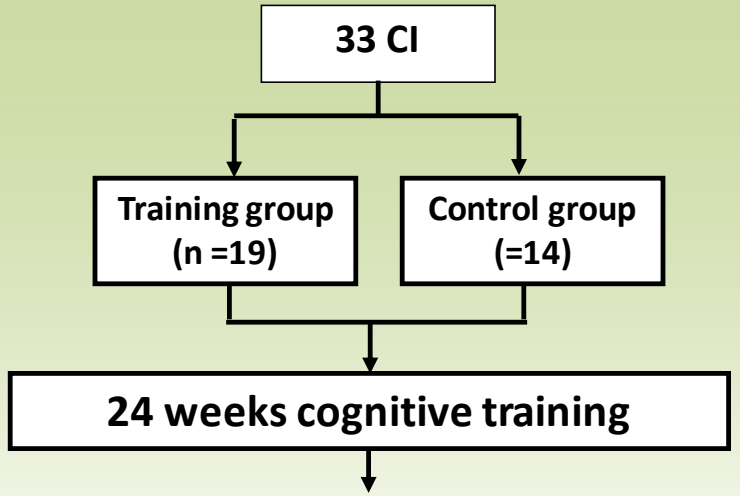
The Impact of Human-Computer Interaction-Based Comprehensive Training on the Cognitive Functions of Cognitive Impairment Elderly Individuals in a Nursing Home

Jun-Peng Zhuang[a,1], Rong Fang[a,1], Xia Feng[b], Xu-Hua Xu[a], Li-Hua Liu[a], Qing-Ke Bai[c], Hui-Dong Tang[a,*], Zhen-Guo Zhao[c,*] and Sheng-Di Chen[a,*]

Cognitive Training protocol

1) Picture memorization
2) Sorting: pick out the salient item (of four) presented on the screen
3) Drawing
4) Opening, required trainees to open the simulated door on the screen
5) Sequencing numbers

Cognitive training improved visuospatial ability in nursing home



Cognitive scores before and after training

Comparison of low and high global cortical atrophy scores (mean ± SD)

	GCA >15 (n=6)	GCA ≤15 (n=7)	p
Δ ACE-R	0.67 ± 9.33	10.29 ± 16.94	0.243
Δ Orientation	0.33 ± 3.20	2.29 ± 5.16	0.440
Δ Memory	0.67 ± 4.55	0.71 ± 4.96	0.986
Δ Fluency	0.60 ± 2.702	0.67 ± 3.72	0.974
Δ Language	3.724 ± 3.66	4.86 ± 5.76	0.204
Δ Visuospatial ability	−1.67 ± 3.83	2.00 ± 1.73	0.043

Δ, After Intervention - Before Intervention; ACE-R, Addenbrooke's Cognitive Examination-Revised.

Our study：18-month cognitive training for MCI

NeuroImage: Clinical 22 (2019) 101691

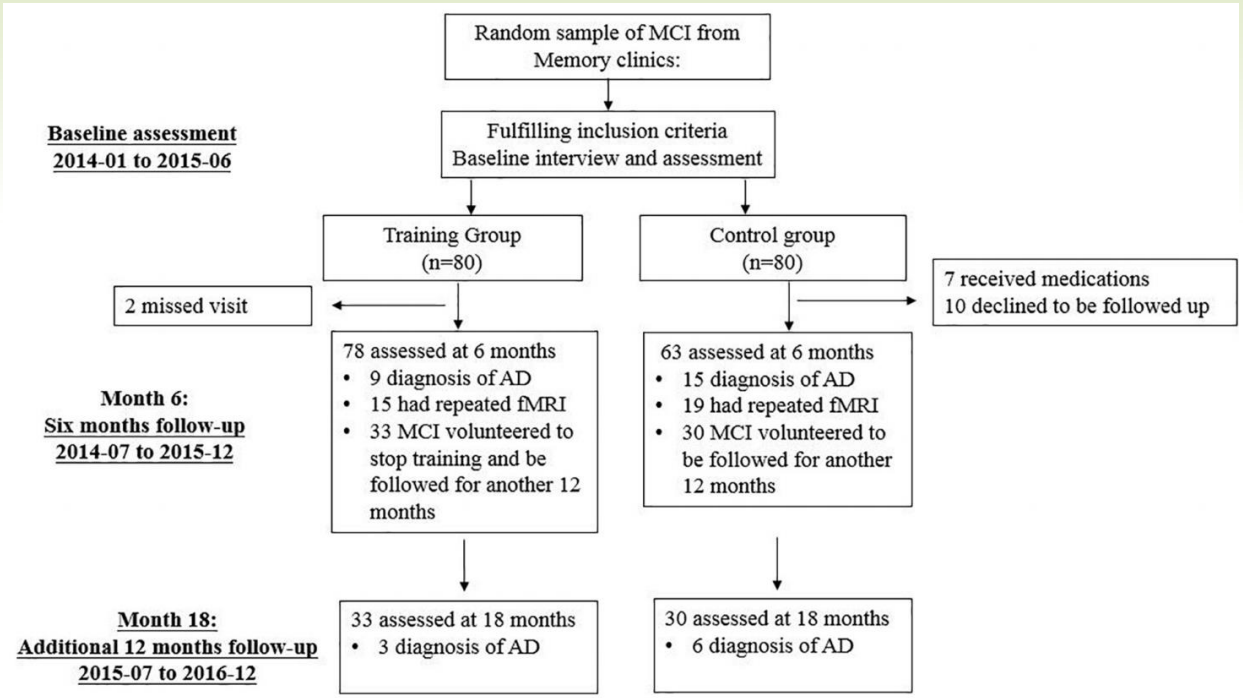
Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Computerized cognitive training for Chinese mild cognitive impairment patients: A neuropsychological and fMRI study

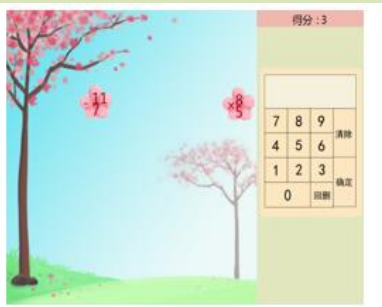
Bin-Yin Li[a,1], Na-Ying He[b,1], Yuan Qiao[a], Hong-Min Xu[b], Yi-Zhou Lu[a], Pei-Jing Cui[c], Hua-Wei Ling[b], Fu-Hua Yan[b,*], Hui-Dong Tang[a,*], Sheng-Di Chen[a,*]



Online cognitive training

A: Mental rotation task

B: Visual search task



C: Speed of calculation

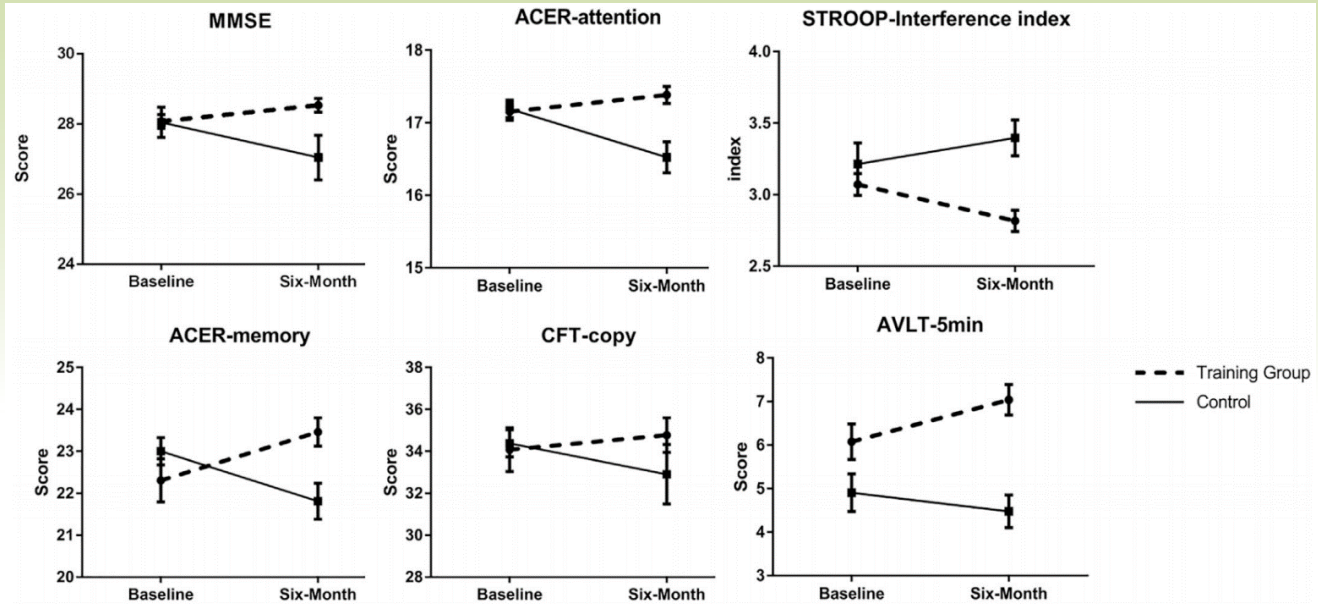
Events displayed

30-second music

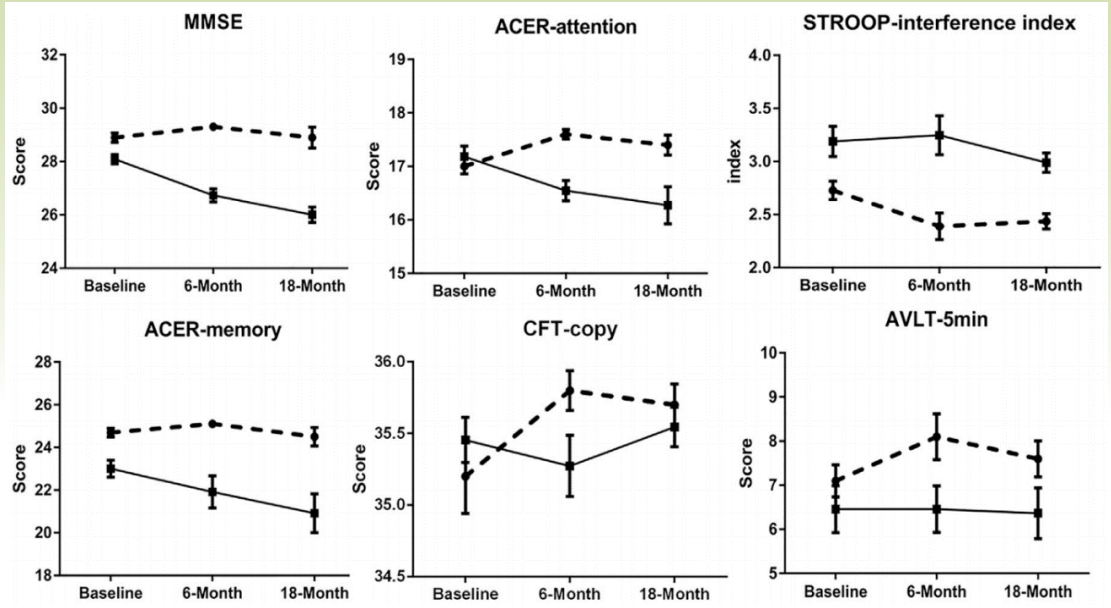
Choose the right event by given clues

Effect size of Training

Effect size of 6-month training



Post-training effect of 6-month training

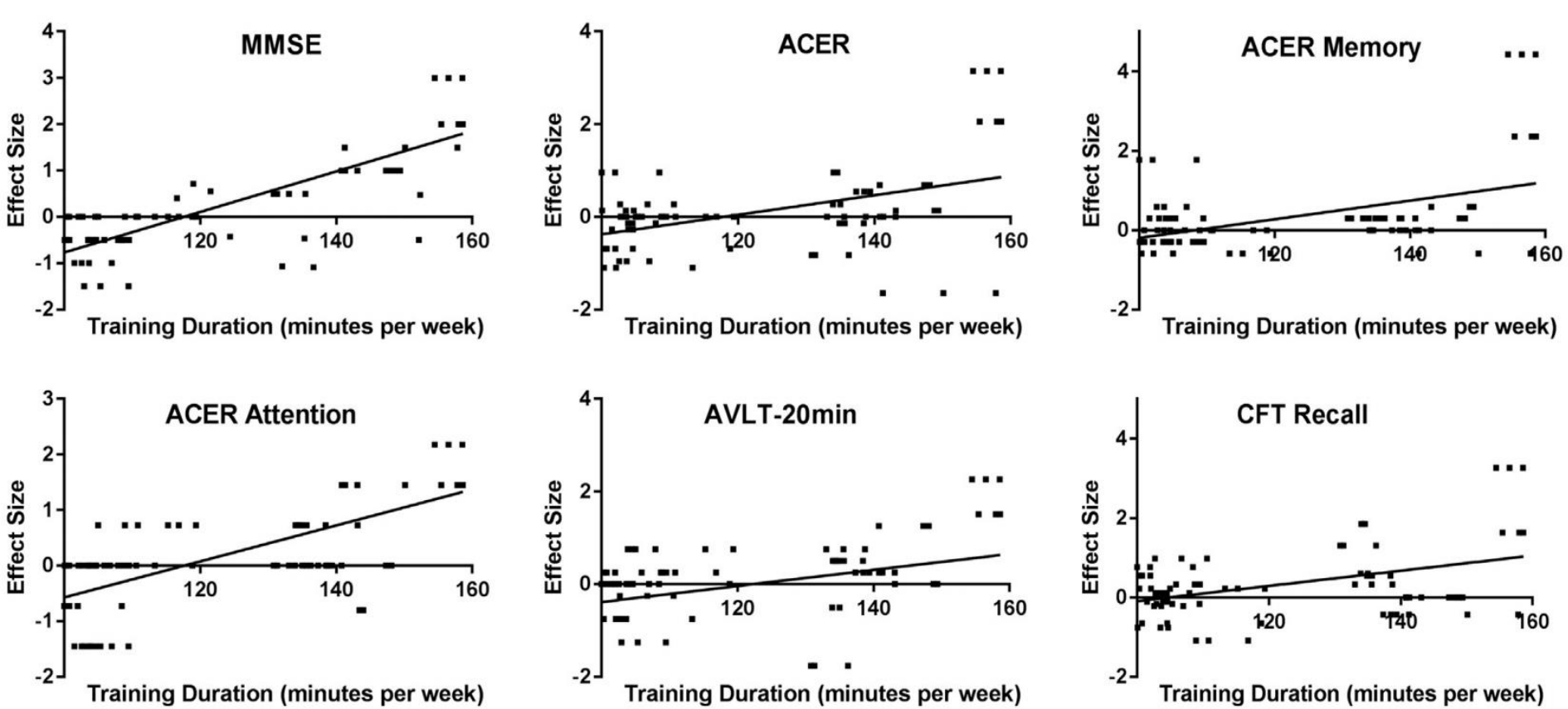


The 6-month cognitive training improved general cognition, attention and memory

- Another 12-month follow-up after 6-month training
- Training effect waned in the 12 months after training

