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Med-X

REVIEW

Comparative efficacy of NIBS and Physical Exercise on cognitive function in patients with MCI or AD: a systematic review and meta-analysis

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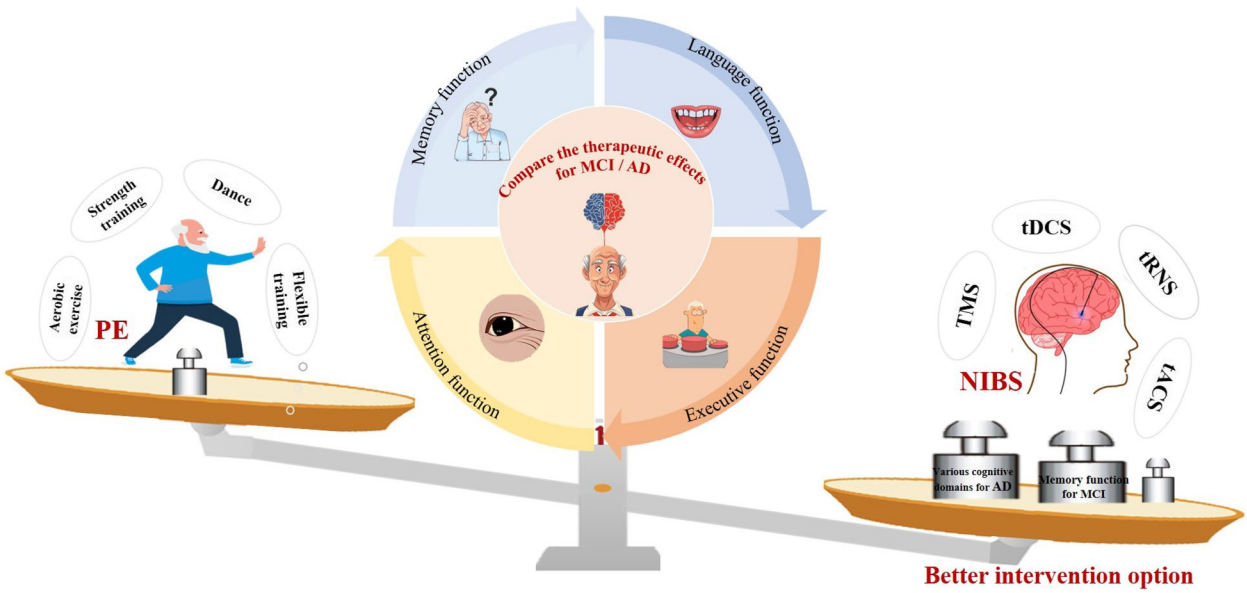
Abstract

Non-invasive brain stimulation (NIBS) and physical exercise (PE) intervention are currently the main and promising non-pharmacologic therapies for Alzheimer's Disease (AD) or Mild cognitive impairment (MCI), but it is not clear which one is the most effective. Therefore, the aim was to compare the effectiveness of NIBS and PE interventions on cognitive function in MCI/AD, which can further elucidate their advantages and disadvantages in cognitive efficacy and facilitate the optimization of treatment strategies based on the specific cognitive status of patients. Randomized controlled trials (RCTs) were searched from online databases until December 2023. Standardized Mean Changes pre- and post-treatment were calculated for cognitive outcomes measures. 79 RCTs met the inclusion criteria. For the global cognitive scale, PE significantly affected AD and MCI. Both NIBS and PE had a sustained and significant impact on AD/MCI based on the follow-up. In sub-category functions, NIBS had a significant effect on memory for both AD and MCI. However, PE only had a significant effect on AD, not on MCI. For executive function, only NIBS had a significant effect on AD. For language, NIBS and PE both had a significant impact only on AD. For attention, the only significant effect was NIBS on AD. NIBS significantly affects more cognitive domains of AD than PE, and significantly improves the memory function of MCI. Given the current evidence, NIBS appears to be a more promising intervention approach for delaying cognitive decline in patients with MCI or AD compared to PE.

Graphical Abstract



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Highlights

- The current study is the first meta-analysis to compare the comparative efficacy of NIBS and PE interventions on various cognitive domains, for MCI or AD patients.
- NIBS intervention has clear positive effect on various cognitive domains for patients with AD, and significant effect on the memory function for MCI.
- NIBS is promising to be a better intervention approach to delay cognitive decline in MCI and AD than PE.

Keywords Alzheimer's disease · Mild cognitive impairment · Non-invasive brain stimulation · Physical exercise

Introduction

Alzheimer's Disease (AD), the foremost manifestation of dementia, is an age-dependent neurodegenerative disorder, affecting 50 million people globally and by 2050, up to 150 million people would be affected (Alzheimer's Disease International, 2015) [1]. Prior to AD onset, Mild cognitive impairment (MCI) is an intermediate status between normal aging, prodromal memory decline, and senile dementia [2]. Individuals with MCI exhibit normal global cognitive function and activities of daily living, but with impaired memory compared to healthy counterparts of the same age. Treating cognitive decline as early as possible is the key to delay the progression from MCI to AD [3]. Current first-line treatments include pharmacological and nonpharmacological treatments. Pharmacological treatments include cholinesterase inhibitors, glutamate antagonists, and memantine hydrochloride. Despite limited success, a number of patients do not benefit sufficiently, either suboptimal benefits for individuals with AD or no effects on MCI. Curative or substantial disease-modifying therapies are still rare [4]. Thus, nonpharmacological, safe, relatively cost-effectively, and measurable interventional options have attracted widespread attention in the research efforts to maintain the cognitive functions in patients with MCI or AD. Among various alternatives, non-invasive brain stimulation (NIBS) and physical exercise (PE) have been proposed as two effective nonpharmacological intervention strategies for patients with MCI or AD [5, 6].

The NIBS techniques, such as transcranial electrical stimulation (tES), transcranial magnetic stimulation (TMS), transcranial random noise stimulation (tRNS), and transcranial focused ultrasound (tFUS), are painless and non-invasive neuromodulation techniques, which could modulate brain function by changing cortical excitability, increasing synaptic plasticity, affecting cortical excitation/inhibition balance, changing localcerebral blood flow, and regulating the connections among different brain regions, *i.e.,* changes in brain network [7–10]. These effects make it a promising candidate for mitigating cognitive decline and neuropsychiatric symptoms [11]. Among them, rTMS and Transcranial direct current stimulation (tDCS) are the two most common technologies. Although limited adverse effects of NIBS have been reported in previous literature [12], it has been widely used to improve cognition in participants with various diseases, including Parkinson's disease, schizophrenia, and depression [13–15]. In animal studies, the potential effectiveness of NIBS on hippocampal spatial learning and memory deficits was reported in rats [16]. For cognitive function intervention in AD/MCI, previous studies have suggested that rTMS [17–21] and tDCS [22–27] have beneficial effects in patients with AD or MCI. However, NIBS was not always effective. For example, a trend toward aggravating the severity of AD assessed by Alzheimer's disease assessment scale (ADAS-cog) at the end of treatment was observed in AD patients treated with real rTMS, compared to sham-treated counterparts [28]. In addition, a two-week tDCS protocol was administered to AD patients, but no measurable difference in the face-name association task performance was found between the treatment group and the control group three months after the intervention [24]. Several meta-analyses have analyzed the validity of NIBS application in AD or MCI, and they indicated inconsistent results caused by the non-homogeneity in quality and methods of the included studies [11, 29–31]. The research community would be benefited from a comprehensive and systematic overview of the research results to date.

PE, as another nonpharmacologic therapy, plays an increasingly important role in preventing cognitive decline and improving the quality of life for patients with cognitive impairment [32]. However, the underlying mechanisms of the effect of PE on cognitive improvement are not well understood, similar to that of NIBS. Recent research results indicated that exercise could increase the level of brain-derived neurotrophic factor (BDNF), which is an important component of neuronal growth and neuronal plasticity [33]. Animal model studies have also shown that exercising can exert protective effects on cognitive function by increasing the level of growth factors, such as BDNF and insulin-like growth factor 1 (IGF-1), regulating inflammatory cytokines, alleviating oxidative stress, increasing cerebral blood flow, and inhibiting τ Phosphorylation [33]. A large amount of research evidence indicated that different types of exercise, such as aerobic exercise, resistance exercise, moderate-intensity and high-intensity exercise could delay the progression of neuropsychological defects in patients with AD

or MCI [34–38]. However, some negative results were also reported. A Dementia And Physical Activity (DAPA) randomized controlled trial (RCT) of 494 dementia patients observed that exercise intervention decreased ADAS-cog score more than that of control group after 12 months [39]. In addition, a RCT of a 24-week physical activity showed that after 18 months of intervention, the intervention group did change significantly in digit symbol coding, but verbal fluency did not change [40]. Several meta-analyses have also made relevant analyses on the current controversy about the effectiveness of PE on AD/MCI, but still obtained inconsistent results [6, 41–44].

Given the limitations of previous meta-analyses on the cognitive efficacy of NIBS and PE, such as the lack of comprehensive analysis of the duration of post-treatment effects and the differences in therapeutic effects of different cognitive domains, particularly in core cognitive domains related to disease progression. In addition, no review and systematic analysis has compared the two main nonpharmacologic interventions for AD/MCI. To the best knowledge of the authors, no study in the literature answered the critical question—how to choose an optimal therapy from these interventions to treat older adults with AD or MCI. Comparing different intervention measures can illuminate their respective advantages and disadvantages, enabling the optimization of treatment strategies. On the one hand, such comparisons empower patients and their families with a deeper understanding of the pros and cons associated with various treatment plans. This, in turn, fosters greater satisfaction and confidence in the chosen treatment approach. On the other hand, clinical practitioners can tailor personalized treatment plans for patients, taking into account their unique conditions and the proven effectiveness of different intervention measures. Therefore, we investigated the published RCTs to perform a meta-analysis comparing the relative efficacy of the two intervention methods based on all accessible evidence. We also aimed to understand if the two approaches have different effects on different cognitive domains in patients with MCI or AD, and to examine the sustained effect or subsequent effect of different interventions on cognitive impairment.

Method

For identification of randomized controlled trials on NIBS and PE, our research was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) declaration and Cochrane intervention system evaluation manual [45, 46]. All analyses were from previously published articles, so no ethical approval and patient consent were required.

We searched PubMed, Web of Science, Embase, and the Cochrane Library databases for RCTs until December 2023. To identify RCTs that examined the effects of NIBS, the search terms were used: ("*Alzheimer's disease*" OR "*dementia*" OR "*AD*" OR "*mild cognitive impairment*" OR "*MCI*" OR "*neurocognitive disorder*" OR "*cognitive dysfunction*" OR "*cognitive deficit*") AND ("*repetitive transcranial magnetic stimulation*" OR "*transcranial magnetic stimulation*" OR "*non-invasive brain stimulation*" OR "*TMS*" OR "*rTMS*" OR "*NIBS*" OR "*transcranial direct current stimulation*" OR "*transcranial electric stimulation*" OR "*tDCS*" OR "*tACS*"OR "*tES*" OR "*Transcranial random noise stimulation*" OR "*tRNS*" OR "*transcranial focused ultrasound*" OR "*tFUS*"). To identify RCTs that examined the effects of PE, the following search terms were used: ("*Alzheimer's disease*" OR "*dementia*" OR "*AD*" OR "*mild cognitive impairment*" OR "*MCI*" OR "*neurocognitive disorder*" OR "*cognitive dysfunction*" OR "*cognitive deficit*") AND ("*physical activity*" OR "*physical exercise*" OR "*exercise*" OR "*aerobic fitness*" OR "*strength training*" OR "*training*").

