



Review

The more the better? A meta-analysis on effects of combined cognitive and physical intervention on cognition in healthy older adults



Xinyi Zhu^{a,c}, Shufei Yin^b, Minjia Lang^{a,c}, Rongqiao He^d, Juan Li^{a,d,*}

^a Center on Aging Psychology, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

^b Department of Psychology, Faculty of Education, Hubei University, Wuhan, China

^c University of Chinese Academy of Sciences, Beijing, China

^d State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

ARTICLE INFO

Article history:

Received 6 April 2016

Received in revised form 3 July 2016

Accepted 12 July 2016

Available online 14 July 2016

Keywords:

Meta-analysis

Combined intervention

Cognitive intervention

Exercise

Cognition

Healthy older adults

ABSTRACT

Both cognitive intervention and physical exercise benefit cognitive function in older adults. It has been suggested that combined cognitive and physical intervention may induce larger effects than cognitive or physical intervention alone, but existing literature has shown mixed results. This meta-analysis aimed at assessing the efficacy of combined intervention on cognition by comparing combined intervention to control group, cognitive intervention and physical exercise. Eligible studies were controlled trials examining the effects of combined intervention on cognition in older adults without known cognitive impairment. Twenty interventional studies comprising 2667 participants were included. Results showed that the overall effect size for combined intervention versus control group was 0.29 (random effects model, $p = 0.001$). Compared to physical exercise, combined intervention produced greater effects on overall effect size (0.22, $p < 0.01$), while no significant difference was found between combined intervention and cognitive intervention. Effects of combined intervention were moderated by age of participants, intervention frequency and setting. The findings suggest that combined intervention demonstrates advantages over control group and physical exercise, while evidence is still lacking for superiority when compared combined intervention to cognitive intervention. More well-designed studies with long follow-ups are needed to clarify the potential unique efficacy of combined intervention for older adults.

© 2016 Elsevier B.V. All rights reserved.

Contents

1. Introduction.....	68
2. Methods.....	69
2.1. Search strategy.....	69
2.2. Selection criteria.....	69
2.3. Data extraction and analysis.....	69
2.4. Study quality assessment.....	69
3. Results.....	70
3.1. Included studies.....	70
3.2. Post-intervention effects of combined intervention.....	73
3.2.1. Combined intervention versus control group.....	73
3.2.2. Combined intervention versus cognitive intervention.....	73
3.2.3. Combined intervention versus physical exercise.....	73
3.3. Long-term effects of combined intervention.....	73
3.4. Moderator analysis.....	73

* Corresponding author at: Institute of Psychology, Chinese Academy of Sciences, 16 Lincui Road, Chaoyang District, Beijing 100101, China.

E-mail address: lijuan@psych.ac.cn (J. Li).

4.	Discussion	73
4.1.	Immediate effects of combined intervention	74
4.2.	Simultaneous versus separate combination	75
4.3.	Long-term effects and generalization	76
4.4.	Moderators: age, intervention setting and frequency	76
4.5.	Control group and comparison design	76
4.6.	Implication for future research and limitations	77
5.	Conclusion	77
	Conflict of interest	77
	Acknowledgements	77
	Appendix A. Supplementary data	77
	References	77

1. Introduction

Aging-related cognitive decline and cognitive impairment affects older adults' life expectancy, quality of life and well-being (MacDonald et al., 2011; Wilson et al., 2013), causing great public health and economic concern worldwide. As the incidence of cognitive impairment vastly increases, interventions for attenuating cognitive decline raise great research interest.