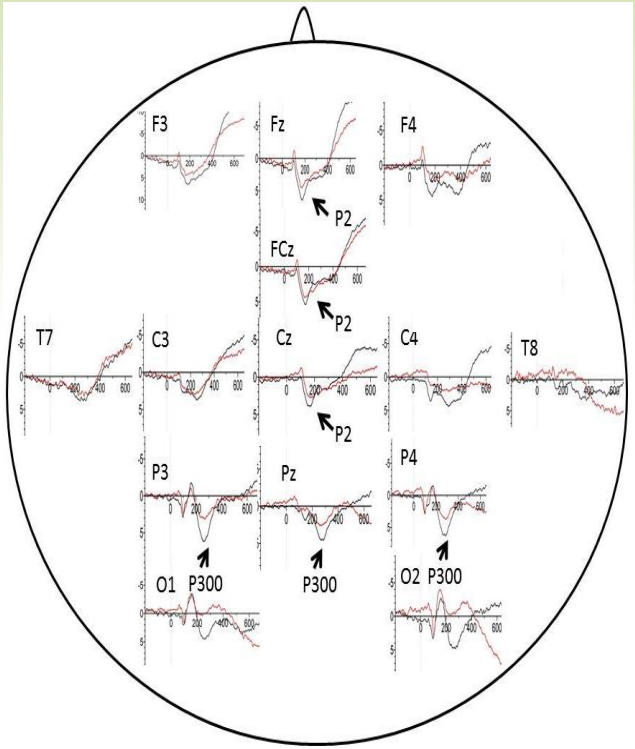
Training Duration and Effect Size

Training duration correlated with effect size of training measured by various tests

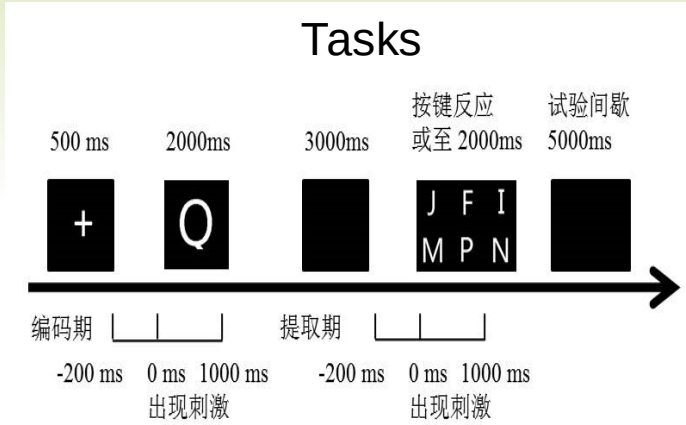


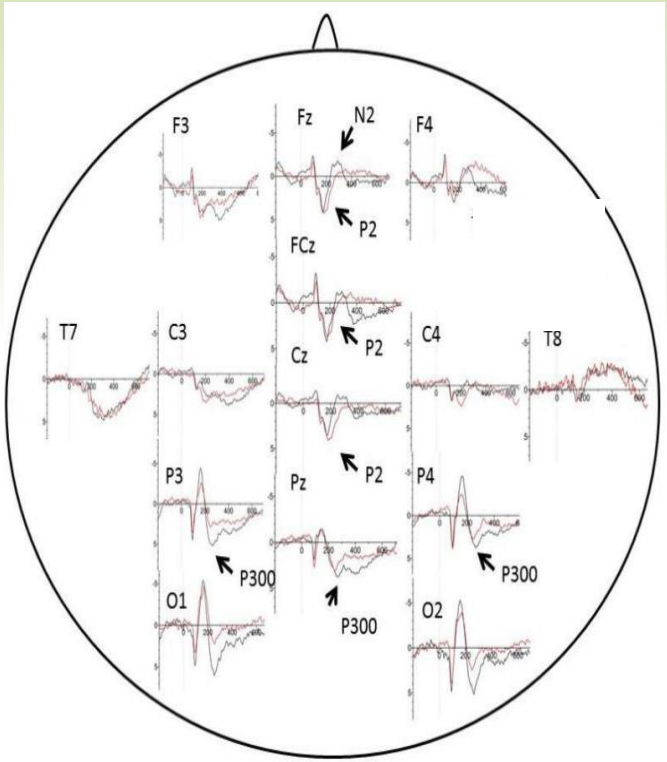
Mechanism: ERP study in cognitive training for MCI

- We compared encoding and retrieval phase of working memory before and after training
- Training group: amplitude of P300 significantly increased in retrieval phase of memory
- Control group: a slight increase.
- It suggests positive training effect in retrieval phase of memory



Training Group



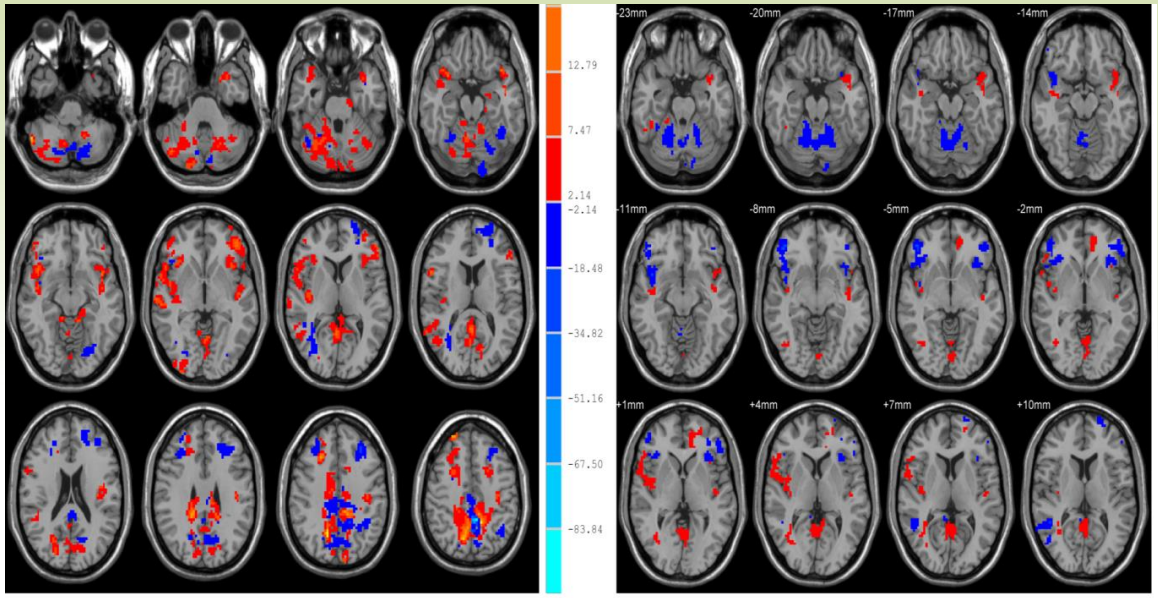


Control Group

Mechanism: fMRI study in cognitive training for MCI

Time effect: repeated measure in MCI

Significantly increased neural activities (by fALFF) in temporal and parietal lobe



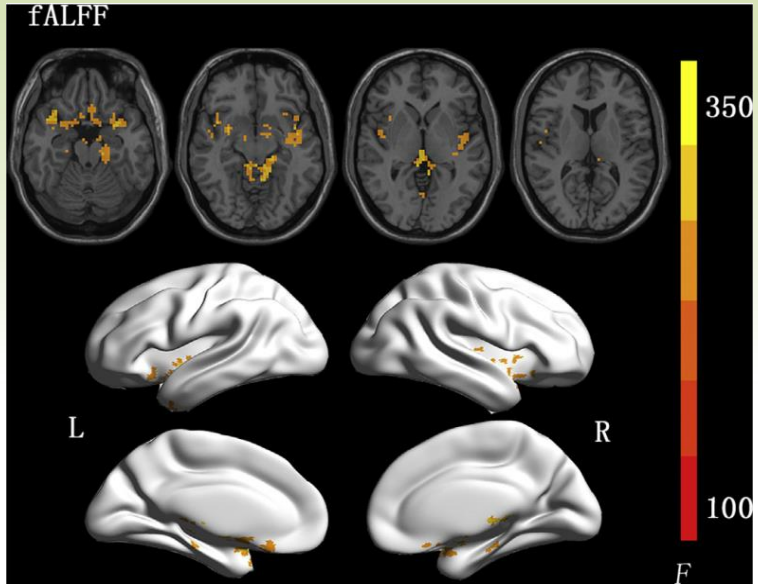
Training Group

Control Group

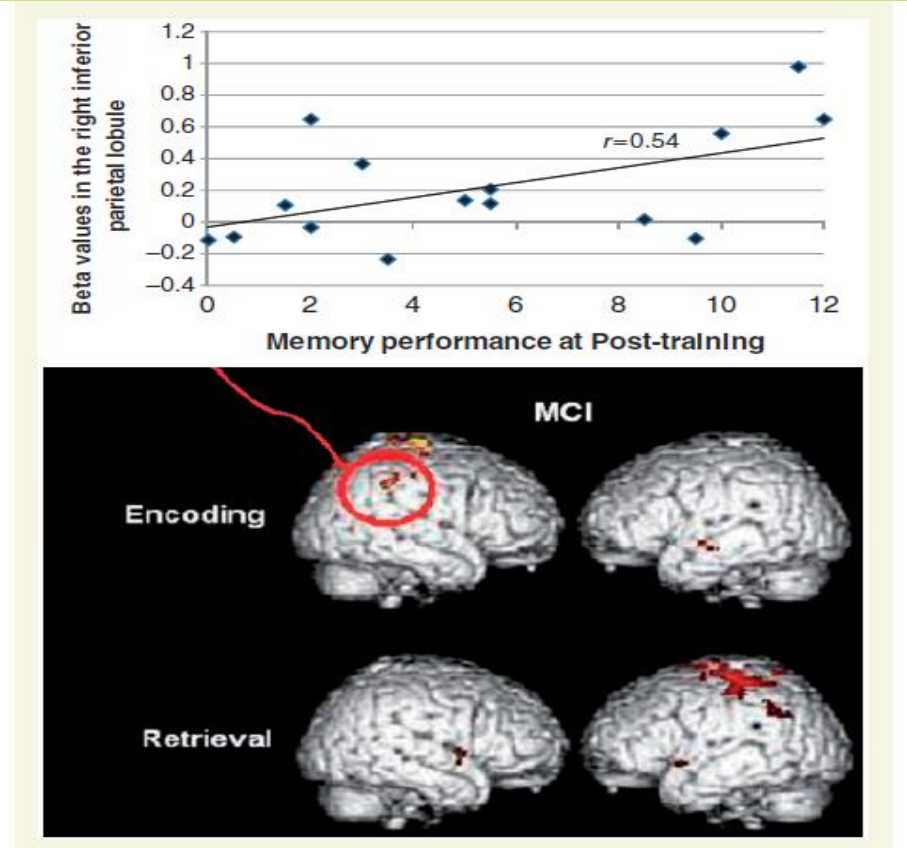
(Blue = Decreased activity, Red = Increased activity)

Training effect: Group × Time interaction

Significantly increased fALFF in bilateral temporal poles and insular cortex

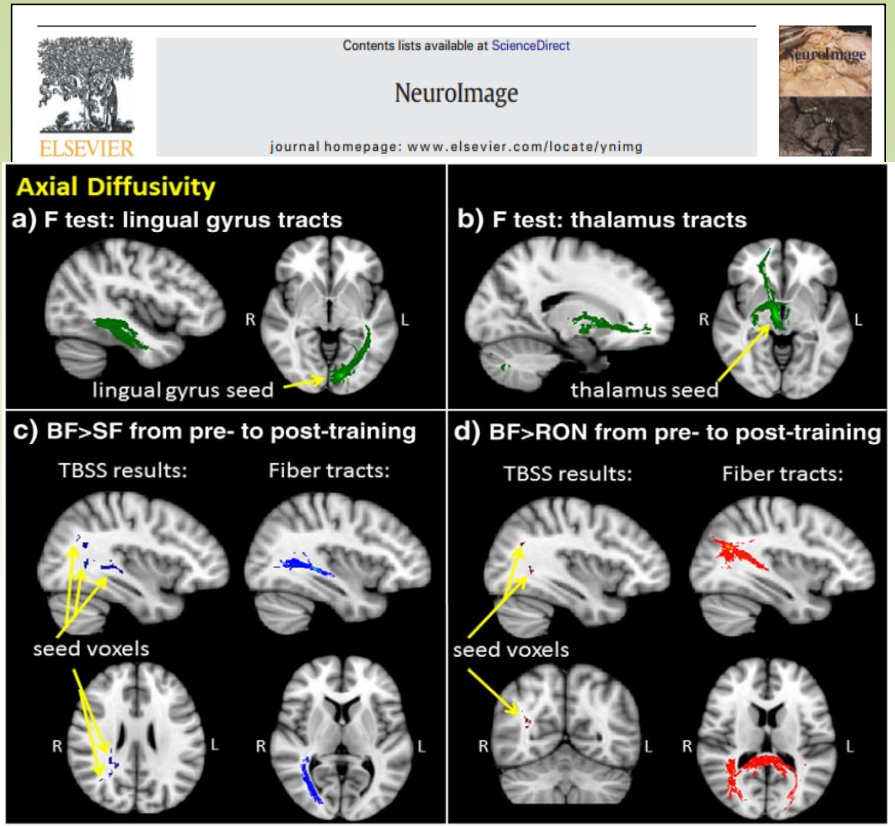


Mechanism: fMRI study in cognitive intervention



Local neural activity intensified after training:

- Encoding and Retrieval in memory： Bilateral cerebral hemisphere more activated after memory training
- Right inferior parietal lobule showed increased BOLD signals