Inclusion and exclusion criteria

Given that systematic reviews and meta-analyses already embody extensive analyses and evaluations of existing research, they fundamentally do not meet the criteria of only including original studies for comprehensive analysis. Additionally, incorporating articles derived from systematic reviews and meta-analyses into a subsequent analysis could lead to duplication and redundancy of information, thereby potentially introducing extraneous biases and errors into the analytical process. Case reports, case–control studies, and non-randomized controlled trials may demonstrate considerable variability in their results, stemming from inherent design constraints and bias factors. This variability can present substantial challenges in synthesizing research findings within a systematic evaluation, ultimately resulting in unreliable or ambiguous outcomes. Therefore, To ensure the quality of the studies, case report, case–control studies, systematic reviews, meta-analyses, and non-RCTs were excluded. Among non-RCTs included non randomized concurrent controlled studies, self controlled studies before and after, historical controlled studies, and cohort studies.

All included studies must meet the following inclusion criteria: (1) patients previously were diagnosed with AD or MCI, according to eligible criteria. Diagnostic criteria for AD/MCI, included the Petersen criteria, the International Classification of Diseases (ICD-10) by the World Health Organization, the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) Diagnostic and Statistical Manual for Mental Disorders, the National Institute on Aging-Alzheimer's Association (NIA/AA 2011) diagnostic criteria for AD in the United States, National Institute of

Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADR), and European Consortium on AD criteria; (2) article was written in English; (3) clinical assessments of cognitive functions were performed; (4) original data of studies were displayed as mean ± standard deviation (SD), or other data types if they could be converted to mean ± SD.

For NIBS studies, a study is included if it compared the treatment to a patient control group receiving sham stimulation. In case of combined interventions, the control group must receive the same NIBS component of the intervention (e.g., brain stimulation + medication vs. sham + medication).

PE is defined according to the American College of sports medicine (ACSM) [42, 47]. A PE study is included if it compared the treatment to a control group with patients who did not participate in any exercise intervention. In case of combined interventions, the control group must receive the same PE component of the intervention (e.g., PE intervention + medication vs. none-PE + medication).

Studies were excluded if any of the following criteria is met: (1) sample overlap; (2) multimodal interventions; (3) studies without available data for analysis.

Study quality estimate

The two independent reviewers used the Cochrane Collaboration tool of Revman 5.3 (London, UK) (https://training.cochrane.org/online-learning/core-software/revman) to assess the risk of bias. When there was any disagreement, a third reviewer was consulted. The following criteria were used to evaluate the quality of each included trial: (1) random sequence generation; (2) allocation concealment; (3) blindness of participants and operators; (4) blindness of result evaluation; (5) integrity of result data; (6) selective reporting; (7) other prejudices.

Data extraction

Sample characteristics (e.g., gender, age, diagnosis), intervention types and intervention parameters (e.g., stimulation frequency, intensity, treatment time), control conditions and outcome measures were extracted from each study. The mean value and SD of all neurocognitive scales of before, after the intervention and long-term follow up assessments were extracted from the intervention group and the control group in each study. If a confidence interval or standard error is provided, it is converted to SD. Data extraction was independently conducted by two individuals to minimize errors. During the extraction process, the data extractor meticulously recorded the source of the data, the extraction method employed, and any potential deviations, and carefully examined the logical consistency and rationality of the data. To ensure the integrity and authenticity of the dataset, missing values were addressed by reaching out to the authors of the original study to inquire about any unpublished data or more detailed results. Additionally, statistical methods such as boxplots and Z-scores were utilized to identify outliers within the data.

Whenever the data of the scale was displayed graphically, the software GetData graphics digitizer was used to extract the data (http://getdata-graph-digitizer.com).

Based on the classification of cognitive function summarized in the literature [48], five categories involving memory function, executive function, attention, language function, as well as global cognitive function were analyzed in this meta-analysis. The global cognitive function could be assessed by the mini mental state examination (MMSE), the cognitive part of ADAS-cog, Mini Examination Cognition (MEC), Montreal Cognitive Scale (MoCA), and Neurobehavioral cognitive status examination (NCSE). The following cognitive scales were included to detect the memory function: Cambridge Neuropsychological Test Automated Battery (CANTAB)-delayed matching to sample, Visual recognition memory task (VRM), Visual recognition task (VRT), California speech learning test version 2 (CVLT-II), Face name association task (fant), Auditory speech learning test (AVLT), Rivermead behavioral memory test (RBMT), Ray auditory speech learning test (RAVLT), Cambridge Cognitive Test (CAMCOG)-memory recall, Associative memory task, Spatial working memory (SWM), Wechsler Memory Scale, 2-back task accuracy, Story memory, Modified versions of the logical memory subtest, FuId Object Memory Evaluation. The following cognitive scales were included to detect the executive function: Trail Making Test (TMT)-A, Trail Making Test (TMT)-B, Stroop Colour Word Test (ST), Clock-drawing test (CDT), Digit Symbol Substitution Test (DSST), Symbol Digit Modalities Test (SDMT), Execution of function comparison program, Digit symbol-coding, CAMCOG-executive function, Rey Complex Figure Test (RCFT), Frontal Assessment Battery (FAB). To detect the attention: Digit span, Complex visual scene encoding task, Barrage test, Visual Attention Task (VAT), Digit Detection, and Rapid visual information processing were adapted. In addition, Correct actions and object answers, Sentence understanding, Picture naming tasks, Word fluency (WFT), Language graphic naming, Boston Naming Test (BNT), Wechsler Adult Intelligence Scale (WAIS)-vocabulary, CAMCOG -Verbal fluency, Language fluency, Semantic word fluency, Verbal Fluency test (VFT), and Letter/Phonemic Fluency Test were included for the language function. As shown in Table 1.

Table 1 Neurocognitive scales in different cognitive domains

Global cognitive function	*Memory function*	*Executive function*	*Attention*	*Language function*
Mini Mental State Examination	CANTAB-delayed matching to sample	Trail Making Test-A	Digit span	Correct actions and object answers
ADAS-cog	Visual recognition memory task	Trail Making Test-B	Complex visual scene encoding task	Sentence understanding
Mini Examination Cognition	Visual recognition task	Stroop Colour Word Test	Barrage test	Picture naming tasks
Montreal Cognitive Scale	California speech learning test-II	Clock-drawing test	Visual Attention Task	Word fluency
Neurobehavioral cognitive status examination	Face name association task	Digit Symbol Substitution Test	Digit Detection	Language graphic naming
	Auditory speech learning test	Symbol Digit Modalities Test	Rapid visual information processing	Boston Naming Test
	Rivermead behavioral memory test	Execution of function comparison program		WAIS-vocabulary
	Ray auditory speech learning test	Digit symbol-coding,		CAMCOG-Verbal fluency
	CAMCOG-memory recall	CAMCOG-executive functio		Language fluency
	Associative memory task	Rey Complex Figure Test		Semantic word fluency
	Spatial working memory	Frontal Assessment Battery		Verbal Fluency test
	Wechsler Memory Scale			Letter/Phonemic Fluency Test
	2-back task accuracy			
	Story memory			
	Modified versions of the logical memory subtest			
	Fuid Object Memory Evaluation			

ADAS-cog Alzheimer's disease assessment scale, *CANTAB* Cambridge Neuropsychological Test Automated Battery, *CAMCOG* Ambridge Cognitive Test, *WAIS* Wechsler Adult Intelligence Scale

Quantitative analysis

Revman 5.3 (https://training.cochrane.org/online-learning/core-software/revman) was used for meta-analysis Cochrane Collaboration (London, UK). Standardized mean difference (SMD) and its application selected 95% confidence interval to display the comprehensive results. The effect model was determined by the heterogeneity which was assessed by using the Cochran's Q statistic and I^2 test. If the I^2 value was greater than 50%, the random effect model was used for analysis. Otherwise, a fixed model was used.

Funnel charts were used to test potential publication bias. The statistically significant p value was set as 0.05. Subgroup analysis was carried out to determine the efficacy of different interventions in different cognitive areas for AD/MCI. A sensitivity analysis was performed to check whether our results included some secondary or exploratory cognitive measures in our study.

Result

Characteristics of the included studies

We followed the PRISMA guidelines for literature retrieval, and the detailed description was shown in Fig. 1. A total of 79 studies, involving 43 NIBS studies [17, 21, 28, 49–53] [20, 23, 24, 54–79], and 36 PE studies [34, 37, 80–113]. met the inclusion criteria. Figure 2 and (Supplementary file 1, Figure S1) showed the degree of bias risk of the included studies. The risks in randomness, outcome data integrity and the results were low in most studies. In contrast, allocation of concealment patterns and blindness of patients and researchers were often unclear. The overall quality included in our study was moderate.

The protocol for the present review was registered to PROSPERO (registration number: CRD42022380500).

NIBS: A total of 43 studies with 1298 patients were identified, including 23 TMS studies, 19 tES studies, and one tRNS

studies. A total of 30 studies were parallel designs and others used crossover design. A total of 25 RCTs included patients with AD, 16 RCTs included patients with MCI, and two studies included patients with MCI and early-stage AD. Demographic information (e.g., age, gender etc.), intervention parameters, evaluation results, adverse reports, and follow-up information of these studies were described in Table 2.

PE: A total of 36 studies with 3002 patients were identified, including 35 studies were parallel design and one crossover design. A total of 10 RCTs included patients with AD, 24 RCT included patients with MCI, and two studies included patients with MCI and mild AD. Demographic information (e.g., age, gender), intervention parameters, evaluation results, adverse reports, and follow-up information of these studies were described in Table 3.

Global cognition

NIBS: A total of 19 studies with 735 AD patients and six studies with 155 MCI patients reported the effect on the global cognition. The results showed that NIBS had no significant effect on the global cognition in AD (SMD = 0.11 $p = 0.53$) or MCI (SMD = 0.56, $p = 0.08$) (see Table 4 and Supplementary file1, Figure S2). The corresponding funnel plot was approximately symmetrical, indicating limited publication bias (see Supplementary file1, Figure S3).

PE: A total of 11 studies with 596 AD patients and 23 studies with 1769 MCI patients reported the effect on the global cognition. The results showed that PE had significant effect on global cognition in AD (SMD = 0.57, $p = 0.004$) and MCI (SMD = 0.8, $p < 0.00001$) (see Table 4 and Supplementary file1, Figure S4). The corresponding funnel plot was approximately symmetrical which indicated no significant publication bias (see Supplementary file 1, Figure S5).

Memory

NIBS: A total of 16 studies with 599 AD patients and eight studies with 340 MCI patients reported the effect on memory. The results showed that NIBS had significant effect on memory in AD (SMD = 0.7, $p = 0.0002$) and MCI (SMD = 0.71, $p < 0.0001$) (see Table 4 and Supplementary file1, Figure S6). The corresponding funnel plot was approximately symmetrical which indicated no significant publication bias (see Supplementary file 1, Figure S7).

PE: Three studies with 1300 AD patients and eight studies with 1129 MCI patients reported the effect on memory. The results showed that PE had significant effect on memory in AD (SMD = 0.61, $p = 0.02$), but not in MCI (SMD = 0.21, $p = 0.05$) (see Table 4 and Supplementary file1, Figure S8). The corresponding funnel plots was approximately symmetrical which indicated no significant publication bias (see Table 4 and Supplementary file 1, Figure S9).

Executive function

NIBS: Six studies with 181 AD patients and seven studies with 180 MCI patients reported the effect on the executive function. The results showed that NIBS had significant effect on executive function in AD (SMD = 0.39, $p = 0.01$), but not in MCI (SMD = 0.24, $p = 0.12$) (see Table 4 and Supplementary file1, Figure S10). The corresponding funnel diagram was not significantly symmetrical, indicating a slight publication bias (see Supplementary file 1, Figure S11).

PE: Five studies with 568 AD patients and 13 studies with 981 MCI patients reported the effect on the executive function. The results showed that PE had no significant effect on executive function in AD (SMD = 0.27, $p = 0.13$), and MCI (SMD = 0.22, $p = 0.14$) (see Table 4 and Supplementary file 1, Figure S12). The corresponding funnel plots was approximately symmetrical which indicated no significant publication bias (see Supplementary file 1, Figure S13).

Language function

NIBS: Seven studies with 273 AD patients and three studies with 116 MCI patients reported the effect on the language function. The results showed that NIBS had significant effect on the language function in AD (SMD = 1.08, $p = 0.0005$), but not in MCI (SMD = 0.61, $p = 0.08$) (see Table 4 and Supplementary file1, Figure S14). The corresponding funnel plots was approximately symmetrical which indicated no significant publication bias (see Supplementary file 1, Figure S15).

PE: Six studies with 585 AD patients and seven studies with 807 MCI patients reported the effect on the language function. The results showed that PE had significant effect on the language function in AD (SMD = 0.64, $p = 0.02$), but not in MCI (SMD = 0.08, $p = 0.41$) (see Table 4 and Supplementary file1, Figure S16). The corresponding funnel diagram was not significantly symmetrical, indicating a slight publication bias (see Supplementary file 1, Figure S17).

Attention

NIBS: Four studies with 174 AD patients and five studies with 114 MCI patients reported the effect on attention. The results showed that NIBS had significant effect on attention in AD (SMD = 0.55, $p = 0.0004$), but not in MCI (SMD = 0.28, $p = 0.28$) (see Table 4 and Supplementary file1, Figure S18). The corresponding funnel plot was

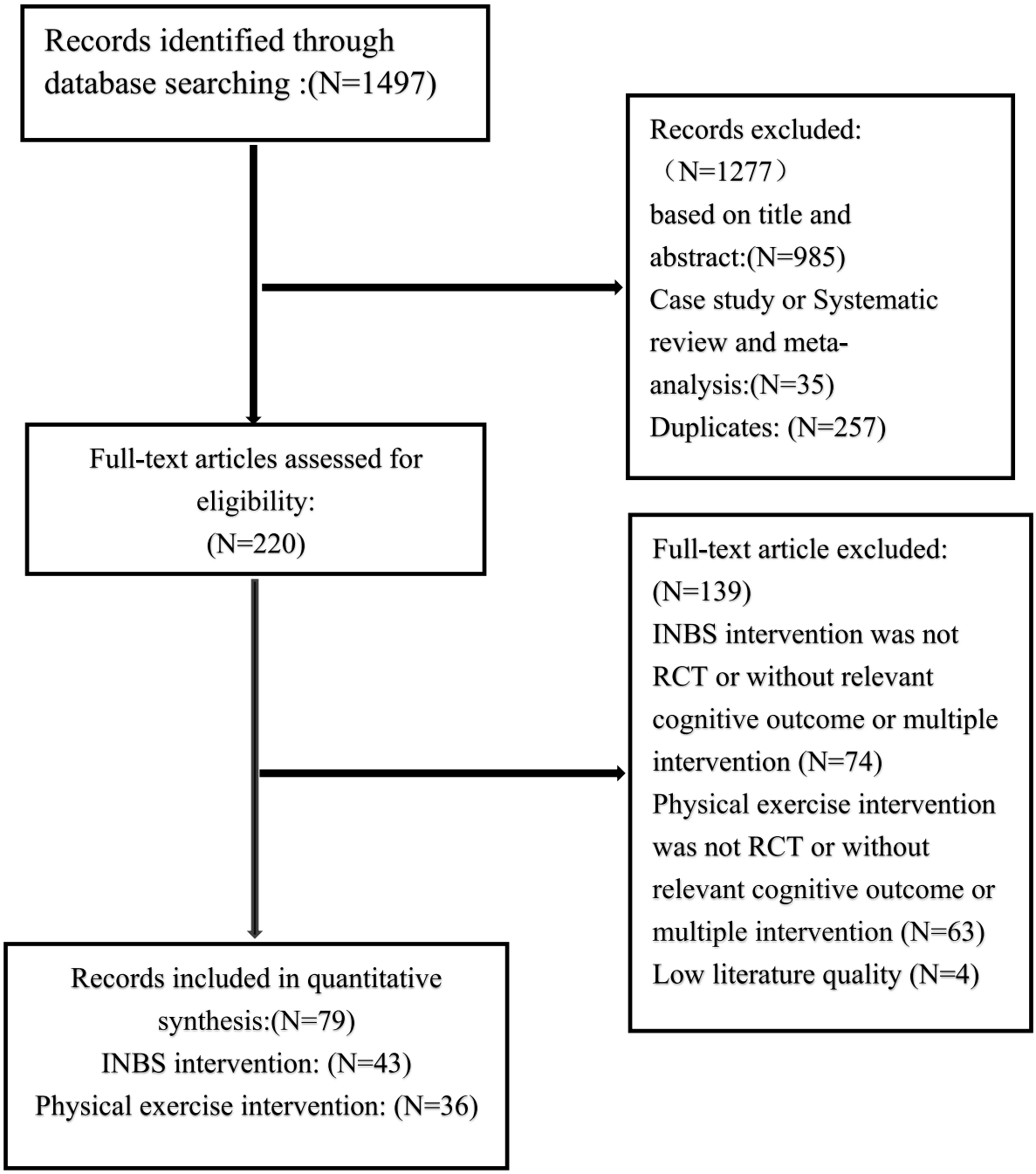

Fig. 1 Screening flow chart

approximately symmetrical which indicated very small publication bias (see Supplementary file 1, Figure S19).

PE: Two studies with 210 AD patients and five studies with 546 MCI patients reported the effect on attention. The results showed that PE had no significant effect on attention in AD (SMD = 0.06, $p = 0.65$) or MCI (SMD = 0.25, $p = 0.08$) (see Table 4 and Supplementary file1, Figure S20). The corresponding funnel plot was approximately symmetrical which indicated very small publication bias (see Supplementary file 1, Figure S21).

Long-term effect on global cognition

As for the long-term effect of the two interventions on AD or MCI, only the scale of global cognitive function was analyzed, due to the limited number of studies and the lack of neurocognitive scales.

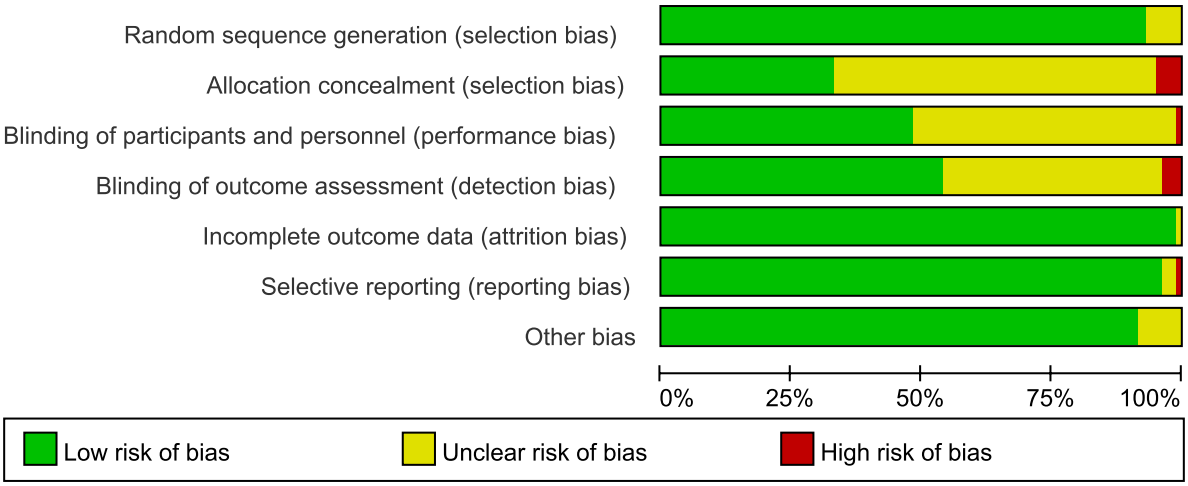

Fig. 2 Risk of bias graph

NIBS: Nine studies with 367 patients reported the long-term effects of NIBS on the global cognitive function in patients with AD or MCI. The results showed that NIBS had significant long-term sustained effect on the global cognitive function in AD and MCI (SMD = 0.52, $p = 0.01$) (see Table 4 and Supplementary file 1, Figure S22). The corresponding funnel plot was approximately symmetrical which indicated no significant publication bias (see Supplementary file 1, Figure S23).

PE: Five studies with 223 patients reported the long-term effects of PE on the global cognitive function in patients with AD or MCI. The results showed that PE had significant long-term sustained effect on the global cognitive function in AD or MCI (SMD = 0.94, $p = 0.005$) (see Table 4 and Supplementary file 1, Figure S24). The corresponding funnel plot was approximately symmetrical which indicated no significant publication bias (see Supplementary file 1, Figure S25).

Sensitivity analyses

Considering the significant difference in the degree of cognitive impairment between AD and MCI, specifically, the main characteristic of MC patients is impaired memory function, while AD patients have cognitive impairment in multiple cognition domains. Given that the therapeutic effect of PE on memory function had no significance, in order to ensure the stability of the combined results, we conducted sensitivity analysis to determine whether deleting these studies would significantly affect the estimation of the combined effect. The analysis of the effect of PE on memory in individuals with MCI showed that the result after excluding one study was significant with heterogeneity < 50% (SMD = 0.26, $p = 0.01$) (see Supplementary file1, Figure S26).

Adverse events

NIBS: A total of 12 studies including a total of 61 patients reported adverse events, including headache, cervical pain, scalp pain, pruritus, dizziness, shock, and facial convulsion, etc. These adverse effects were mild and transient which would disappear without any special treatment.

PE: Two studies including a total of 62 adverse events were reported, including musculoskeletal problems, dizziness or faintness, symptoms related to AD, somatic disease (i.e., cold, anemia, erysipelas), pneumonia, urinary tract infection, and pulmonary edema, etc. The most common adverse events were musculoskeletal problems, and only a few of them were directly related to PE intervention.