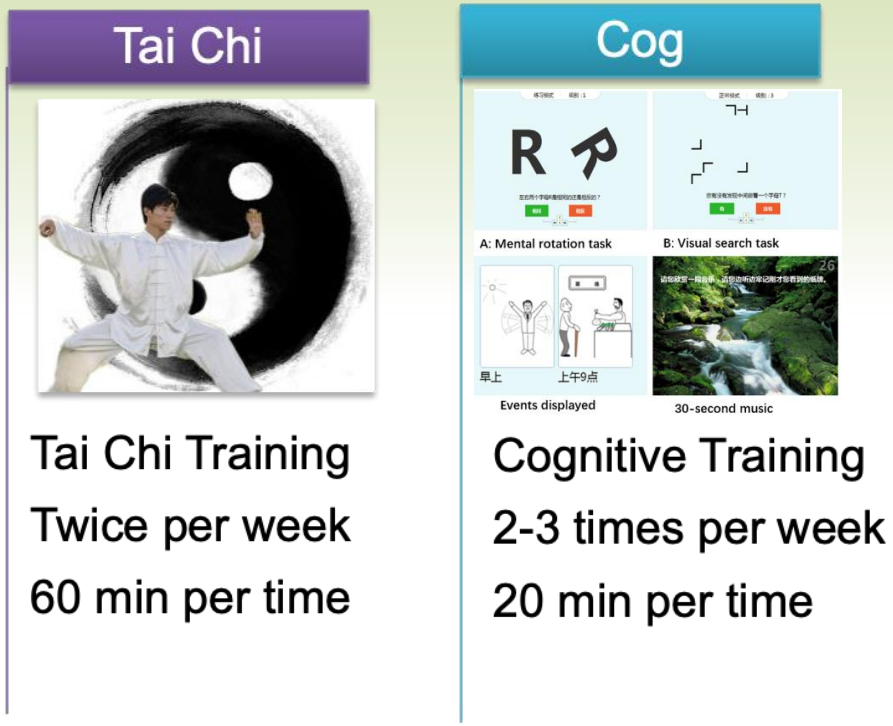
Connectivity intensified after training:

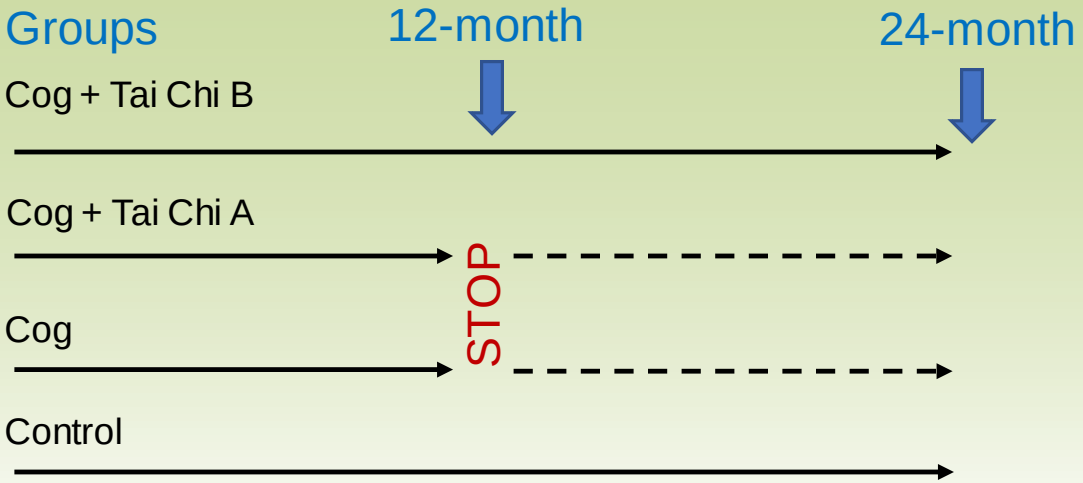
- Temporal lobe-lingual gyrus connectivity
- Occipital-temporal lobe, occipital-occipital lobe connectivity

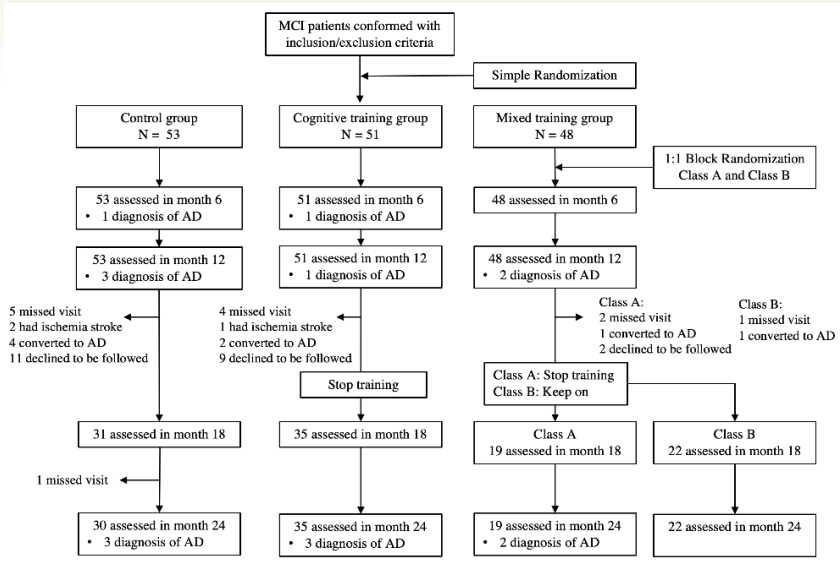
Belleville, S., et al., Brain, 2011. 134(6): p. 1623-1634.

Our study: 24-month cognitive & Tai Chi training for MCI

Mixed Training:
Cognitive training + Tai Chi training

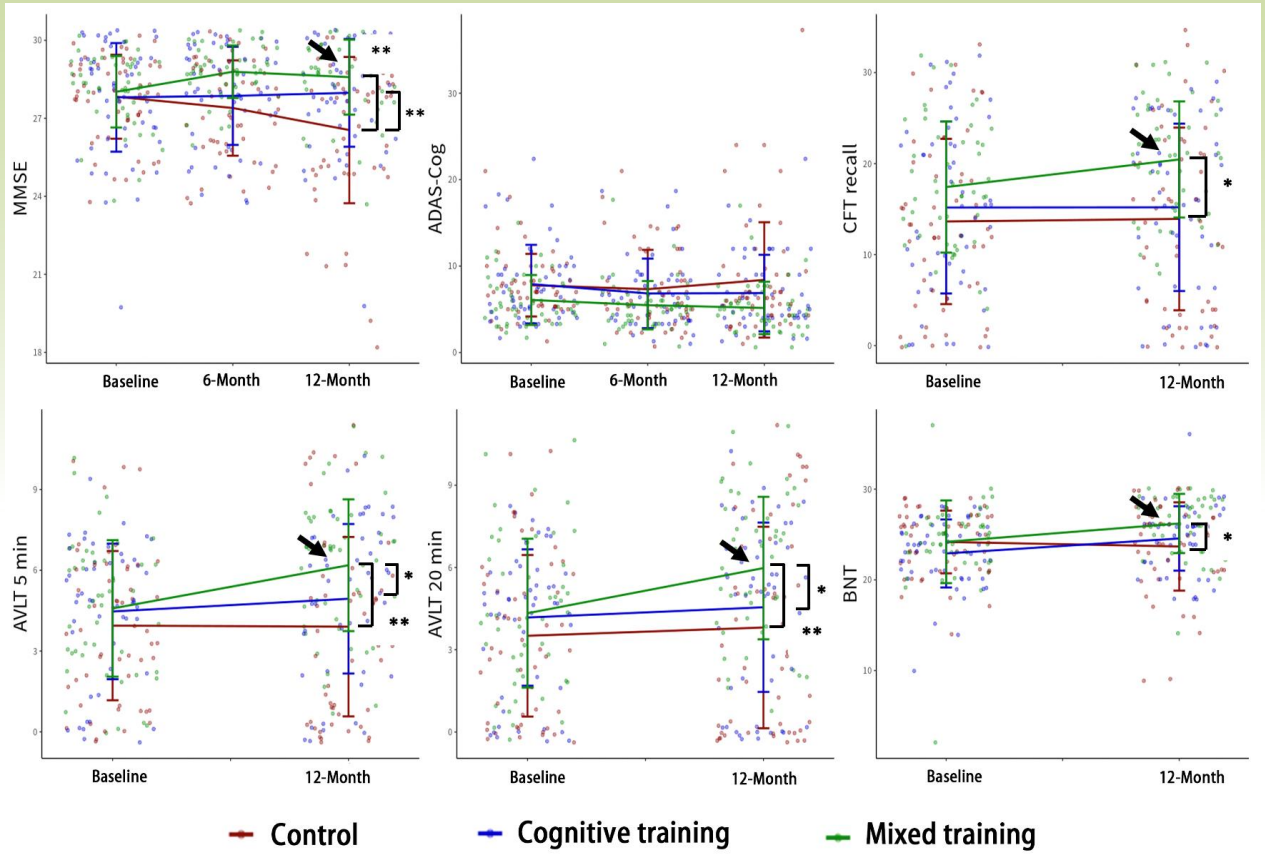




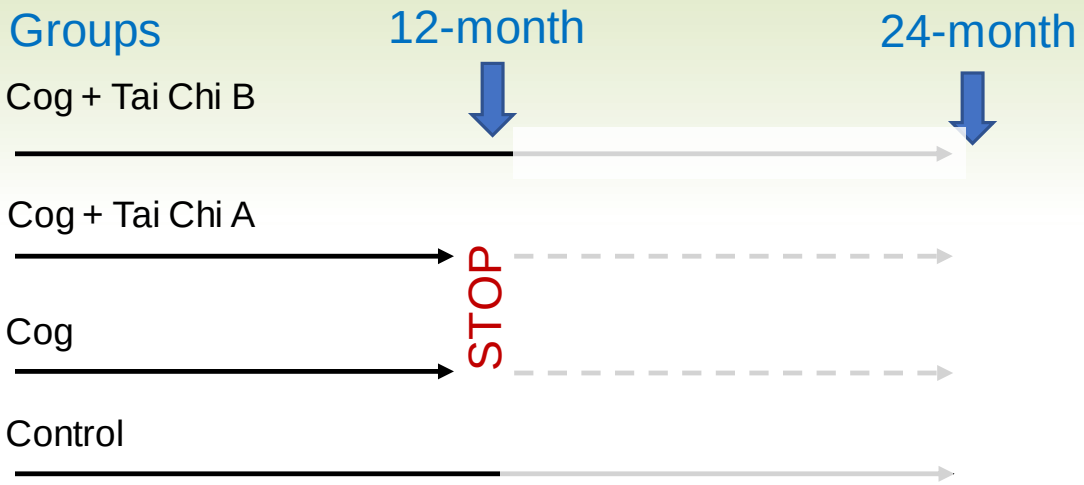


Li B, et al. Alzheimer & Dementia(accepted)

First phase (Month 0 - 12): 12-month mixed training for MCI



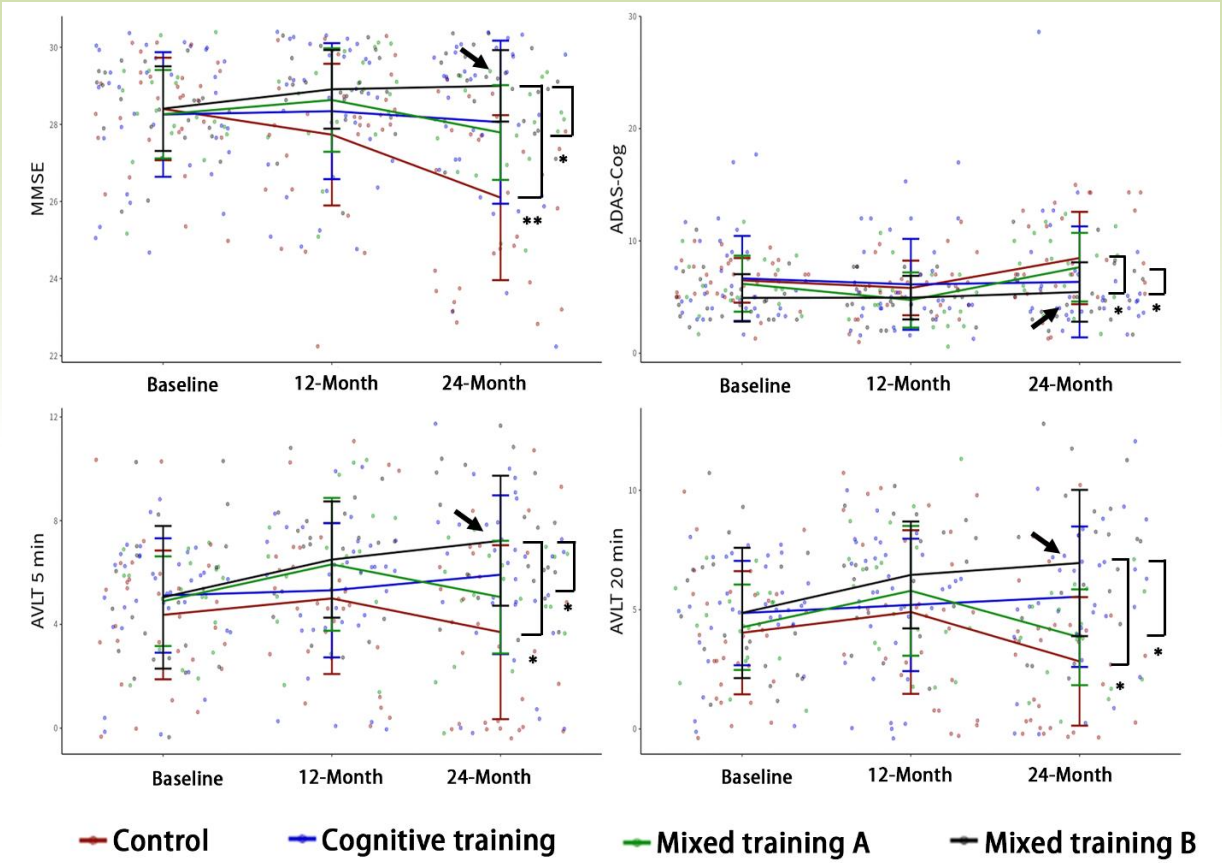
The 12-month mixed training enhanced effect of cognitive training in MMSE and verbal memory.

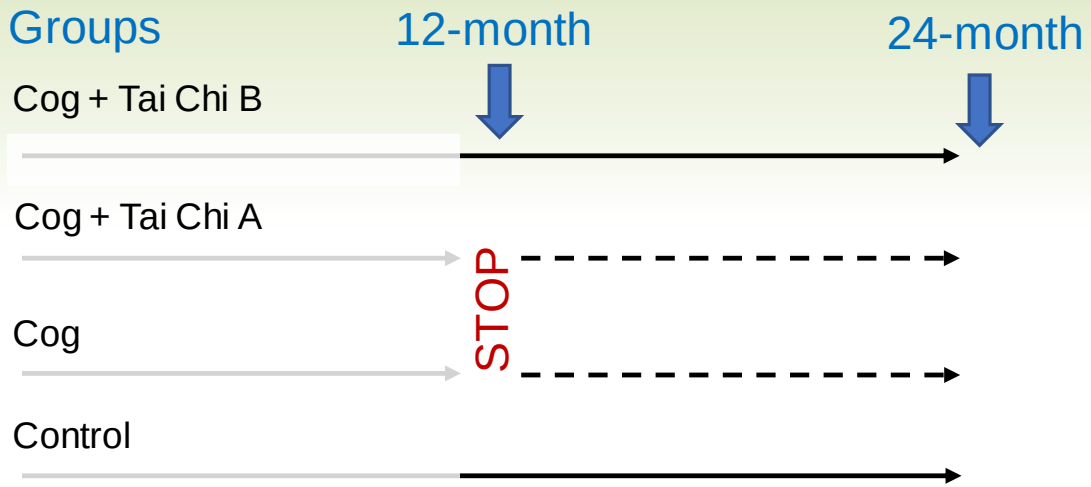


Li B, et al. Alzheimer & Dementia(accepted)

Second phase (Month 12 - 24): post/prolonged training effect

- **Prolonged training showed continuously positive effect in MMSE, ADAS-Cog and AVLT**
- **Training effect waned in the mixed training A group**



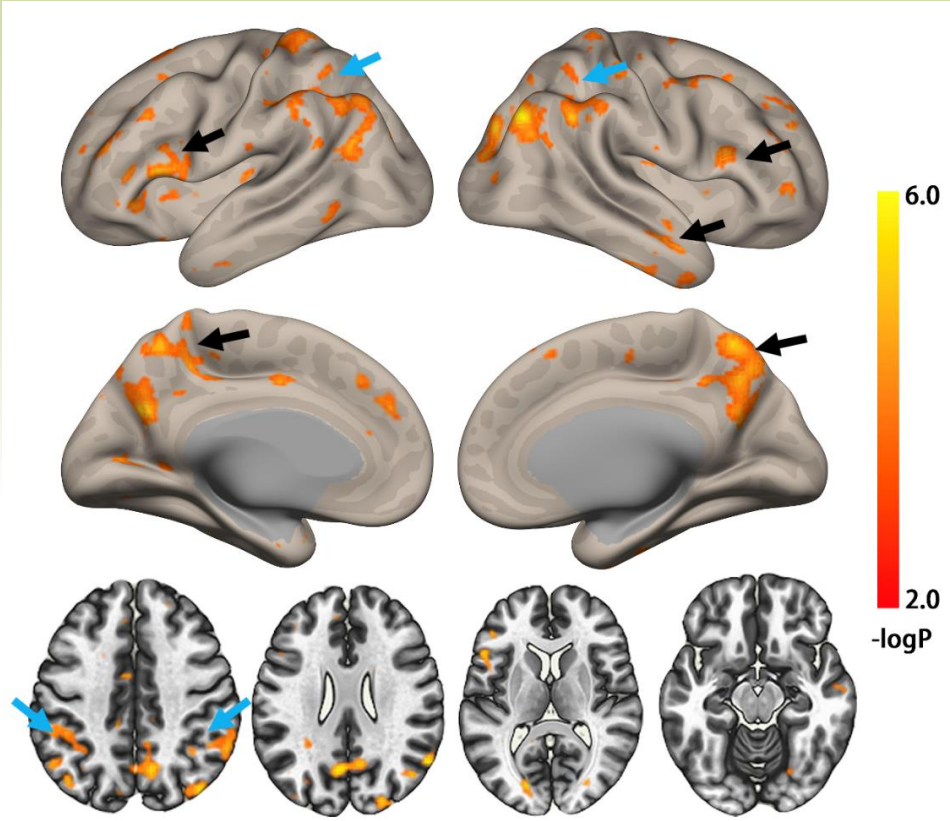


Li B, et al. Alzheimer & Dementia(accepted)

Mechanism: fMRI study in cognitive training for MCI

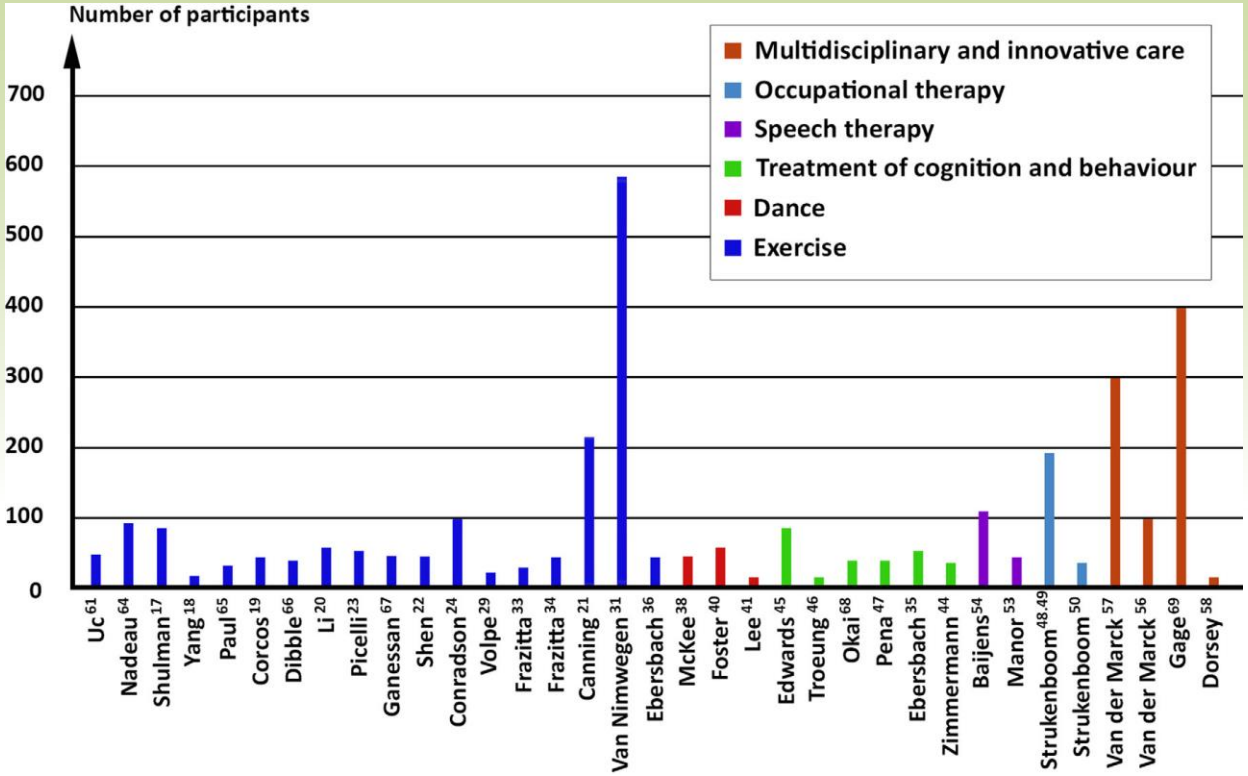
Training effect: Group × Time interaction

- **Training group (Cog and Mixed) significantly increased fALFF in bilateral temporal poles, medial temporal cortex, insular cortex and posterior cingulate cortex**
- **No difference between Cog and Mixed training groups**



Li B, et al. Alzheimer & Dementia(accepted)

Exercise training for PD



- Aerobic exercise
- Cued exercise
- Strength training
- Balance & Gait training
- Dance intervention
- Tai Chi therapy
- Occupational therapy
- Swallowing therapy
- Multidisciplinary & Innovative care

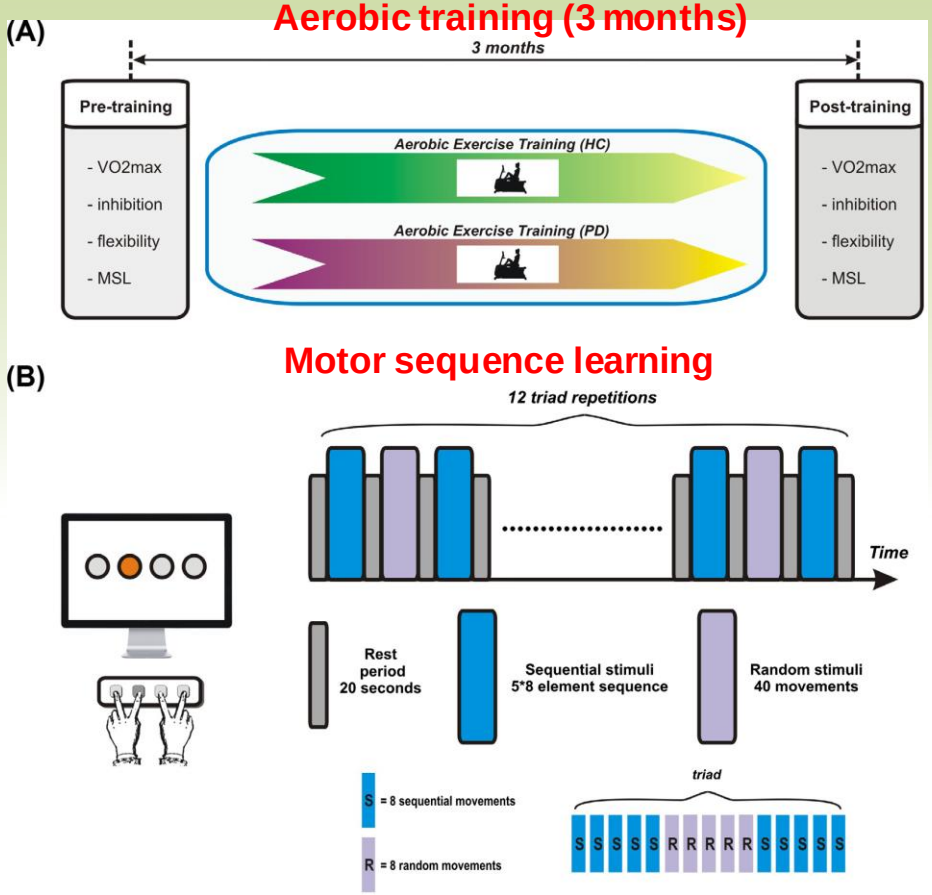
Exercise

Mov Disord, 2015; 30 (11):1504-20.

Mov Disord, 2015; 30 (11):1504-20.
Nat Rev Neurol. 2017 Nov;13(11):689-703.

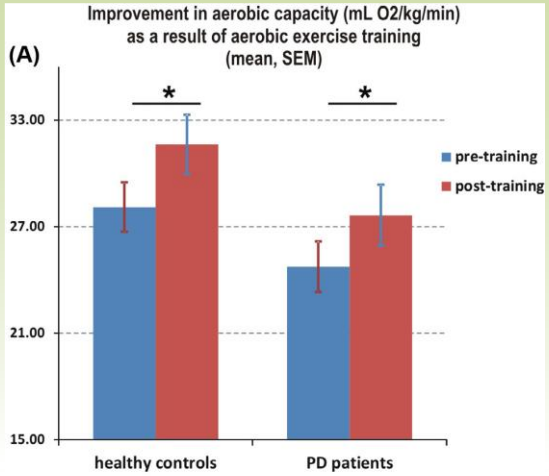
Exercise training for PD

Aerobic training for PD

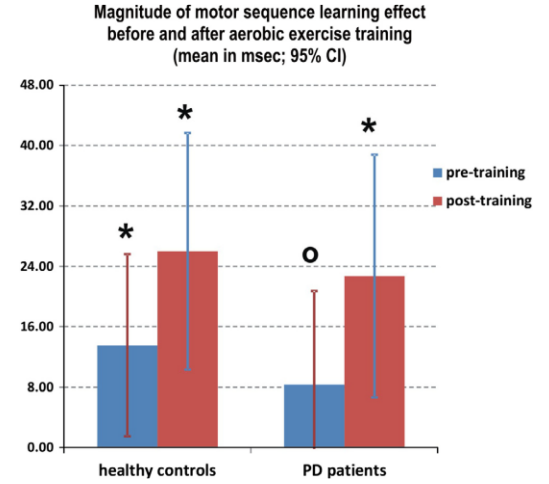


Brain and Cognition 99 (2015) 68–77

Aerobic exercise enhance both motor and cognitive function in PD



Aerobic exercise improved physical fitness in PD



Aerobic exercise improved executive functioning in PD

Brain and Cognition 99 (2015) 68–77

Exercise training for PD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tai Chi and Postural Stability in Patients with Parkinson's Disease

Fuzhong Li, Ph.D., Peter Harmer, Ph.D., M.P.H., Kathleen Fitzgerald, M.D., Elizabeth Eckstrom, M.D., M.P.H., Ronald Stock, M.D., Johnny Galver, P.T., Gianni Maddalozzo, Ph.D., and Sara S. Batya, M.D.

RESEARCH ARTICLE

A Randomized Controlled Trial of Patient-Reported Outcomes With Tai Chi Exercise in Parkinson's Disease

Fuzhong Li, PhD,[1*] Peter Harmer, PhD, MPH,[2] Yu Liu, PhD,[3] Elizabeth Eckstrom, MD, MPH,[4] Kathleen Fitzgerald, MD,[5] Ronald Stock, MD,[4] and Li-Shan Chou, PhD[6]

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

The effect of Tai Chi exercise on gait initiation and gait performance in persons with Parkinson's disease

Shinichi Amano [a], Joe R. Nocera [b,d], Srikant Vallabhajosula [c], Jorge L. Juncos [d], Robert J. Gregor [e,f], Dwight E. Waddell [g,h], Steven L. Wolf [b,i,j,k], Chris J. Hass [a,*]

Tai Chi can improve gait and posture

N Engl J Med 2012;366:511-9.