Discussion

To the best of our knowledge, the current study is the first meta-analysis to compare the comparative efficacy of NIBS and PE interventions on the global cognition, executive function, memory, language function, and attention, for MCI or AD. Our study showed PE intervention had a significant effect on the global cognitive function for AD and MCI, while NIBS did not. Both NIBS and PE exhibited a significant long-term sustained effect on individuals with MCI and AD following treatment. Further analysis of different cognitive domains showed that, for AD, NIBS had significant effects on multiple cognitive domains, including memory, executive function, language function, and attention, while PE intervention only had a significant effect on memory and language function. For MCI, NIBS only had a significant effect on memory, while PE intervention did not have any positive effect for MCI in any of the cognitive domains.

Table 2 Essential Characteristics of the Included Studies Researching the Effect of NIBS on MCI and AD Patients

Study	*Design*	*Diagnosis*	*Diagnosis criteria*	*Number*	*Gender(M/F)*	*Mean age(y)*	*Duration of Disease (y)*	*Level of Cognition (MMSE Scores)*
Ahmed 2012	Parallel	AD	NINCDS-ADRDA	54	16/29	68.4	NR	14.84(5.5)
Boggio 2008	Crossover	AD	NINCDS-ADRDA	10	4/6	79.1(8.8)	4.5 (2.2)	17.0(4.9)
Boggio 2012	Crossover	AD	NINCDS-ADRDA DSM-IV	15	8/7	71.1(5.8)	5.0 (1.1)	20.3(1.0)
Bystad 2016	Parallel	AD	NINCDS-ADRDA	47	18/29	70.0(8.0) 75.0(8.7)	NR	20.0(2.8) 21.2(3.9)
Cotelli 2008	Crossover	AD	NINCDS-ADRDA	24	NR	77.6(5.8) 75.0(6.2)	NR	14.3(2.6) 19.7(1.6)
Cotelli 2011	Parallel	AD	NINCDS-ADRDA	10	NR	71.2(6.1) 74.4(3.8)	NR	16.2(2.7) 16.0(2.0)
Cotelli 2014	Parallel	AD	NINCDS-ADRDA	24	5/19	76.6(4.6) 74.7(6.1)	NR	20.1(2.4) 20.8(2.1)
Cui 2019	Parallel	aMCI	2011 NIA-AA	21	NR	50—80	NR	NR
Drumond 2015	Parallel	MCI	NR	34	22/12	65.1(3.5) 65.2(4.1)	NR	24.5(1.8) 24.2(2.3) (MoCA)
Eliasova 2014	Crossover	7AD 3aMCI	NR	10	6/4	72 (8)	3.90 (1.57)	23(3.56)
Fileccia 2019	Parallel	MCI	NR	34	24/10	71.6(1.4) 69.7(1.6)	NR	25.9(0.5) 26.1(0.6)
Im 2019	Parallel	AD	NINCDS-ADRDA DSM-IV	18	3/15	71.9(9.2) 74.9(5.0)	NR	20.1(3.8) 22.1(4.6)
Khedr 2014	Parallel	AD	NINCDS-ADRDA	34	19/15	69.7(4.8)	3.1 (2.1)	18.1(3.3)
Khedr 2019	Parallel	AD	NINCDS-ADRDA	44	26/18	65.7(6.4)	1.17 (0.48)	14.17(3.67) 13.90(3.46)
Koch 2018	Crossover	AD	CSF or imaging evidence	14	7/7	70.0(5.1)	1.15 (0.42)	26.1(1.8)
Marcos 2019	Parallel	MCI	NR	58	20/38	73.0(9.2) 71.6(7.9)	NR	26.93(0.50) 27.31(0.37)
Padala 2018	Crossover	MCI	Petersen's criteria	9	8/1	65.(9.3)	NR	25.6(2.1)
Rutherford 2015	Crossover	AD	NR	10	3/7	57–87	NR	5–26 (MoCA)
Sole-padulles 2006	Parallel	aMCI	DSM-IV	39	11/28	> 50	> 1	26.50(2.06) 26.16(1.92)
Suemoto 2014	Parallel	AD	NINCDS-ADRDA	40	12/28	80.5(7.5)	NR	15.0(3.1) 15.4(2.6)
Turriziani 2012	Crossover	MCI	Petersen's criteria	8	6/2	66.4(5.7)	1–2	26.9(2.0)
Turriziani 2019ab	Crossover	AD	NR	24	9/15	72.40(5.2)	NR	22.0(1.2)
Turriziani 2019c	Parallel	AD	NR	14	5/9	71.28(3.5)	NR	22.44(2.1)
Wu 2015	Parallel	AD	NINCDS-ADRDA	52	21/31	71.4(4.9) 71.9(4.8)	5.1 (1.5)	15.3(3.1)
Zhao 2017	Parallel	AD	DSM-IV	30	13/17	70.8(5.6)	NR	22.5(2.7)
Li 2021	Parallel	AD	DSM-V	75	44/31	66.0(8.47) 64.6(7.88)	3.70 (1.75) 3.97 (1.62)	16.13(4.27) 15.97(4.12)
Prasad R. 2020	Parallel	AD	NR	20	18/2	77.3(7.2)	NR	22.9(3.4) 21.4(3.3)
Roque GY 2021	Crossover	MCI	(DSM-5)/NIA-AA	22	9/13	66.36 (5.12)	NR	28.6(1.5) 28.5(1.1)
Wu 2021	Parallel	AD	NINCDS-ADRDA	49	21/26	66.46 (8.25) 66.35 (7.99)	NR	20.54(4.67) 21.7(4.67)
Yuan 2020	Parallel	aMCI	Petersen's criteria	24	11/13	65.08 (4.89) 64.67 (4.77)	4.25 (2.26)3.50 (2.23)	22.83(1.11) 22.00(1.28) (MoCA)
Gangemi 2020(a)	Parallel	mild AD	DSM-V and NINCDS-ADRDA	26	NR	67.5(2.8) 69.01(3.1)	NR	14.9(1.8) 15.3(1.8)
Gangemi 2020(b)	Parallel	mild AD	DSM-V and NINCDS-ADRDA	18	NR	68.5(2.8) 68.7(3.1)	NR	15.8(1.8) 15.9(1.6)
He 2021	Parallel	MCI	DSM-IV	43	11/32	63.5(4.80)65.6(3.53)	NR	25.13(0.79) 24.89(1.1)
Gu 2022	Parallel	MCI	Peterson, DSM-5	40	22/18	63.2(6.98) 65.2(6.16)	NR	22.20(2.48) 21.40(2.64)
Smirni 2021	Parallel	mild AD	diagnostic criteria for prodromal AD	40	13/27	73.4(5.67) 73.0(5.55)	NR	22.45(2.12) 22.8(2.42)
Liu 2019	Crossover	MCI mild AD	DSM-V	17	10/17	77.0(5.0)	NR	20.8(4.0) (MoCA)

Table 2 (continued)

Study	*Design*	*Diagnosis*	*Diagnosis criteria*	*Number*	*Gender(M/F)*	*Mean age(y)*	*Duration of Disease (y)*	*Level of Cognition (MMSE Scores)*
Chernkhuan 2020	Parallel	MCI	European Consortium-AD criteria	45	41/4	68.4(8.4) 69.7(7.6)	NR	22.1(1.9)
Leocani 2021	Parallel	AD	NINCDS-ADRDA	28	14/14	70.9(8.1)	4.2 (1.7)	16.9(5.5)
Rosa 2018	Parallel	MCI	Petersen criteria	18	10/8	75.3(4.8) 75.3(2.2)	2.3 (0.9)	26.0(1.2) 26.3(1.7)
Esposito 2022	Parallel	MCI	NIA-AA	27	14/13	67.85(9.28)	NR	NR
Chen 2022	Crossover	MCI	NR	9	NR	NR	NR	NR
Benussi 2022	Crossover	AD	NIA-AA	60	29/31	72.3(7.0)	3.1 (2.4)	23.9(4.2)
Zhou 2022	Parallel	AD	NR	50	NR	NR	NR	16.25(1.1) 17.37(0.94)
Monastero 2020	Crossover	MCI	NR	10	10/0	70.6(7.8)	4.8 (4.07)	NR
Intervention	*Sham stimulation*	*Stimulation site*	*Stimulation protocol*			*Outcome measures*	*Follow-up*	*Adverse effects*
rTMS	Coil away from the head	R, L-DLPFC	(1)20 Hz,90%RMT,2000pulses per session,5 days (2)1 Hz,100%RMT,2000pulses per session,5 days			MMSE	1 and 3 months	NO
tDCS	First 30 s current	L-DLPFC, LTC	Anode: 2 mA,30 min/day,1 day			VRM, ST, Digit Span	NR	NO
tDCS	First 30 s current	Bilateral temporal lobes	Anode:2 mA,30 min/day,5 days			MMSE, ADAS-Cog, VRT, VAT	1 week,1 month	NO
tDCS	First 30 s current	L-temporal lobe	Anode:2 mA,30 min/day,6 days			CVLT-II, MMSE, CDT, TMT	NR	NO
rTMS	Stimulating Cz	R, L-DLPFC	20 Hz,90%RMT,1 session for each target			Action and object naming	NR	NR
rTMS	Sham coil	L-DLPFC	20 Hz,100%RMT,2000pulses per session,10 days			MMSE	4 and 12 weeks	NO
tDCS	Last 10 s current	L-DLPFC	Anode:2 mA,25 min/day,5 days			MMSE, FANT, Picture naming task	3 and 6 months	NR
rTMS	A 90° coil	R-DLPFC	10 Hz,90%RMT,1500pulss per session,10 days			AVLT	8 weeks	NO
rTMS	Placebo coil	L-DLPFC	10 Hz,110%RMT,2000pulss per session,10 days			RBMT, LM, RAVLT, TMT, VFT	1 month	4
rTMS	Stimulating VTX	R-Inferior frontal gyrus (IFG) R-STG	10 Hz,90%RMT,2250pulss per session,1 day			TMT, ST, CVSET	NR	NR
tDCS	First 20 s current	L-DLPFC	Anode:2 mA,20 min/day,20 days			MMSE, RAVLT, Attention-Barage test, BMDM	NR	NR
tDCS	Last60s cu rrent	R, L-DLPFC	Anode:2 mA,29 min/day, 3 days			MMSE, Digit Span, BNT, RCFT	2, 6 months	NR
tDCS	Last 30 s current	L-DLPFC	Anode/cathode: 2 mA,25 min/day,10 days			MMSE	1 and 2 months	NO
tDCS	Last 30 s current	R, L-TP	Anode: 2 mA,20 min/day,10 days			MMMSE, CDT, MoCA	NR	3
rTMS	Sham coil	Precuneus	20 Hz,100%RMT,1600pulses persession,10 days			AVLT, DSST, MMSE, FAB	NR	NR
tDCS	First 30 s current	L-DLPFC	Anode: 2 mA,30 min/day,10 days			CAMCOG, MMSE, TMT, SVF, BNT	NR	NR
rTMS	Sham coil	L-DLPFC	10 Hz,120%RMT,3000pulses persession,10 days			AES-C, 3MS, MMSE, TMT, IADL, CGI, EXIT-25	6 weeks	16
rTMS	Wooden block coil	R, L-DLPFC	10 Hz,90%−100%RMT,2000pulses per session,13 days			ADAS-Cog, RMBC MoCA	4 weeks	NR
rTMS	Tilted coil	L-DLPFC	5 Hz,80%RMT,500pulses per session,1 days			associative memory	NR	NR
tDCS	First 20 s current	L-DLPFC	Anode:2 mA,20 min/day,6 days			Apathy Scale	1 week	2
rTMS	Tilted coil	R, L-DLPFC	1 Hz,90%RMT,600pulses per session,1 day			Accuracy RTs	NR	NR
rTMS	A 90° coil	R, L-DLPFC	1 Hz,90%RMT,600pulses per session,1 day			Accuracy (Memory)	NR	NR
rTMS	A 90° coil	R-DLPFC	1 Hz,90%RMT,600pulses per session,10 days			Accuracy (Memory)	4 weeks	NR
rTMS	A180° coil	L-DLPFC	20 Hz,80%RMT,1200pulses per session,20 days			BEHAVE, ADAS-Cog	NR	1