Our study: Tai Chi training for PD

Training for Early PD patients

Tai Chi

Tai Chi Training

Twice per week

90 - 120 mins per time

One-year follow-up

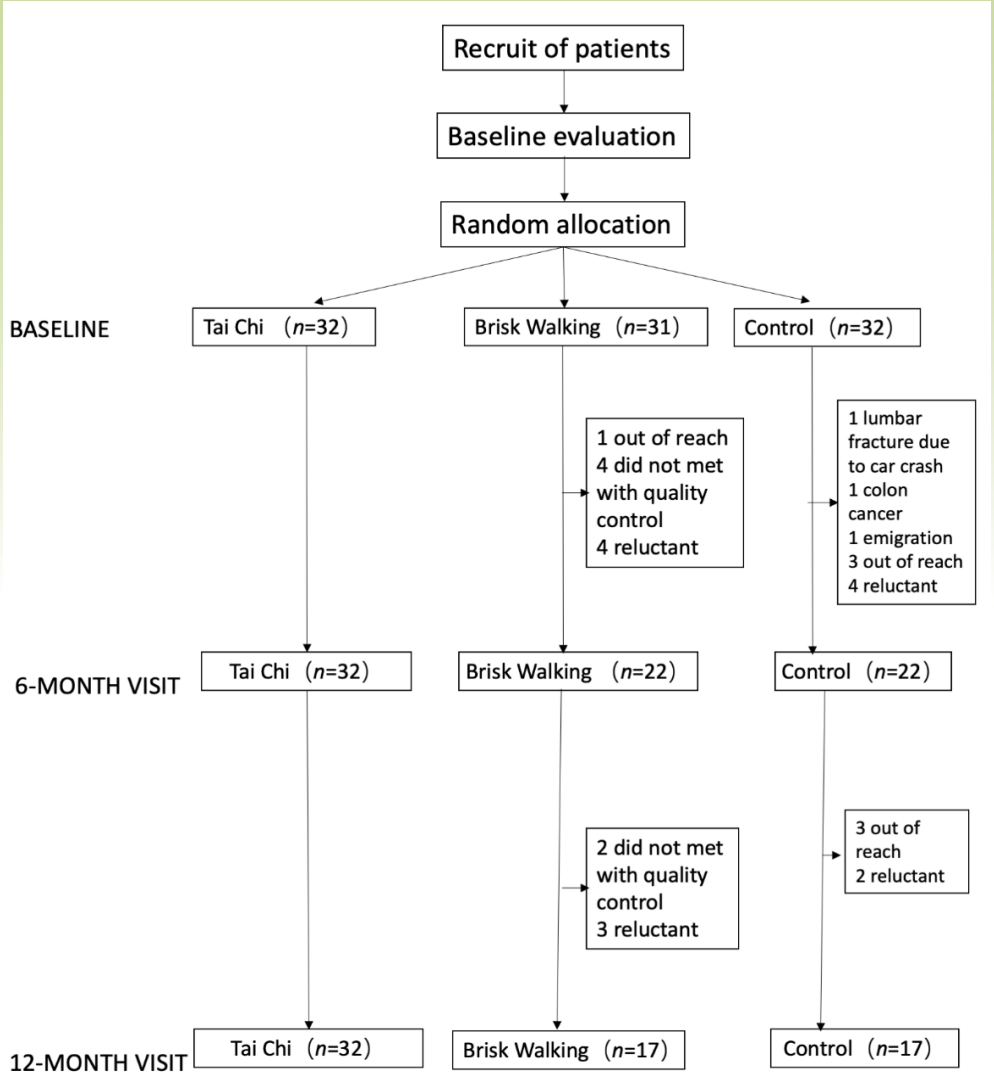
Brisk Walking

Brisk Walking Training

Three times per week

60 mins per time

One-year follow-up



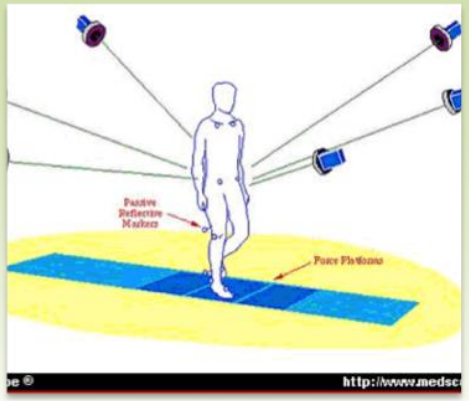
Li G, et al. Transl Neurodeg 2022:11:6

Assessments

Rating Scales

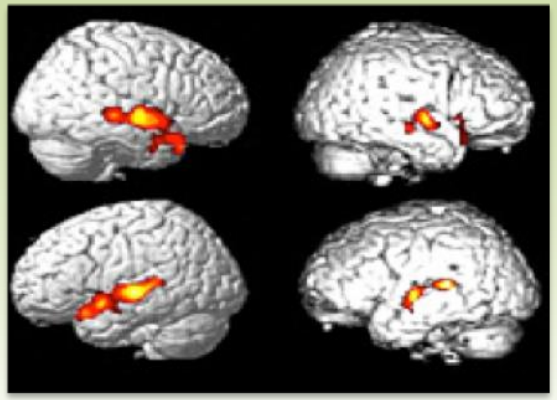
- Movement assessment
- assessment for Non-motor symptoms
- Quality of Life

3D gait assessment



- Spatiotemporal parameters
- Surface EMG for lower limbs
- Weight and balance

functional MRI



- BOLD - connectivity
- DTI - white matter fiber tracts
- 3D T1 – Volume of gray matter
- MRS - metabolism

blood test

- Whole blood - RNA
- serum
- plasma
- DNA

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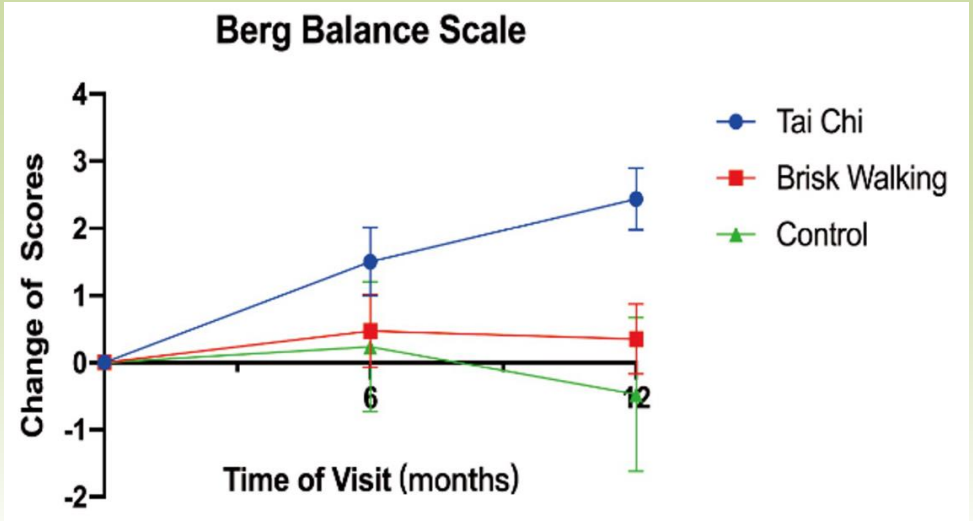
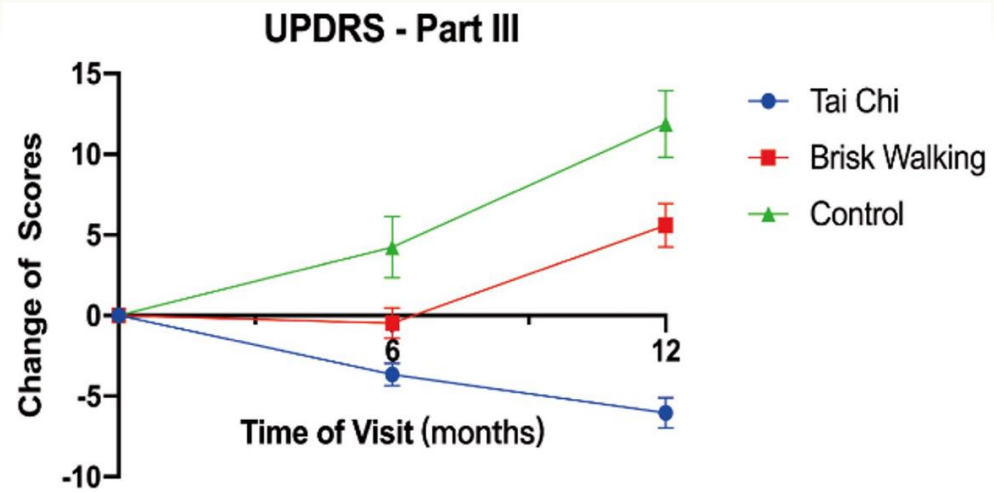
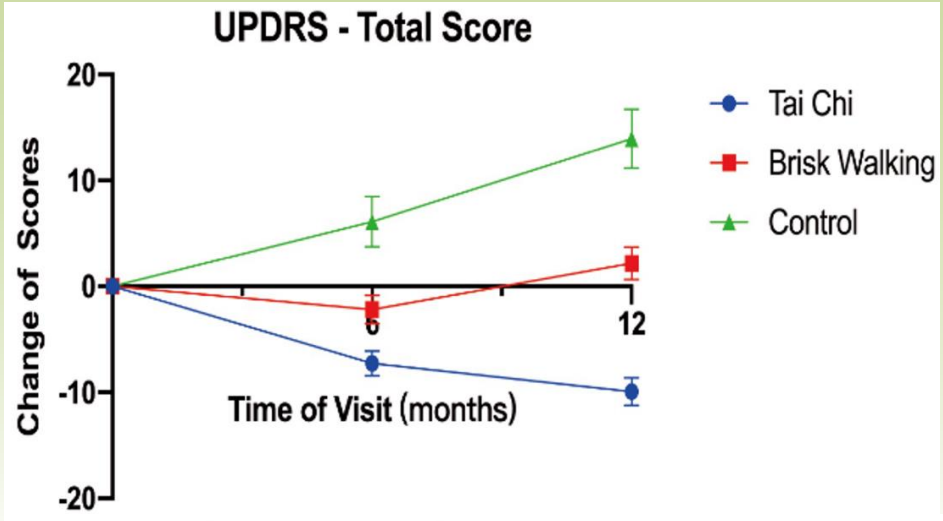
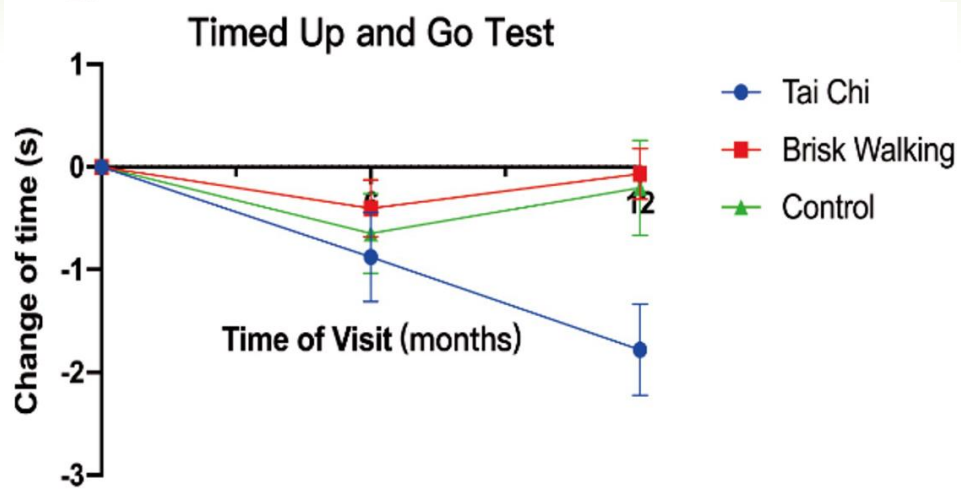
Tai Chi improved motor symptoms









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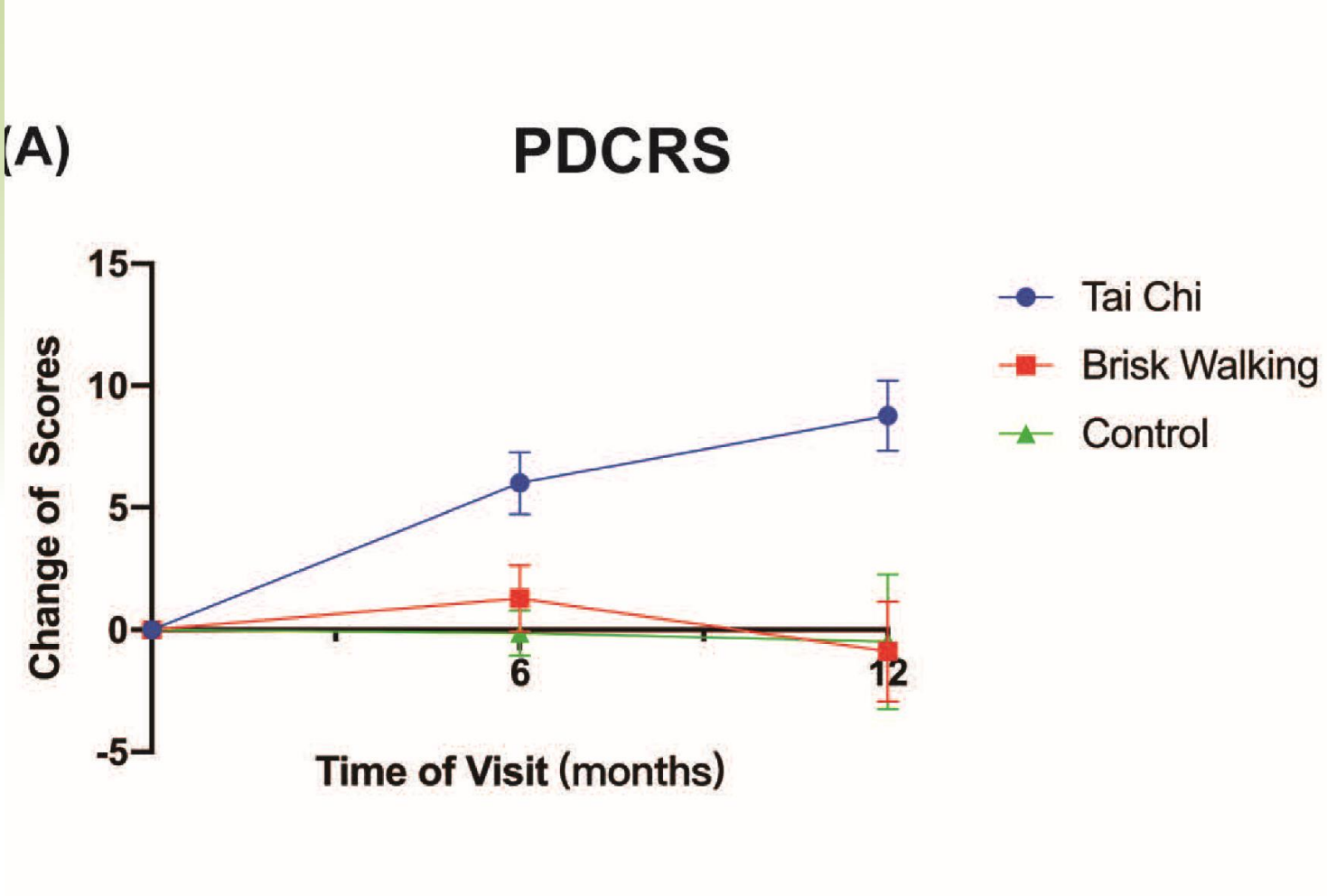
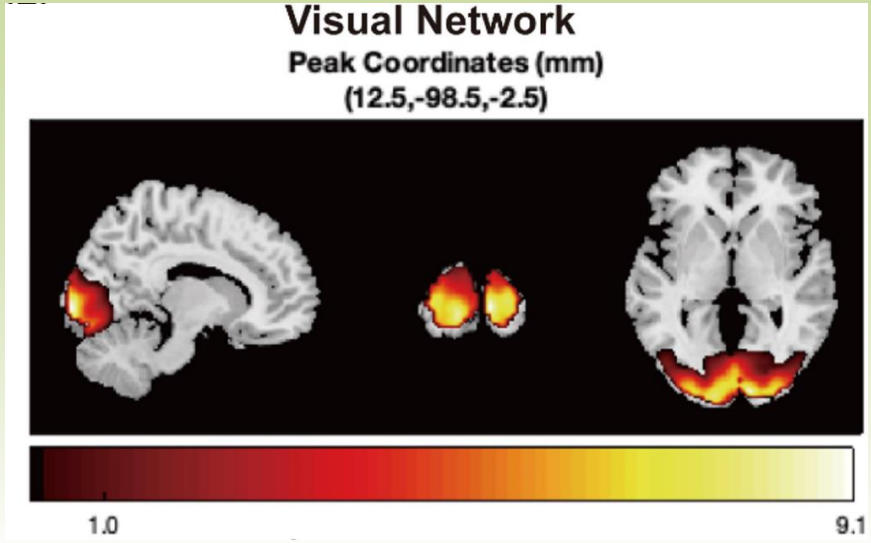
Tai Chi improved the cognition