Table 2 (continued)

Study	*Design*	*Diagnosis*	*Diagnosis criteria*	*Number*	*Gender(M/F)*	*Mean age(y)*	*Duration of Disease (y)*	*Level of Cognition (MMSE Scores)*
rTMS	Sham coil with sound	Bilateral parietal region and posterior temporal areas	20 Hz,4000pulses per session,30 days			ADAS-Cog, MMSE, MoCA, AVLT	NR	2
rTMS	Sham figure-of-eight coil	L-DLPFC	20 Hz,100%RMT,20 min/day,30 day,2000pulses/day			ADAS-Cog MMSE	3 months	NR
rTMS	Sham coil with sound	L-DLPFC	10 Hz, 120% MT, 3000 pulses/day,20 day			MMSE, TMT-A, TMT-B,	4 weeks,8 weeks	11
rTMS	Sham coil	L-DLPFC	5HZ,100%RMT,1500pulse/day,30 day,			MoCA, MMSE, ROCF, ST	4 weeks	NR
iTBS	Placebo coil with sound	L-DLPFC	3 pulses, 50 Hz bursts given every 200 ms, 5 Hz,1800 pulses/day,14 day			MMSE, MoCA, AVLT, Digital Span, SDMT, CDT, HVOT, JLOT, BNT, VFT	8 weeks	8
rTMS	A 90° coil	L-DLPFC	10HZ,80%RMT,400 pulses/session,20session			MoCA	NR	4
tDCS	Last 10 s current	L-frontotem (F7-T3)	Anode:2 mA,20 min,/daily10-day,			MMSE	NR	NR
tDCS	Last 10 s current	L-frontotem (F7-T3)	Anode:2 mA,20 min,/daily,80-day,			MMSE	NR	NR
tDCS	1 mA for 1 min	L-DLPFC anode F3	Anoda:1 mA,20 min/day,10 day			MMSE, MoCA	NR	NR
tDCS	Last 30 s current	L-temporal area	Anode:2.0 mA,20 min/day, 5 days			MoCA, WMS	1 month	NO
tDCS	NR	L-DLPFC or R-DLPFC	Anode:1 mA,20 min/day,1 day			MMSE, VFTs, DS, The Corsi Span, forward and backward, RMT-Faces, AVLT, BADA, ST, CD, CDP	NR	1
tDCS	First 30 s current	Bitemporal and bifrontal lobes	Anode: 2 mA, 20 min/d, 7 day			ADAS-Cog, 2-back task accuracy	NR	4
tDCS	First 30 s current	R-DLPFC	Anode: 2 mA, 20 min/d, 12 d			CANTAB	4 weeks	5
rTMS	Sham coil	Bilateral frontalparietal-temporal regions	10.0 Hz, 120% RMT, 840 pulses per session, 12 d			ADAS-Cog	4 months	NO
tDCS	First 10 s and last 10 s current	L- PFC	Anode: 1.5 mA, 15 min/d, 1 day			Recognition Task	1 month	NR
rTMS	Placebo coil	R, L-DLPFC	10.0 Hz, 80% RMT, 2000 pulses per session, 20 days			RBANS	6 months	NO
TBS	Sham coil	Hippocampus	θ- iTBS, cTBS, 2 days			FNAME	NR	NR
tACS	Sham_tACS	Precuneus	Anode:1.5 mA, 40HZ, 60 min, 1 day			FNAME, Rey_RAVL	NR	NO
tACS	Sham_tACS	Bilateral temporal lobes	Anode:2 mA, 40 Hz, 20 min, 30 days			MMSE, ADAS-COG	12 weeks	NO
tNRS	Stimulation only 30 s	Left M1	1.5 mA,100–600 Hz,15 min,1 week			Digit Symbol, Digit Span, Visual Search, ST, Letter Fluency	NR	NR

Data in Table 2 is expressed as mean ± standard deviation (SD). AD indicates Alzheimer disease; M/F, male/female; *NINCDS-ADRDA* National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association, *DSM-IV* Diagnostic and Statistical Manual–IV, *CSF* Cerebrospinal fluid, *NR* Not report, *rTMS* Repetitive transcranial magnetic stimulation, *tDCS* Transcranial direct current stimulation, *tRNS* Transcranial random noise stimulation, *VTX* Vertex, *R,L-DLPFC* Right and left dorsolateral prefrontal cortex, *LTC* Left temporal cortex, *R-IFG* Right inferior frontal gyru, *R-STG* Rightsuperior temporal gyrus, *TP* Temporo-parietal region, *RMT* Resting motor threshold, *MMSE* Mini-mental status evaluation, *VRM* Visual Recognition Memory, *ADAS-Cog* AD assessment scale cognitive subscale, *RMT-Faces* Recognition Memory Test for Faces, *VRT* Visual recognition task, *SDMT* Symbol Digit Modalities Test, *VAT* Visual attention task, *CVLT-II* California Verbal Learning Test–Second Edition, *FANT* Face Name Associations Task, *JLOT* Judgment of Line Orientation Test, *CDT* Clock-drawing test, *TMT* Trail Making Test, *HVOT* Hooper Visual Organization Test, *AVLT* Auditory Verbal Learning Test, *BADA* Aphasic Deficit Analysis; (CD, CDP),Copying drawings without and with programming elements, *RBMT* Rivermead Behavioural Memory Test, *LM* Logical memory, *RAVLT* Rey Auditory-Verbal Learning Test, *VFT* Verbal fluency test, *CVSET* Complex visual scene encoding task, *BMDM* Brief Mental Deterioration Battery, *BNT* Boston Naming Test, *RCFT* Rey Complex Figure Test, *MMMSE* Modified Mini Mental State Examination, *MoCA* Montreal Cognitive Scale, *DSST* Digit Symbol Substitution Test, *FAB* Frontal Assessment Battery, *CANTAB* Cambridge Neuropsychological Test Automated Battery, *CAMCOG* Cambridge Cognitive Examination, *SVF* Semantic Verbal Fluency test, *AES-C* Apathy evaluation scale-clinician version, *3MS* Modified Mini Mental State Exam, *CGI* Clinical Global Impression improvement, *EXIT* Executive Interview, *RBANS* Assessment of Neuropsychological Status, *FNAME* Face–name associative memory

Table 3 Essential Characteristics of the Included Studies Researching the Effect of PE on MCI and AD Patients

Study	*Design*	*Diagnosis*	*Diagnosis criteria*	*participants*	*Gender (M/F)*	*Mean age(y)*	*Duration of Disease (y)*	*Level of Cognition (MMSE Scores)*
Arcoverde 2013	Parallel	mixed AD	NINCDS-ADRDA/ CDR1) NINDS	20	9/11	(EG) 78.5 (64- 81.2) (CG) 79 (74.7- 82.2)	(EG) 4.3(2.8) (CG) 4.1(2.1)	(EG) 20.4 (2.7) (CG)19.9 (3.4)
Langoni. 2019	Parallel	MCI	2011 NIA/AA	52	12/40	(EG) 72.6 (7.8), (CG) 71.9 (7.9)	NR	(EG)21.9 (4.8) (CG)23.7 (3.7)
Ohman 2016	Parallel	AD	NINDS-ADRDA	210	129/81	(GE)78.3 (5.1) (HE) 77.7(5.4) (CG) 78.1 (5.3)	NR	(GE)18.5 (6.3) (HE)17.8(6.6) (CG)17.7(6.2)
Lazarou 2017	Parallel	aMCI	Petersen criteria	129	28/101	(EG) 65.89 (10.76), (CG) 67.92 (9.47)	NR	(EG)27.60 (2.19) (CG) 26.88 (2.1)
Hoffmann 2016	Parallel	AD	NINDS-ADRDA	200	113/87	(EG) 69.8 (7.4), (CG) 71.3 (7.3)	NR	(EG) 23.8 (3.4) (CG) 24.1 (3.8)
Lü 2015	Parallel	MCI	MMSE MoCA	45	13/32	(EG) 69 (3.83), (CG) 70.43 (5.53)	NR	(EG)27.23 (1.63) (CG) 26.43 (2.0)
Holthoff 2015	Parallel	mild to moderate AD	NINCDS-ADRDA	30	15/15	(EG) 72.40 (4.43), (CG) 70.67 (5.41)	NR	(EG)22.05(0.54) (CG)21.95 (0.54)
Lam 2015	Parallel	Mix MCI	NR	278	63/215	(EG)75.5 (6.7), (CG) 75.4 (6.1)	NR	(EG) 25.8(2.3) (CG) 25.6(2.4)
Wei 2014	Parallel	MCI	DSM-IV	60	40/20	(EG) 66.73 (5.48), (CG) 65.27 (4.63)	NR	(EG) 24.33(1.65) (CG) 25(1.29)
Suzuki 2013	Parallel	MCI	Petersen criteria	100	51/49	(EG) 74.8 (7.4), (CG) 75.8 (6.1)	NR	(EG) 26.8 (2.3) (CG) 26.3(2.7)
Varela 2012	Parallel	MCI	NR	48	21/27	(EG) A group 79.24 (10.07) (EG) B group76.44 (11.38) (CG) 79.40 (6.72)	NR	(EG)A19.86 (5.12) (EG)B20.81 (4.69) (CG)21.80 (3.23)
Vreugdenhil 2012	Parallel	AD	DSM-IV, NINCDS-ADRDA	40	16/24	(EG) 73.5, (CG) 74.7	4.2 (0.5–10) (EG)3.8 (0.5–10) (CG)	(EG)22.9(13–28) (CG)21.0(10–28)
Uffelen 2008	Parallel	MCI	Petersen criteria	304	160/144	(EG)75.03, (CG1)75 (FA/B12/B6)76.42, (CG2),74.89	NR	(EG)29(CG1)29 (FA/B12/B6),28.44, (CG2),29
Yoon, 2017	Parallel	MCI	MMSE MoCA	30	0/30	Exercise HSPT 75.00 (3.4) Exercise LSST 76.00 (3.94) (CG) 78.00 (2.77)	NR	(HSPT)21.00 (1.04) (LSST) 21.56 (0.73) (CG) 22.29 (1.11)
Nakatsuka 2015	Parallel	MCI	MMSE CDR	56	25/31	(EG) 81.3 (3.8), (CG) 81.2 (4.0)	NR	(EG) 23.5(2.4) (CG) 22.2(3.2)
Venturelli 2011	Parallel	AD	NR	21	9/15	(EG)83 (6.0) (CG) 85 (5.0)	NR	(EG) 13 (2) (CG) 12 (2)

Table 3 (continued)

Study	*Design*	*Diagnosis*	*Diagnosis criteria*	*participants*	*Gender (M/F)*	*Mean age(y)*	*Duration of Disease (y)*	*Level of Cognition (MMSE Scores)*
Bademli 2018	Parallel	MCI	NR	60	25/35	(EG) 72.24 (7.16) (CG)70.67 (8.34)	NR	(EG)23.27(2.17) (CG) 23.42 (1.07)
Doi 2017	Parallel	MCI	Petersen criteria	134	69/65	(EG) 75.7 (4.1) (CG) 76.0 (4.9)	NR	(EG)26.0(2.6) (CG)25.8 (2.4)
Song 2019	Parallel	MCI	MoCA	120	30/90	(EG) 76.22 (5.76) (CG)75.33(6.78)	NR	MoCA (EG)22.03 (1.81) (CG)22.10 (1.92)
Tao 2019	Parallel	MCI	Petersen's criteria	69	18/39	Baduanjin 66.17(4.17) Walking 64.32(2.60) (CG) 65.97(5.66)	NR	MoCA baduan-jin22.45(2.16) walking21.47(2.27) (CG)21.00(2.36)
Cardalda 2019	Parallel	mild to moderate MCI	NR	77	23/54	(strength training-TG 85.54 (8.09) Callisthenic train-ing83.76 (8.33) (CG) 85.17 (7.38)	NR	
Silva 2019	Parallel	MCI/AD	DSM-IV	46	19/27	MCI (EG) 71.85(5.69) MCI (CG) 78.20 (5.26) AD (EG) 81.22 (8.88) AD (CG) 77.54 (8.05)	NR	MCI (EG) 29 (28 −30) MCI (CG) 29 (26 −30) AD (EG) 20.66 (5.19) AD (CG) 20.90 (4.34)
LEE 2020	Parallel	MCI	CDR MMSE	40	16/24	(EG) 73.77(4.64) (CG) 74.22(4.46)	NR	(EG) 23.8(2.9) (CG) 23.4(1.3)
Wang 2020	Parallel	MCI	MMSE MoCA	111	43/68	(EG) 68.37 (5.27) (CG)68.37 (5.27)	NR	MoCA (EG)21.65(2.22) (CG)21.41 (2.11)
Li (2021)	Parallel	MCI	Petersen's criteria	84	33/51	NR	NR	(EG)26.50(1.33) (CG)26.62(1.46)
P.Yu 2022	Parallel	MCI	MoCA-HK	34	9/25	67.3 (4.2) [TC] 67.2 (6.8) [EG] 67.6 (8.1) [CG]	NR	(Tai Chi) 19.7 (1.5) (EG) 19.3(2.0) (CG) 18.2 (3.8)
L.FLAW 2022	Parallel	MCI	NIA-AA	73	28/45	(EG) 77.35(6.66) (CG) 74.14(7.53)	NR	(EG) 6.65 (1.2) (CG) 6.53 (1.61)
Christofoletti 2008	Parallel	AD	ICD-10	54	17/37	(EG) 70.0 (1.8) (CG) 79.4 (2.0)	NR	(EG) 12.7 (2.1) (CG) 14.6 (1.2)
Yang 2015	Parallel	AD	NINDS-AIREN	50	17/33	(EG) 72.00 (6.69) (CG) 71.92 (7.28)	NR	(EG) 21.33 (2.24) (CG)20.00 (3.50)

Table 3 (continued)

Study	*Design*	*Diagnosis*	*Diagnosis criteria*	*participants*	*Gender (M/F)*	*Mean age(y)*	*Duration of Disease (y)*	*Level of Cognition (MMSE Scores)*
Wincke 2004	Parallel	AD	NINCD S-ARDRA	25	0/25	(EG) 81.339 (4.24) (CG) 81.909 (4.18)	NR	(EG)12.87 (5.01) (CG) 10.8 (5.01)
Cancela 2015	Parallel	AD	DSM-IV	189	63/126	(EG) 80.63 (8.32) (CG) 82.90 (7.42)	NR	NR
Amjad 2018	Parallel	MCI	MMSE MoCA	40	21/19	(EG) 58 (2) (CG) 60 (3)	NR	(EG)20.78 (0.42) (CG)21.24(0.5)
Awee 2016	Crossover	MCI	MMSE	24	0/24	65–87	NR	18.7(4.0)
Kohanpour 2017	Parallel	MCI	MMSE	40	NR	67.86 (3.89)	NR	(EG)22.7(1.63) (CG)24.3 (0.94)
Hong 2017	Parallel	MCI	DSM-IV-TR	22	6/16	man 78.33 (3.21) female 77.71 (3.40) man 78.33 (5.50) female 75.11 (4.45)	NR	NR
Fonte 2019	Parallel	MCI/AD	NR	87	32/55	(EG) AD 79(9) MCI 75(5) (CG) AD 80(7) MCI 79(3)	NR	(EG)AD 17.8(5.7) (EG)MCI 27(2.2) (CG)AD 18.7(2.3) MCI 25.7(1.8)

Intervention	*control group*	*Outcome measures*	*Intervention length*	*frequency*	*intensity*	*adverse*	*Follow up*
BH fitness- Explorer Pro Action for four weeks, Warm-up exercises on the treadmill for ten minutes at an intensity of 40% VO2max;2) 20 min at an intensity of 60% VO2max; 3) 5 min of super-vised stretching exercises	Routine clinical treatment	CAMCOG, MMSE, CDT, VF, TMT-A (sec), ST (sec) Digit Span (score), WAIS-R Scale, RAVLT	3 months	twice per week	30 min	No	No
Aerobic and strength exercises	Life as usual	MMSE	24 weeks	twice per week	60 min	NR	No

Table 3 (continued)

Study	*Design*	*Diagnosis*	*Diagnosis criteria*	*participants*	*Gender (M/F)*	*Mean age(y)*	*Duration of Disease (y)*	*Level of Cognition (MMSE Scores)*
Aerobic exercises, strength exercises and balance and toning training (group-based exercise) (GE) ($N=70$) Aerobic exercises, strength exercises and balance and toning training (home-based exercise) ($N=70$) (HE)	Usual care	MMSE, CDT, VF	12 months	twice per week		4_hours (GE) 60-min (HE)	NR	No
International Ballroom dance classes	Life as usual	MMSE, MoCA, RBMT, RAVLTl, TEA, ROCF; TMT-B	10 months	twice per week		60 min	NR	No
Aerobic and strength building exercises	Treatment as usual	MMSE, SDMT, ST, VFT, ADAS-Cog	16 weeks	three per week		60 min	58	No
Dumbbell-training sessions	Treatment as usual	ADAS-Cog, TMT-B, DST	12 weeks	three per week		60 min	No	No
Lower-body movement training	Counselling sessions without physical activity ($N=15$)	MMSE, semantic word fluency	12 weeks	three per week		30 min	NR	1 year
Stretching and toning exercises, Tai Chi sessions and aerobic exercise (i.e. static bicycle riding)	Social group (social activities, e.g. tea gathering, film watching)	ADAS-Cog, CMMSE, CVFT	12 months	at least once per week		60 min	NR	No
Handball training	Life as usual	MMSE	6 months	5 days per week		30 min	NR	No
Aerobic exercises and strength and balancing exercises ($N=50$)	Educational classes	MMSE, ADAS_Cog, WMS-LM1	6 months	twice per week		90 min	4	No
Aerobic exercise at 40% HR (Group A) or Aerobic exercise at 60% HR (Group B)	Recreational activities (no physical activity)	MMSE	3 months	three per week		30 min	NR	3 months

Table 3 (continued)

Study	*Design*	*Diagnosis*	*Diagnosis criteria*	*participants*	*Gender (M/F)*	*Mean age(y)*	*Duration of Disease (y)*	*Level of Cognition (MMSE Scores)*
Upper and lower muscle building exercises, balance training and brisk walking (community-based home exercise) ($N=20$)	Usual care	MMSE, ADAS_Cog	4 months	daily		30 min	NR	No
Walking program ($N=77$) or Placebo activity program [Relaxation, posture exercises, low intensity] ($N=93$)	Placebo pill or Vitamin	MMSE, AVLT, VFT, DSST, ST,	12 months	twice per week		60 min	0	No
High-speed training with elastic band ORLow-speed physical Activity training	Life as usual	MMSE, MoCA-K	12 weeks	twice per week		60 min	NR	No
Walking and step aerobics	Conversation classes	MMSE, WF, TMT-A	12 weeks	once per week		60 min	NR	No
Walking group	Routine medical care	MMSE	24 weeks	4 times per week		30 min	NR	No
Physical activity program	Life as usual	MMSE	20 weeks	4–7 days per week		40 min	NR	No
Dance program	Health education program ($N=67$)	MMSE, TMT-A,TMT-B, story memory recall test	40 weeks	weekly sessions		60 min	0	No
Moderate-intensity aerobic stepping exercise program	Health education	MoCA-C	16 weeks	three per week		60 min	NR	No
Ba duanjin or brisk walking	Non-exercise health education control	MoCA	24 weeks	three per week		60 min	NR	No
Strength program with therabands or exercise program of multi-callisthenics	No physical activity	MMSE, a Pfeiffer text	12 weeks	twice per week		60 min	NR	No

Table 3 (continued)

Study	*Design*	*Diagnosis*	*Diagnosis criteria*	*participants*	*Gender (M/F)*	*Mean age(y)*	*Duration of Disease (y)*	*Level of Cognition (MMSE Scores)*
Multimodal physical training, including aerobic exercises, strength, balance andstretching	Not perform any physical training	MMSE, CDT VF, ST	12 weeks	twice per week		60 min	NR	No
The elastic band-based high-speed power training	A small group lecture	(FAB-K)	8 weeks	three per week		50 min	NR	No
Structured limbs-exercise program	Health promotion classes	MoCA	12 weeks	three per week		60 min	NR	No
Multi-component exercise training including aerobic exercise, strength training, balance training, coordination training, and sensitivity training	Health instruction	CM-PPT, MMSE, MoCA	6 months	5mornings a week,		30 min	NR	No
Yang-style Tai Chi training or static stretching exercises muscle-strengthening exercises, aerobic exercises	Usual daily activities	MoCA-HK, TMT-A, TMT-B, Delay Recall Test, Digit span, Victoria stroop test, VF, N-back Task	24 weeks	three per week		60 min	NR	No
Moderate intensity aerobic exercise	Usual daily activities	NCSE, TMT-A/B, VF	8 weeks	12 session all		60 min	0	5 months
Specific kinesio therapeutic exercises (stimulated strength, balance)	Not perform any physical training	MMSE, delayed memory, CDT, VF	6 months	three per week		60 min	NR	No
Exercise intensity is moderate, 70% maximum heart rate	Health education	MMSE, ADAS-Cog,	3 months	three per week		40 min/day	NR	No
Music-based dance therapy	Conversation	MMSE, Amsterdam Dementia Screening Test 6	3 months	daily		30 min/day	NR	No
Aerobic physical activity program	Activities as usual	MEC, FOME	15 months	daily		15 min/daily	NR	No