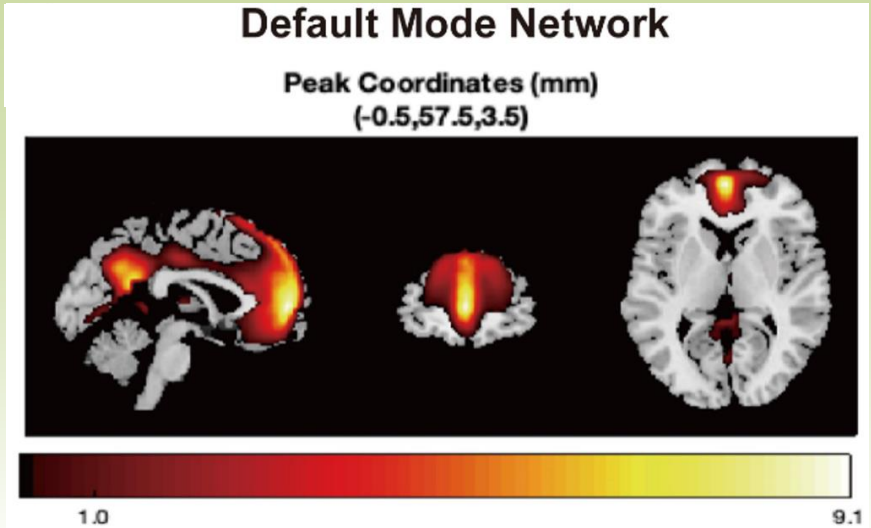


Mechanism: motor improvement related to enhanced brain network function

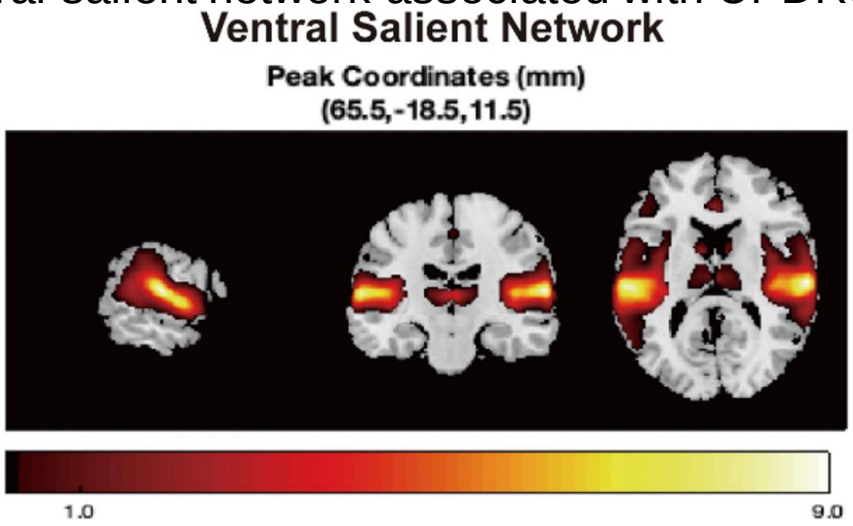
Visual network associated with Berg Balance scale



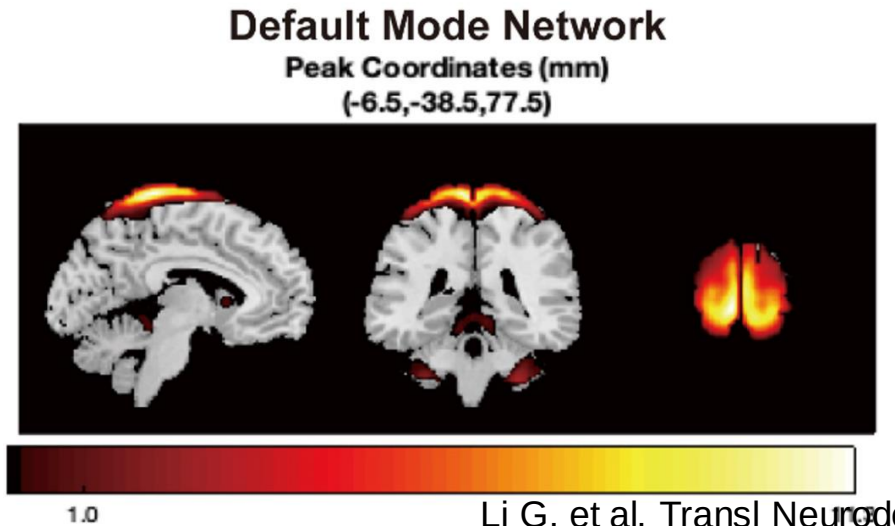
Default mode network associated with UPDRS total score



Ventral salient network associated with UPDRS total score



Default mode network associated with UPDRS Part III



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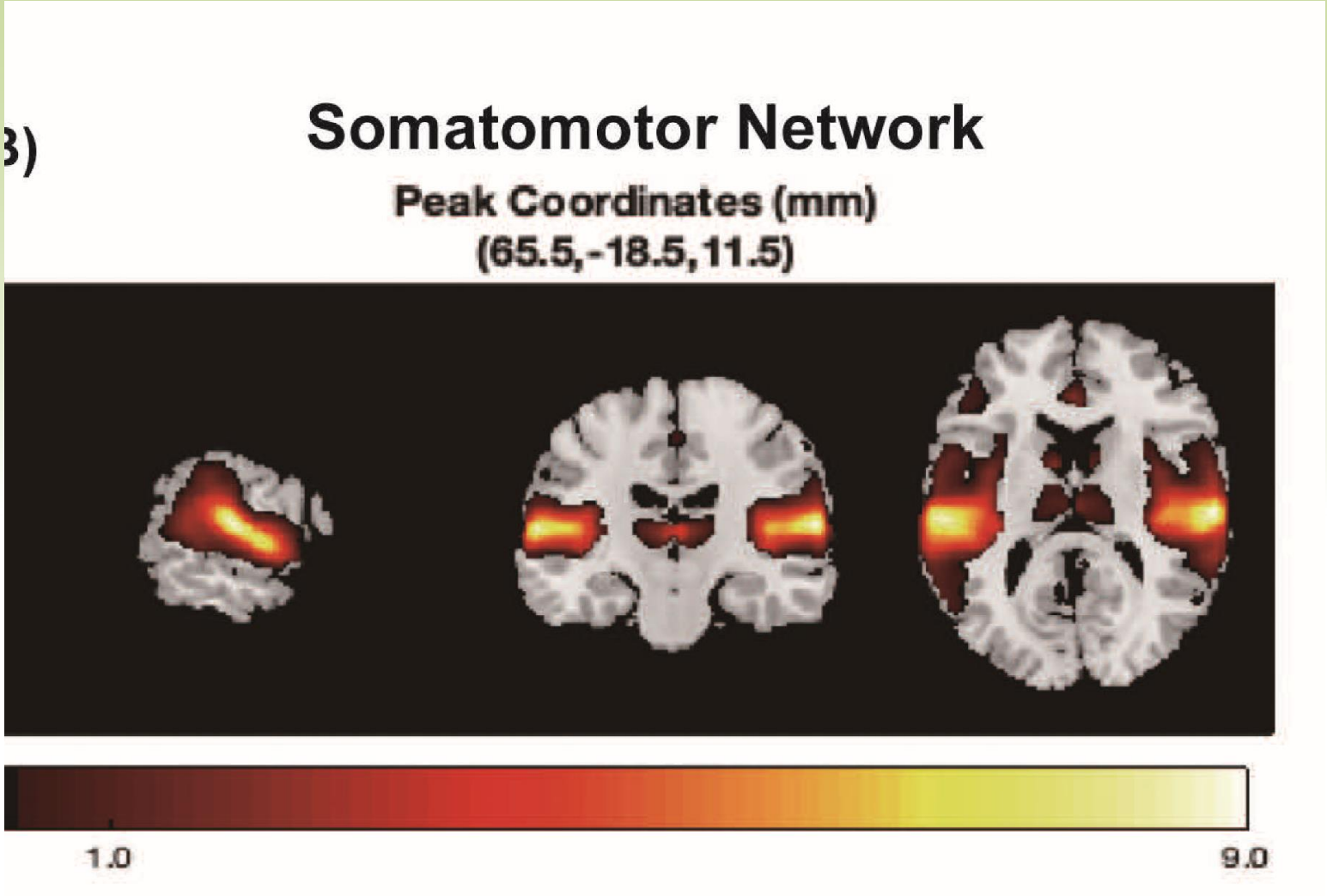
Mechanism: Improved cognition related to enhanced somatomotor network



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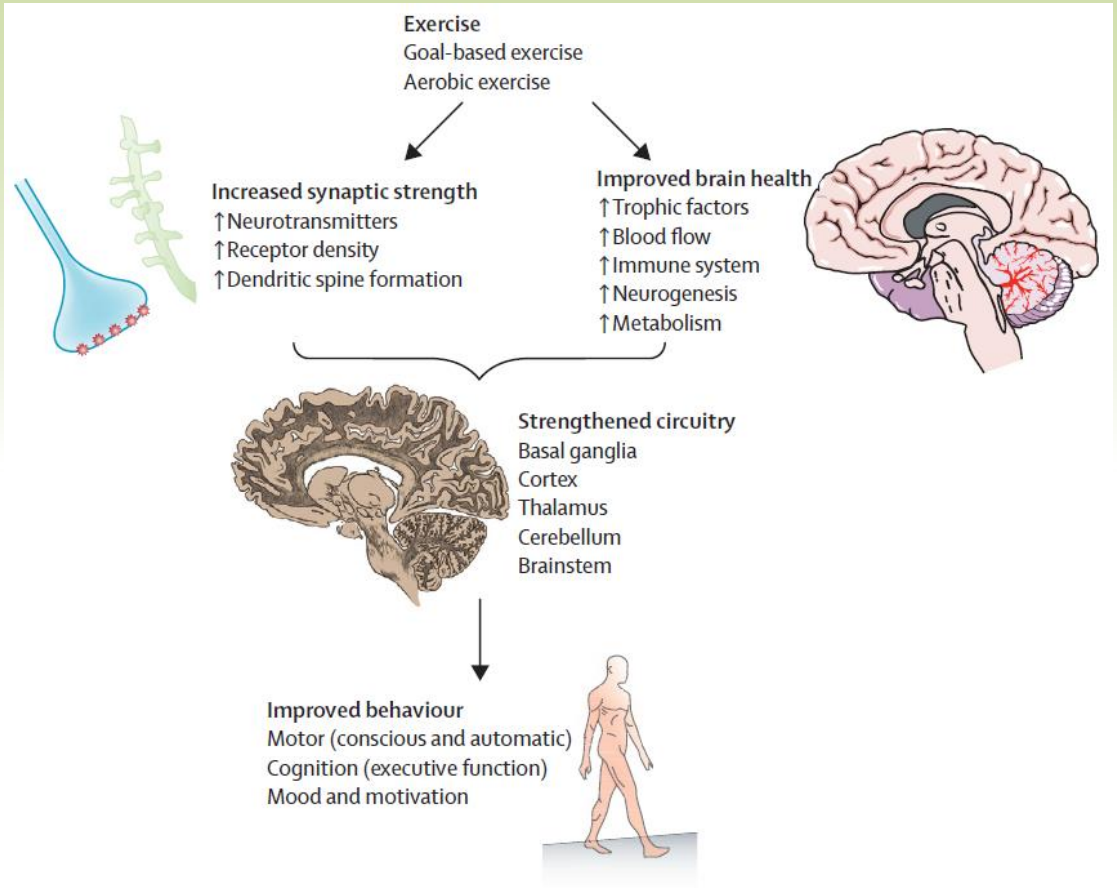
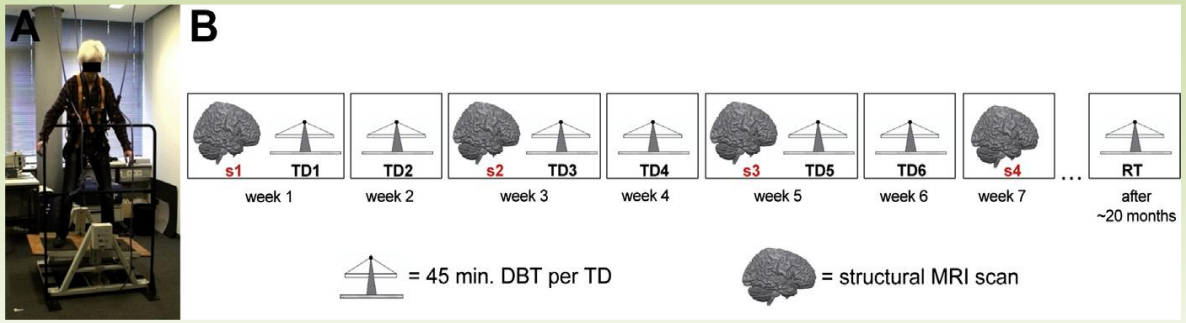
Mechanism: exercise improved neuroplasticity in PD