Table 3 (continued)

Study	*Design*	*Diagnosis*	*Diagnosis criteria*	*participants*	*Gender (M/F)*	*Mean age(y)*	*Duration of Disease (y)*	*Level of Cognition (MMSE Scores)*
Aerobic physical activity (a treadmill and a stationary bicycle)	Not perform any physical training	MMSE, MoCA, TMT-A and TMT-B	6 weeks	three per week		20 min to 40 min/day	NR	No
Arm swing exercise (ASE) training	Not perform any physical training	MMSE, SRT, CRT	12 weeks	5 day/week		130 min	NR	No
Aerobic exercise: running	Not perform any physical training	MMSE,	12 weeks	three per week		26 min/day	NR	No
Resistance exercise with an elastic band	Current lifestyle	MoCA, COWAT, category semantic fluency test, letter/phonemic fluency test, Digit Span, RMT	12 weeks	twice per week		60 min	NR	No
Physical activity treatment	Not perform any physical training	MMSE, TMTA, TMTB, Digit Cancellation Test, ADAS-Cog, RBM	6 months	three per week		90 min	NR	3 months

Data in Table 3 is expressed as mean (standard deviation) (SD). *AD* indicates Alzheimer disease, *M/F*, male/female, *NINCDS-ADRDA* National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association, *DSM-IV* Diagnostic and Statistical Manual–IV, *CSF* Cerebrospinal fluid, *NR* Not report, *MMSE* Modified Mini Mental State Examination, *MoCA* Montreal Cognitive Scale, *CAMCOG* Cambridge Cognitive Examination, *DTC* The Clock Drawing Test, *VF* Verbal Fluency (score), *TMT-A* Trail Making TEST -A (sec), *ST* Stroop Test (sec);Digit Span (score), WAIS-R Scale; *RAVLT* Rey Auditory Verbal Learning Test, *RBMT* Behavioral Memory Test, *TEA* Test of Everyday Attention, *ROCF* Rey Osterrieth Complex Figure Test, *SDMT* Symbol Digit Modalities Test, *DST* The Digit Span Test, *CVFT* Category verbal fluency test, *WMS-LM1* Modified versions of the logical memory subtest, *DSST* Digit Symbol Substitution Test, *WF* Word fluency, *CM-PPT* Mini-Physical Performance Test, *MEC* Mini-Mental State Examination, *NCSE* Neurobehavioral cognitive Status examination, *FOME* Fuld Object Memory Evaluation, *SRT* the simple reaction times, *CRT* Choice reaction time, *COWAT* The Controlled Oral Word Association Test, *RMT* Rey 15-Item Memory Test, *RBM* Rivermead Behavioral Memory Test

Table 4 Results of different subgroups

Cognitive domain	*Disease type*	*Studies*	*(EG/CG) subjects*	*SMD*	*95%CI*	*p*	I^2
Global cognitive function							
NIBS	AD	19	379/356	0.11	(−0.24,0.47)	0.53	81%
	MCI	6	79/76	0.56	(−0.07,1.19)	0.08	69%
PE	AD	11	300/296	0.57	(0.19,0.96)	0.004	78%
	MCI	23	890/879	0.8	(0.49,1.11)	< 0.00001	89%
Memory function							
NIBS	AD	16	335/324	0.7	(0.33,1.07)	0.0002	79%
	MCI	10	178/189	0.71	(0.37,1.06)	< 0.0001	57%
PE	AD	3	78/93	0.61	(0.09,1.14)	0.02	52%
	MCI	8	518/611	0.21	(−0.00,0.42)	0.05	59%
Executive function							
NIBS	AD	6	93/88	0.39	(0.09,0.69)	0.01	6%
	MCI	7	87/93	0.24	(−0.06,0.53)	0.12	0%
PE	AD	5	289/279	0.27	(−0.08,0.62)	0.13	72%
	MCI	13	484/497	0.22	(−0.07,0.51)	0.14	79%
Language function							
NIBS	AD	7	129/144	1.08	(0.48,1.69)	0.0005	80%
	MCI	4	54/62	0.61	(−0.07,1.29)	0.08	61%
PE	AD	6	298/287	0.68	(0.09,1.27)	0.02	90%
	MCI	7	406/401	0.08	(−0.11,0.27)	0.41	36%
Attention function							
NIBS	AD	4	88/86	0.55	(0.25,0.86)	0.0004	29%
	MCI	6	69/76	0.28	(−0.22,0.78)	0.28	52%
PE	AD	2	112/98	0.06	(−0.21,0.33)	0.65	0%
	MCI	5	272/274	0.25	(−0.03,0.53)	0.08	58%
Follow up of global cognition							
NIBS	AD/MCI	10	184/183	0.52	(0.1,0.93)	0.01	71%
PE	AD/MCI	5	112/111	0.94	(0.28,1.6)	0.005	80%

NIBS Noninvasive brain stimulation, *AD* Physical exercise, *PE* Alzheimer's Disease, *MCI* Mild cognitive impairment, *EG* Experimental group, *CG* Control group, *SMD* Standardized mean difference

Global cognition

Global cognition of the brain reflects a series of complex cognitive functions. Consistent to the previous meta-analyses [6, 43], our results showed PE significantly improved the global cognition for MCI and AD, while NIBS could not. Another meta-analysis which also investigated the relative efficacy of different types of exercise on overall cognition showed positive and effective results [44]. For NIBS, although previous meta-analyses have shown a positive effect on the overall cognition, the reliability was limited due to small sample sizes which ranged from 5 to 28 studies [11, 31, 114, 115]. In addition, they didn't include some negative reports for NIBS which showed NIBS has little effect on the global cognition [78, 116], or it could decrease the ADAS cog scale scores [28]. Another important factor is the heterogeneity of the scales included in the study. In contrast, our study included 43 RCTs. Our analysis includes multiple scales for the global cognition, and many studies only use MMSE to reflect the overall cognitive status. The application of MMSE is strongly influenced by non-cognitive fields, such as accent, education level, and considerable mathematical ability. Due to the limitations of global cognitive function scale for screening, it is necessary to refine the cognitive domains.

Memory function

Memory is the brain's ability to store, maintain and retrieve knowledge or information. In the progression from MCI to AD, the most common first symptom is memory decline, in which episodic memory damage is the earliest and most serious sign. Our subgroup analysis showed NIBS has significant efficacy in AD/MCI, while PE has significant efficacy

on memory only in AD group. Similarly, it is reported that high- and low-frequency rTMS and tDCS could improve the memory of patients with AD/MCI [56, 65, 117]. These results are in consistent with the findings of an earlier meta-analysis with eighteen studies that reported the effect of NIBS on memory in AD or MCI [31]. Even studies on animal models of dementia have shown high- and low-frequency rTMS stimulation could significantly enhance the memory of animals [118, 119]. For PE intervention on MCI, a previous meta-analysis also showed exercise was ineffective in improving memory [44, 120]. In a study of older adults with MCI, Nagamatsu et al. found that continuous physical training could not increase the functional local blood flow of the brain which is related to memory performance [121]. In another report, posterior cerebral regions, such as the posterior cingulate gyrus (PCC) connected to the hippocampus, entorhinal area and parahippocampal gyrus, had reduced local blood flow after aerobic exercise [122]. And another index related to memory is the level of BDNF in plasma. An RCT of nine consecutive weeks of intermittent aerobic training proved no significant change neither in the plasma BDNF level or in cognitive function [123]. These indirect evidences partially explain the limited effect of PE in our analysis. But, a total of eight studies were included in our analysis, and significant results could be obtained by removing one study. Although the current analysis showed that PE has a significant effect on memory in patients with AD, the result needs to be further verified by more original studies because only three relevant studies were included.

Executive function

Similar to a previous meta-analysis [31], only NIBS was found to have a significant effect on the executive function in AD. For the effects of PE on the executive functions, only six articles of AD and seven articles of MCI were included in our meta-analysis, even with an expanded searching scope, and we found there is no positive effect of PE in AD/MCI. Negative reports in MCI and AD were also reported in other studies [83, 103, 109]. However, a recent meta-analysis including four CRTs trials for MCI patients and one CRT for AD patients showed positive results that the intervention methods were prone to increase muscle strength and strength exercises, such as the use of elastic belts and weight-lifting machines [44]. The main reasons for the controversy may be limited number of articles included and the different types of exercise as intervention. Interestingly, moderate load exercise was found to have more beneficial for cognition than high-intensity or low-intensity exercise [124]. Specifically, moderate load exercise can make the best release of catecholamines (such as dopamine, norepinephrine and 5-hydroxytryptamine) that are related to cognitive behaviors such as executive control, increasing the universal biological arousal effect of the central nervous system and reasonably allocating cognitive resources [124]. The MCI or AD included in our study have an average age of more than 70 years that could hardly complete moderate-intensity training. That's the possible reason for on effect of PE in our current analysis. Furthermore, executive functions are complex high-level cognitive functions with multi-cognitive fusion including inhibition, working memory and organizational strategies necessary for response. The heterogeneity of assessment scales inevitably may lead to the inconsistent result.

Language function

For language function, our analysis showed both NIBS and PE have significant efficacy for AD, but not for MCI. Language dysfunction or fluent aphasia, which is manifested as difficulty in naming people or objects and speech comprehension, often occurs in AD population. Some studies have shown rTMS/tDCS improves the language function of AD [49] [125], which is similar to a previous meta-analysis [31]. However, another meta-analysis reported the negative result of NIBS [126]. One reason for this discrepancy is that the literature size included in the study is too small, with only two language-related studies, and the neurocognitive scales used were also heterogeneous (Action naming and object naming, Battery for analysis of aphasic deficits). As for the effect of PE on language function, we showed it was positive in AD, but not in MCI population. Similar results were also reported by Holthoff and colleagues [37], in which the significant effect on semantic vocabulary fluency in AD intervention group was still maintained even at three months' follow-up after the intervention. So far there are few reviews or meta-analysis focusing on the effect of PE on language function. Only seven articles were included in our study, resulting in great heterogeneity ($I^2 = 90\%$), so the results should be interpreted with caution. Unfortunately, neither NIBS nor PE intervention was shown to be effective for MCI population. The overall cognitive scale scores of most MCI included in our analysis are not particularly low, which means most of them may be mild MCI. Therefore, the patient's language function was basically intact and did not affect daily life communication, which may have led to negative results.

Attention

Attention impairment also exists in the vast majority of AD and some of MCI. Consistent with the previous studies [127, 128], our survey also showed only NIBS can significantly improve the attention in AD. In contrast, no significant effect of PE on attention was found in our study. However, a

previous meta-analysis reported contrary results [129]. One reason for discrepancies is that the studies included by Chan et al. are all dance interventions and do not include other types of exercise. And, the meta-analysis included a total of four published and one unpublished RCTs. Current, only nine articles for NIBS and seven articles for PE interventions included in our study. More RCTs are expected in the future to generate reliable results.

Long-term effect on global cognition

The development of AD/MCI is relatively slow, which can be decades of gradual progresses, before the eventual complete loss of intelligence and cognition. In our analysis, the follow-up time of NIBS ranges from one week to six months, in which one month was the mostly used. The follow-up time of the four articles in the PE intervention group is three months, three months, five months and one year, respectively. Within this time frame, our study showed NIBS had a significant sustained effect in both MCI and AD. However, the long-term effect of NIBS on cognitive function in AD/MCI is still inconclusive, and more systematic investigation is not available in the literature. As for PE intervention, our results showed PE intervention has positive and sustained effect after treatment, resulting in significantly observable long-term effects several months after treatment. However, the heterogeneity of the results is large, which mainly comes from a large variability of the change in cognitive ability of the control group in follow-up. Many previous studies reported that cognitive function decreased rapidly during the follow-up [130, 131]. The current results should still be interpreted with caution and more studies in need to provide evidence for the long-lasting effect of NIBS/PE.

Other considerations

At present, NIBS and PE intervention are still the mainstream methods to intervene cognitive decline. In terms of clinical disease classification, aMCI, characterized by the decline of episodic memory, is the most common type of MCI. Currently, Amnestic mild cognitive impairment (aMCI) is considered to be a potential precursor of AD. And baseline delayed associative memory performance can predict the progression from MCI to AD [132]. Also, the progressive MCI subjects performed worse than stable MCI subjects on the aspects of episodic memory [133]. Every year about 10% to 15% of aMCI progress to AD, and as high as 50% to 70% of aMCI could develop to AD with 5 to 7 years [134]. Therefore, maintaining or improving memory function could be an alternative approach to prevent the progression from MCI to AD. Our results showed NIBS has a better effect on improving memory function than PE, so NIBS may be more suitable for MCI. Compared with MCI, the characteristics of AD are more complex, and its core sign is the impairment of acquired cognitive function, including but not limited to memory, execution, calculation, orientation, understanding, and visuospatial function, etc. Patients with AD often show a significant decline in daily life, social interaction and work ability, which is often accompanied with mental, behavioral and personality abnormalities at a certain stage of the disease. The treatment for AD should target the collaborative intervention involving multi-cognitive domains treatment. Our meta-analysis found that NIBS had positive effects in many cognitive areas including memory function, executive function, attention, and language function in AD group, while PE only had significant effects on memory and language function, which indicates that NIBS has more extensive effects than that of PE for AD. Thus, it is promising to be an optimal clinical treatment for AD. From the perspective of intervention time, in the included studies, the single intervention session of NIBS ranged from 15 min to the maximum of 30 min, with an average intervention time of 23 min. And the overall intervention period ranged from one day to 80 days, with an average of 12 days. While the single intervention session of PE group ranged from 15 to 130 min, with an average of 53 min. And the overall intervention period ranged from 6 weeks to one year, with an average of 5 months. Therefore, compared with PE, NIBS intervention takes less time and is more time-efficient. Furthermore, the intervention mode of NIBS is relatively simple, and is more controllable for obtaining reliable results. While looking at the current situation of experimental design of sports cognition research, we can find the complexity and dynamics of sports make many tasks and design too complex, and the lack of accurate indicators of behavior and mechanism obtained by completing specific tasks leads to the relative macro conclusions. In terms of feasibility and safety, several articles reported some side effects of NIBS included headache, dizziness, nausea, tinnitus, and some physiological feelings of discomfort. However, most subjects had good tolerance and the withdrawal rate was low. In contrast, although few side effects were reported in the PE intervention, some subjects could not adhere to the complete exercise intervention process due to the long-time intervention or intrinsically physical frailty. Consequently, the withdrawal rate for PE intervention is high. The low adherence of PE has also been reported in several studies in individuals with dementia. [135, 136]. Tappen et al. reported an adherence rate of 57% in a 16-week walking and conversation program, while Rolland et al. indicate a low adherence rate in a 12-month study on the effects of moderate exercise on daily life activities in institutionalized individuals with AD (the mean number of participations in the sessions was 33 out of 88). As shown in Table 5. Therefore, it is a key to explore a long-term and stable exercise intervention model suitable for them.

Table 5 Comparison of two intervention modes from different aspects

	Therapeutic effects on cognitive domain		*The feasibility of intervention*				*The safety (Side effect)*
	AD	*MCI*	*Duration of per-session (Minute)*	*overall Duration time (Day)*	*The complexity of model*	*Compliance of subjects*	
NIBS	Memory, Executive function, Language, Attention	Memory	Range:15–30 Mean:23	Range:1–80 Mean:12	Low	High	Minor
PE	Memory, Language	-	Range:15–130 Mean:53	Range:42–365 Mean:150	High	Low	Minor

AD Alzheimer's disease, *MCI* Mild cognitive impairment, *NIBS* Non-invasive brain stimulation *PE* Physical exercise

Potential NIBS treatment parameters

Given that the NIBS seems to be an effective approach to affect many aspects of AD and MCI patients, it is imperative to delve into the potential therapeutic parameters and strategies of INBS for cognitive intervention in AD/MCI, improving treatment effectiveness.There were mainly two types of NIBS methods used in the literature: rTMS and tDCS. For rTMS, the most commonly used frequency was 10Hz, followed by 20Hz; The most frequently utilized threshold was 90%, with 100% being the second most common; The most commonly stimulation targets were located in the left dorsolateral prefrontal cortex, followed by the right dorsolateral prefrontal cortex; the most commonly pulse count was 2000 pluse per-session; The most commonly intervention time was 10 days. Regarding tDCS, the most commonly used current in the included literature was 2mA; The most commonly stimulation targets were located in the left dorsolateral prefrontal cortex, followed by the right dorsolateral prefrontal cortex; the most common duration time was 20 min per-session, followed by 30 min; The most common intervention time was also10 days. As shown in Table 6. The effectiveness of NIBS largely depends on the precise targeting of the target. Only by accurately identifying targets closely related to disease symptoms and applying appropriate stimulation parameters can the best therapeutic effect be achieved. The currently recommended targets were located in the left dorsolateral prefrontal cortex. Recently, Fonteneau et al. demonstrated that a single session of bifrontal tDCS induced dopamine release in the ventral striatum in healthy individuals [137]. Striatal dopamine links to the neural efficiency of the (dorsolateral) striatum, the prefrontal cortex, and associated higher-order cognitive functions, including attention switching and working memory updating [138]. In addition, from the perspective of brain functional and structural imaging, the brain network involved in episodic memory extraction is composed of precuneus ventral lobe, prefrontal ventral lobe, and medial temporal lobe [139]. In particular, the left and right prefrontal lobes of the brain

Table 6 Potential non-invasive treatment parameters for AD/MCI

Intervention	*Target*	*Frequency/ electric current*	*(Pluse/ time) Per-session*	*Days*	*Threshold*
rTMS	L_DLPFC	10 Hz	2000pluse	10	90%,
tDCS	L_DLPFC	2 mA	20 min	10	-

rTMS repeat transcranial magnetic stimulationran, *tDCS* scranial direct current stimulation, *L-DLPFC* Left dorsolateral prefrontal cortex

are responsible for processing language and image information in episodic memory [140], during information processing, activation of the dorsolateral prefrontal lobe can promote information coding and facilitate the formation of long-term episodic memory [141]. Two-photon imaging of mice showed that there were neuronal subpopulations composed of excitatory neurons in the medial prefrontal lobe, which could maintain connections for several minutes in the medial prefrontal lobe to encode short-term memory [142]. In addition NIBS can increased release of dopamine from the striatum and caudate nucleus, thus resulting in increased functional connection between DLPFC and subcortical structures. For instance, cortical brain stimulation was found to induce significant dopaminergic changes in extra-striatal cortical areas: DLPFC-rTMS led to focal dopaminergic changes in the ipsilateral anterior cingulate cortex (ACC) and medial orbitofrontal cortex [143], which are functional brain regions for executive function.This may partially explain why NIBS has a certain effect on improving cognitive function in MCI or AD, but the specific mechanism of its therapeutic effect is still unclear, and further exploration of the regulatory mechanism of NIBS on the brain's neurocognitive network is needed through more refined experimental design and advanced technological means.

Limitations

The current study has some limitations. Firstly, differences in clinical characteristics between different clinical populations

and studies are expected to be heterogeneous. In the studies we included, there are moderate and mild AD, aMCI, mixed MCI, and other comorbid MCI. But most studies did not report the type of AD/MCI, making the initial cognitive assessment results in different studies have an inevitable risk of bias. Further, the heterogeneity of PE is greater than that of NIBS, which may be due to the nature of the intervention itself. PE includes a large range of exercise patterns and parameters. The implementation process is relatively complex and requires a high degree of coordination between subjects and researchers. Furthermore, the sample size of RCTs of sports activities is usually larger than that of NIBS research. Last, this study failed to provide a detailed analysis of different types of NIBS (such as TMS, tDCS, etc.) and different forms of PE (such as aerobic exercise, strength training, yoga, etc.). The lack of detailed analysis may result in our inability to accurately capture the specific impact of each intervention on cognitive function, as well as their differential effects in different populations (such as age, gender, disease status, etc.). In addition, the potential interactions between different intervention methods were not fully explored in this study. For example, certain NIBS may have a synergistic effect with specific types of PE interventions, thereby jointly promoting improvements in cognitive function. However, due to the lack of relevant detailed analysis, we were currently unable to verify this hypothesis or provide clear guidance for future research. Therefore, future research should focus on refining the analysis of the effects of different types of NIBS and PE on cognitive function, as well as their applicability in different populations. Meanwhile, potential interactions between different intervention methods should also be explored to gain a more comprehensive understanding of their combined impact on cognitive function.

Conclusion

Our analysis indicates that NIBS intervention has clear positive effect on various cognitive domains for patients with AD, and significant effect on the memory function for MCI. Compared to PE intervention, the experimental data supports the feasibility of NIBS as a better effective intervention approach to reduce cognitive decline in MCI and AD. These positive effects of NIBS make it a feasible and safe tool to counteract cognitive age-related decline for MCI/AD. However, this effect is limited. Most but not all of the published studies showed variability of the induced neurological and cognitive effects. A multidisciplinary approach to study the best NIBS protocols is required to understand how to deliver an effective prevention against cognitive decline for aging population. Additionally, further exploration of heterogeneity among trials within disorders is warranted to identify sources of variability in treatment effects. So far, the therapeutic mechanism of NIBS interventions for cognitive functions of AD/MCI are still to be explored. The combination of NIBS with other neuroimaging techniques may provide some insights in whether and how brain networks are influenced by transcranial stimulation. Meanwhile, genetic background analysis has also become a valuable ally to provide better insights and guidelines for the more efficient and safe applications of NIBS as a tool to help prevent cognitive aging. Further, combining neuroimaging and genetic tools might be required to better understand the effect of NIBS on AD/MCI pathology, supporting novel avenues for possible new diagnostics methods and therapeutic treatment options.

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