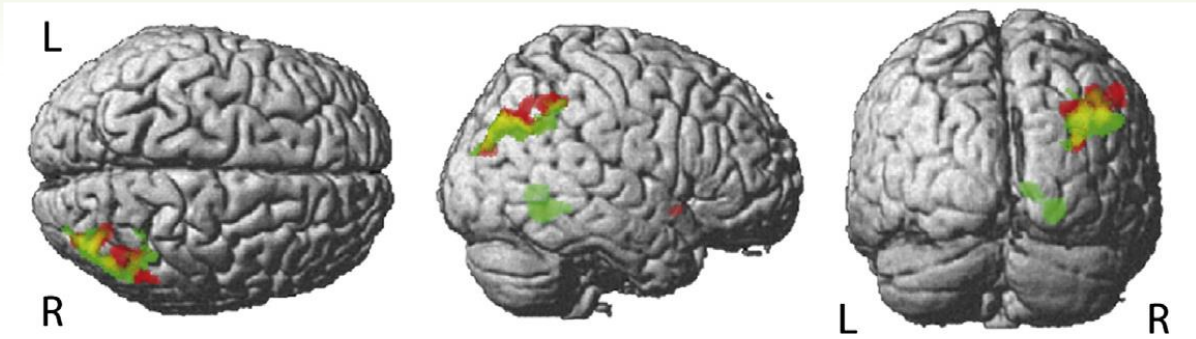
Exercise enhanced neuroplasticity targeting motor and cognitive circuitry in PD



Lancet Neurol 2013; 12: 716–26

Balance training improved structural brain plasticity in PD

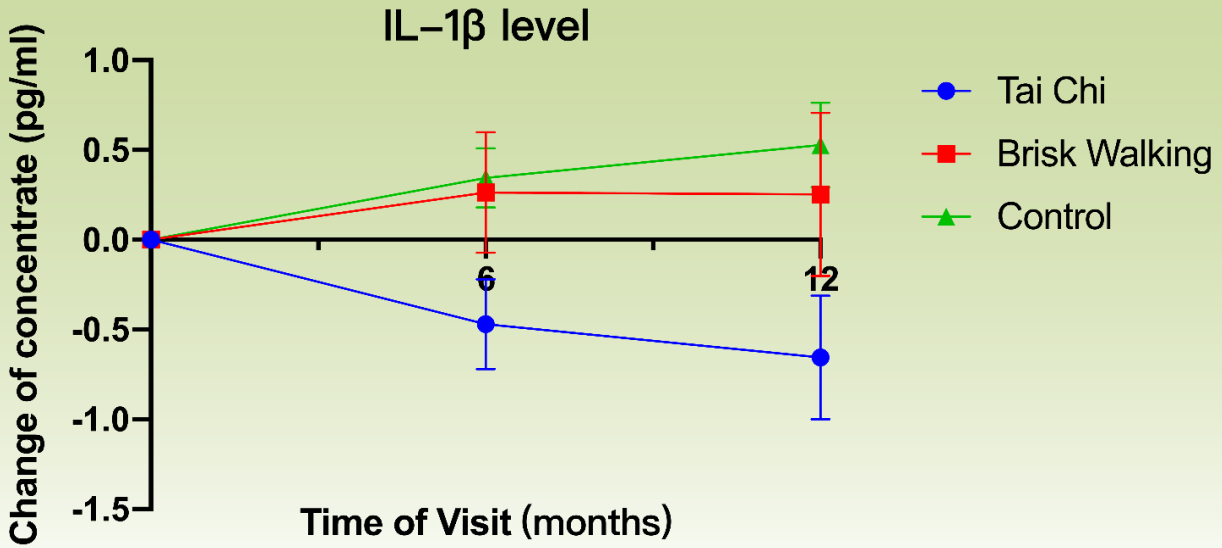


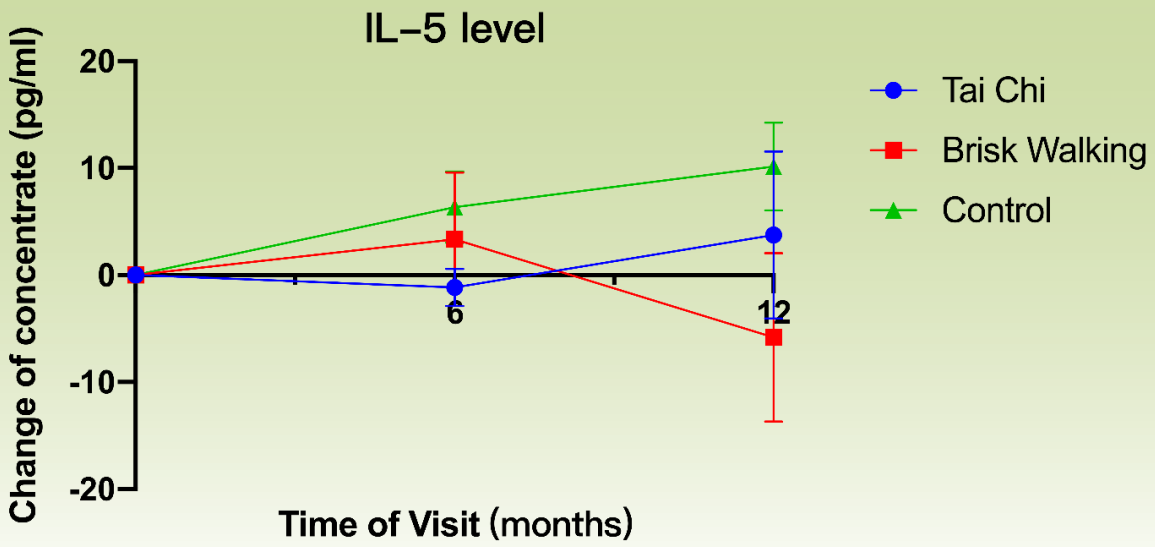


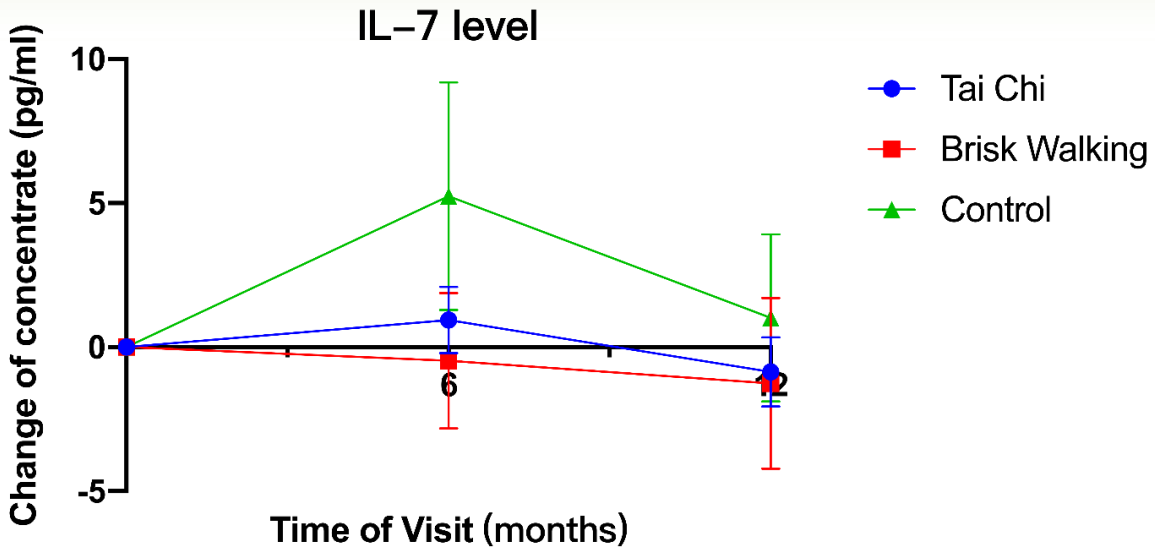
Gray matter volume changes after dynamic balance task

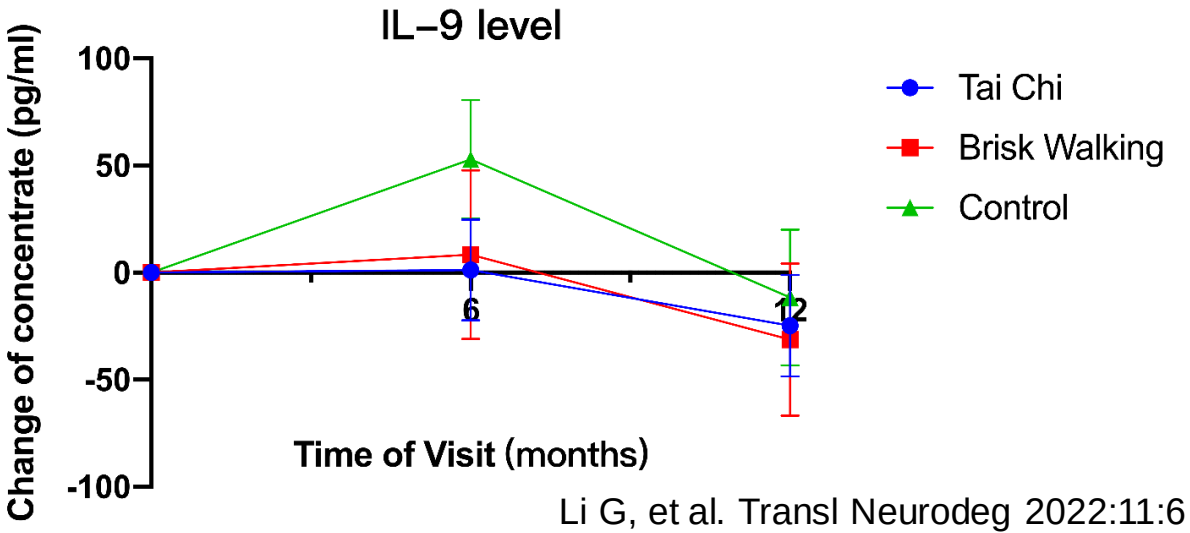
Neurobiology of Aging 35 (2014) 232e239

Mechanism: Anti-inflammation after Tai Chi training









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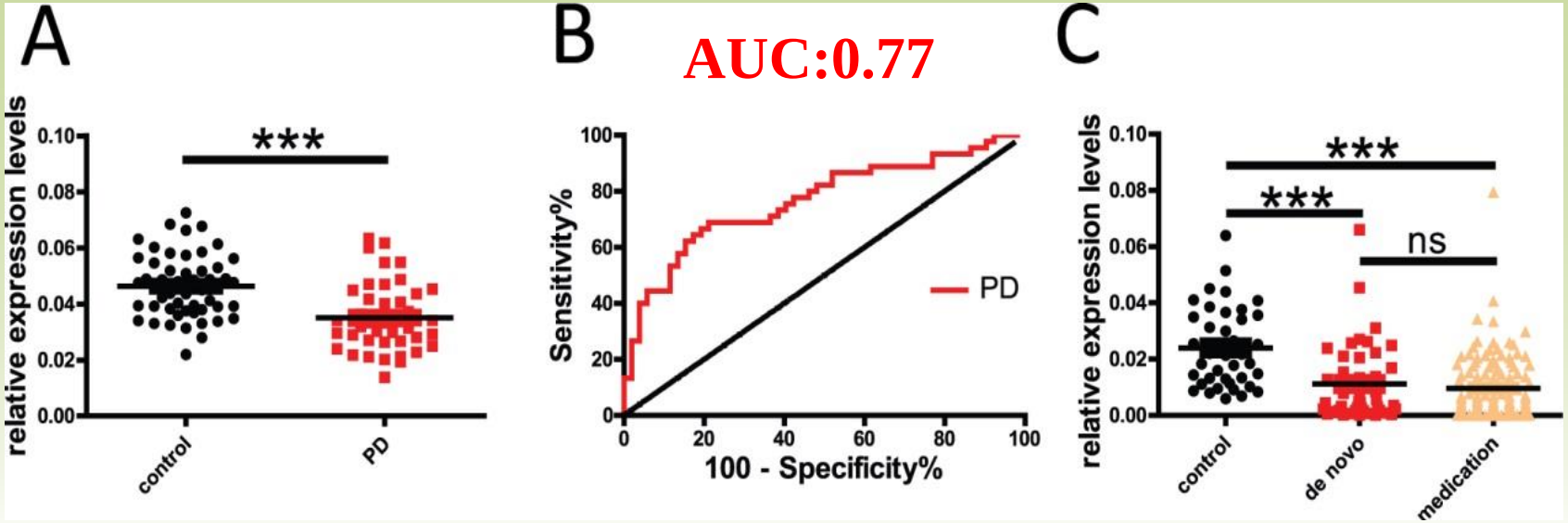
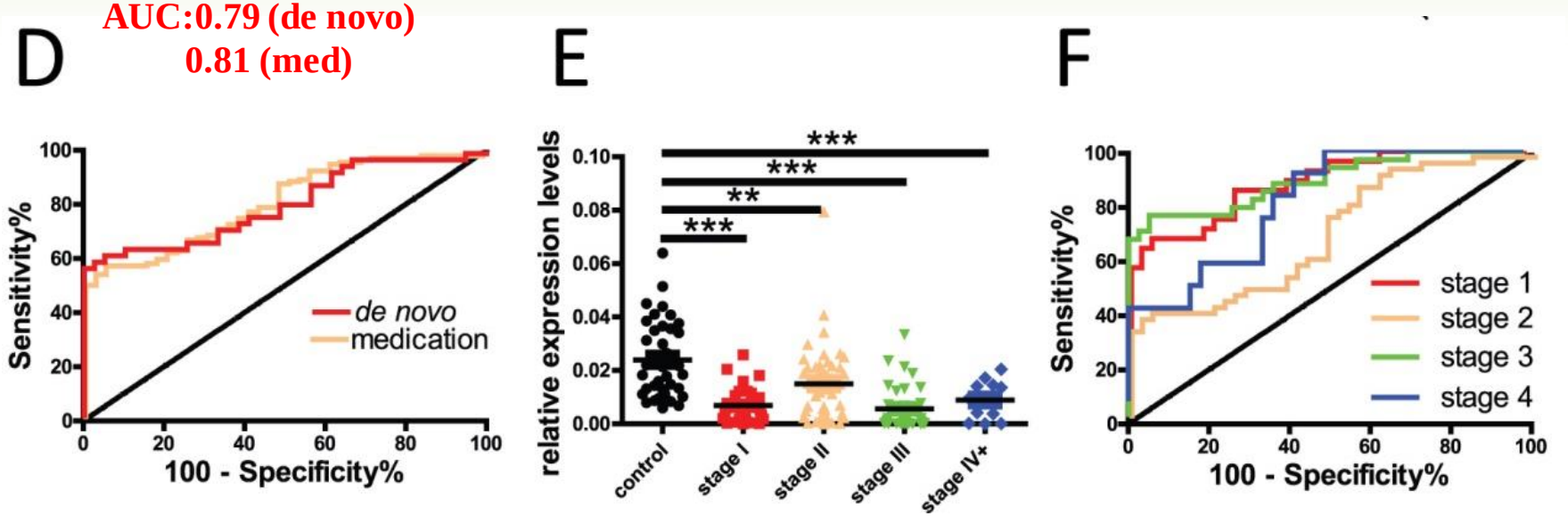
Our study: reduced HIP2 mRNA expression in PD





- **Expression of HIP2 was independent to Levodopa usage.**
- **Diagnostic value to both de novo PD and PD received medication.**
- **Sensitive to H-Y stage I – IV.**

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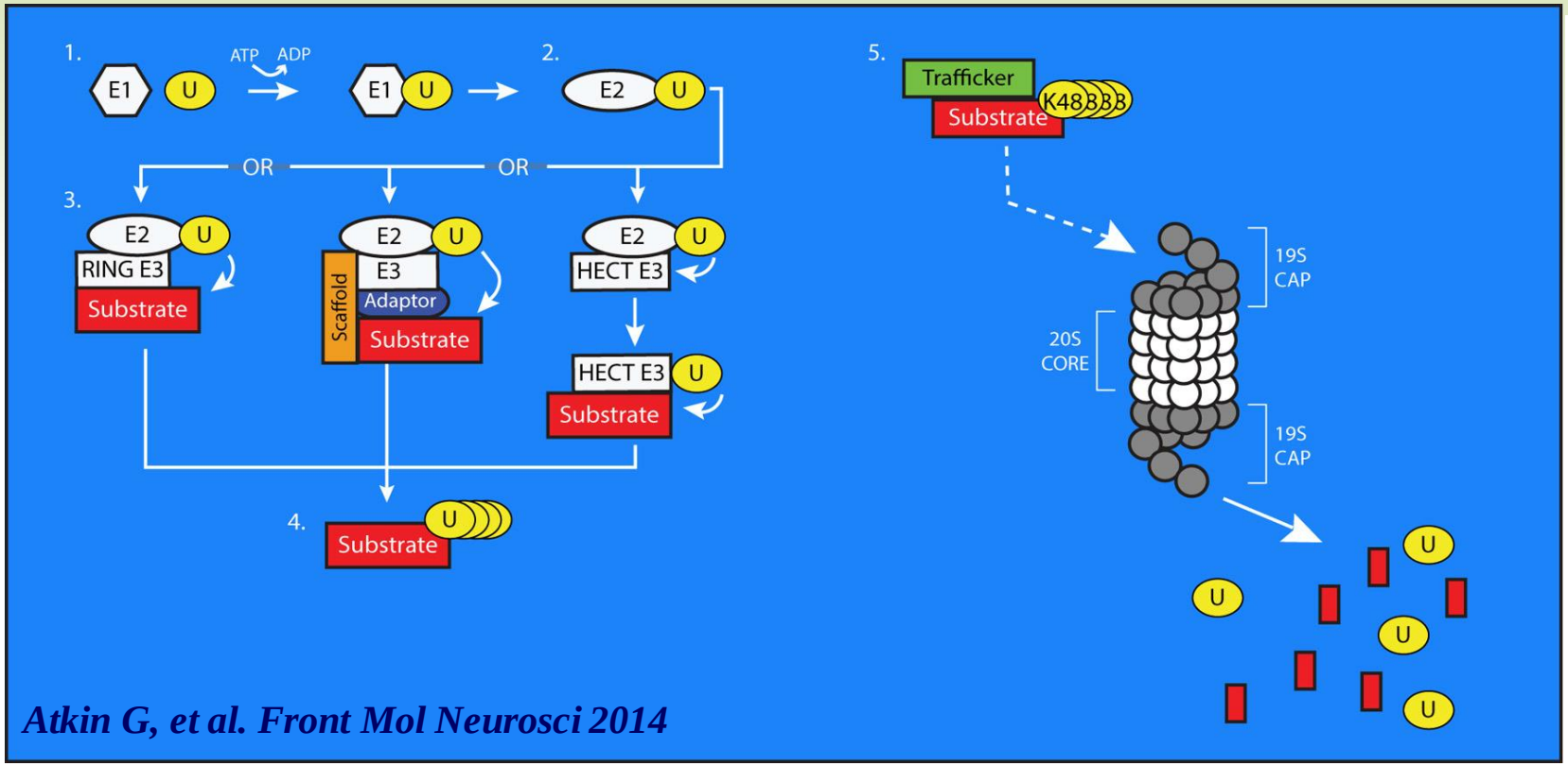
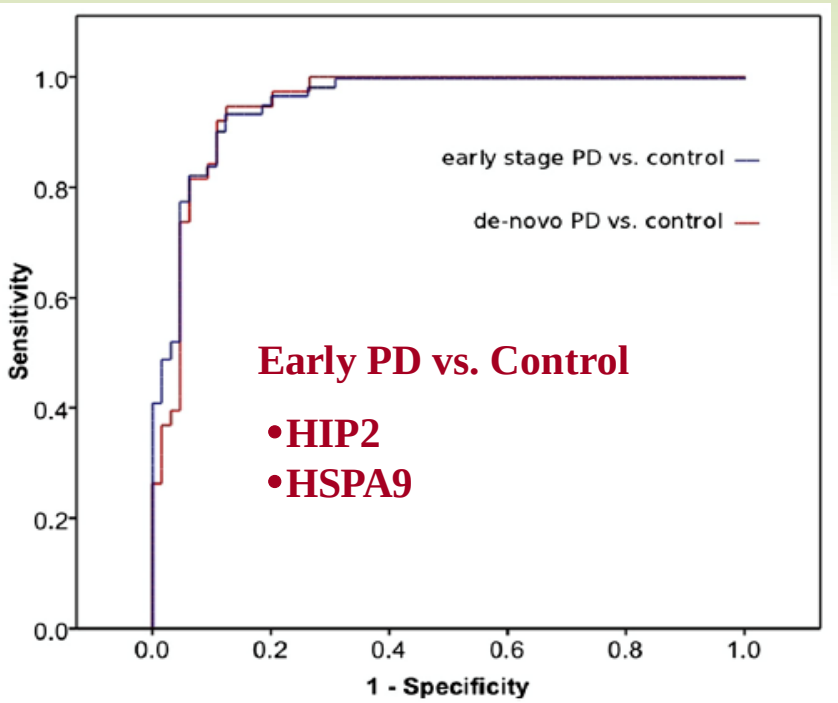
HIP2 (Huntingtin interacting protein 2/Ubiquitin-conjugating enzyme E2K)

- Ubiquitin-conjugating enzyme E2 in Ubiquitin-proteasome system, related with protein degradation and autophagy
- PD: abnormal aggregation of α-synuclein in dopaminergic neurons
- A biomarker of Early Stage PD in peripheral blood

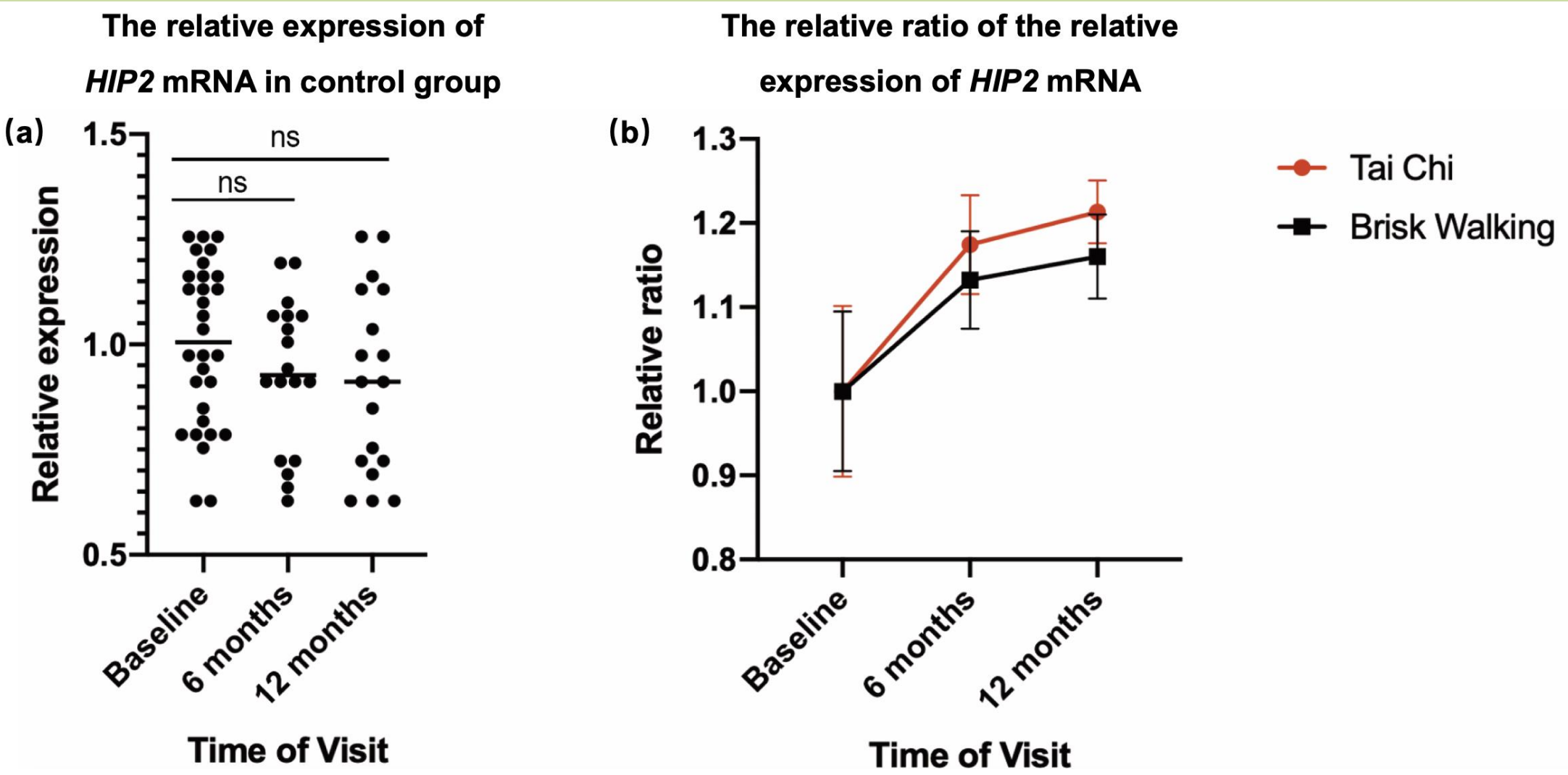


Atkin G, et al. Front Mol Neurosci 2014



Scherzer CR, et al. PNAS 2007
Molochnikov L,et al. Mol Neurodegener 2012

Mechanism: Increased HIP2 mRNA after Tai Chi Training

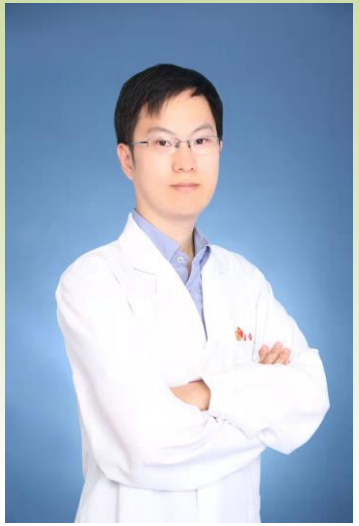


Li G, et al. Transl Neurodeg 2022:11:6

Summary

- Cognitive training can improve the cognition in MCI patients;
- Tai Chi can enhance cognitive training effects on delaying cognitive decline in MCI patients;
- Tai Chi training can improve the motor symptoms and cognitive function of PD patients;
- The mechanisms of cognitive and Tai Chi training effects may be related to increased neuroplasticity, decreased inflammation and others.

Acknowledgements





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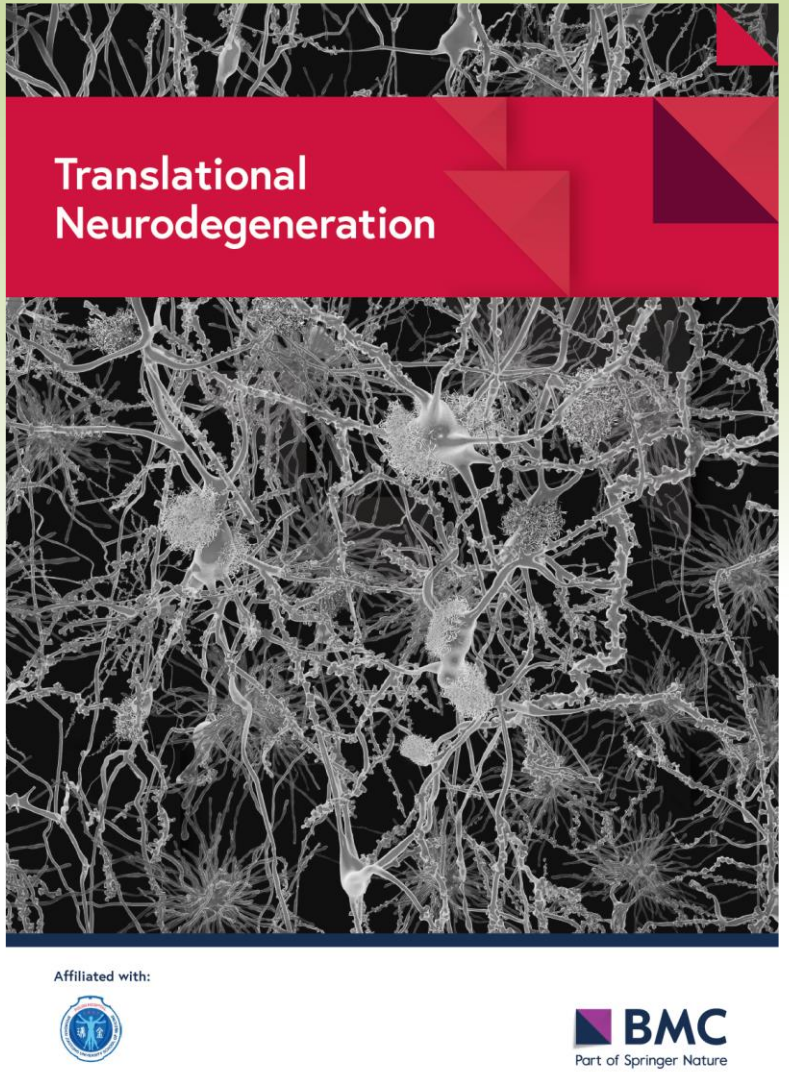

THANK YOU

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