As two important modifiable lifestyle risk factors for dementia (Barnes and Yaffe, 2011), cognitive and physical engagements have high potential for preventing cognitive decline and impairment. Epidemiological evidence consistently linked cognitive activity to reduced risk of dementia and cognitive impairment (Valenzuela et al., 2012; Verghese et al., 2003; Wilson et al., 2012). Cross-sectional studies showed cognitive engagement related with lower brain beta-amyloid burden (Landau et al., 2012) and less hippocampal atrophy (Valenzuela et al., 2008). Recent meta-analyses and reviews have reported that cognitive training can be effective in improving cognitive function of elderly people (Kelly et al., 2014a; Lampit et al., 2014; Reijnders et al., 2013), although whether the training effects could induce far transfer and be generalized to everyday functioning are still ongoing debates (Green et al., 2014; Noack et al., 2014; Zelinski, 2009). Older adults also cognitively benefit from various types of cognitive stimulation, such as video games (Toril et al., 2014), computer course (Klusmann et al., 2010), board games (Cheng et al., 2014), digital-photography and quilt sewing (Park et al., 2014). Positive associations between physical activity and lower risk of dementia and better cognitive status have also been well-established (Buchman et al., 2012; Rovio et al., 2005; Scarmeas et al., 2009). Several meta-analytic reviews indicated that aerobic exercise improved cognition in older adults (Colcombe and Kramer, 2003; Hindin and Zelinski, 2012; Smith et al., 2010), but another two reviews concluded a lack of sufficient evidence for cognitive benefits from aerobic training (Kelly et al., 2014b; Snowden et al., 2011). There are also evidence for the beneficial effects of resistance training and Taichi on cognition in older adults (Chang et al., 2012; Wayne et al., 2014). It has been suggested that multicomponent exercise which combines aerobic and resistance training may be most effective in cognitive enhancement for older adults (Colcombe and Kramer, 2003; Kelly et al., 2014b). A comparative meta-analysis concluded that cognitive training and aerobic exercise intervention produced comparable magnitude of effects on cognitive performance (Hindin and Zelinski, 2012).

It has been proposed that the combined cognitive and physical intervention may result in larger benefits in cognition than either intervention alone (Bamidis et al., 2014; Curlik and Shors, 2013; Fissler et al., 2013; Kraft, 2012; Law et al., 2014). The combination of cognitive stimulation and physical exercise may induce additive and synergistic effects. Physical exercise can facilitate brain plasticity by enhancing cell proliferation and synaptic plasticity; and cognitive training "guides" plasticity by increasing the number

of surviving newborn neurons and integrating new neurons and synapses into pre-existing neural networks (Bamidis et al., 2014; Curlik and Shors, 2013; Fissler et al., 2013). Indeed, an animal study reported that exercise and enriched environment combined in sequence led to more new neurons than exercise or enriched environment alone (Fabel et al., 2009). Combined cognitive and exercise training also produced greater cognitive improvements than either single training in mice (Langdon and Corbett, 2012; Smith et al., 2013). Law et al. (2014) systematically reviewed eight studies of combined cognitive and physical intervention in older adults. They concluded that combined intervention revealed significant cognitive benefits for healthy older adults, while more evidence was needed for studies in elderly with cognitive impairment. However, the question whether combined intervention exceeds single intervention was not answered in this review. To date, existing studies yielded mixed results. Some studies supported greater benefits of combined intervention over single intervention group (Fabre et al., 2002; León et al., 2015; Oswald et al., 2006; Rahe et al., 2015b; Shah et al., 2014; van Het Reve and de Bruin, 2014; You et al., 2009), while others failed to find this superior effect (Barnes et al., 2013; Legault et al., 2011; Linde and Alfermann, 2014; McDaniel et al., 2014; Rahe et al., 2015a). Thus, the primary aim of this meta-analysis is to evaluate the efficacy of combined intervention on cognition in healthy older adults by separately comparing combined intervention to control group, cognitive intervention and physical exercise.

Fissler et al. (2013) attributed the negative findings to separate conduct of cognitive and physical components in combined intervention. Specifically, there are two modes of combining cognitive intervention and physical exercise. In most studies, cognitive and physical intervention are administrated separately in time. In other cases, two components are simultaneously conducted in dual-tasks (Hiyamizu et al., 2012; León et al., 2015; Nishiguchi et al., 2015; You et al., 2009) or exergames (Kayama et al., 2014; Maillot et al., 2012). Dual-task paradigm involves concurrent cognitive and motor tasks, such as completing verbal fluency tasks while performing step exercise (Nishiguchi et al., 2015). Exergame, which has become a tool for health promotion, is a genre of video games that require players to respond by physical movement (Read and Shortell, 2011). Fissler et al. (2013) proposed that simultaneous cognitive and physical intervention might be crucial for interactions. Plasticity facilitation of physical exercise might be most prominent during or right after exercise, as increase in peripheral brain-derived neurotrophic factors (BDNF) induced by acute aerobic exercise would fall below baseline one hour after exercise (Knaepen et al., 2010). To examine whether simultaneous combination produce larger efficacy than separate combination, the mode of combination was considered as a potential moderator. Other moderator variables included intervention frequency, intervention length, session length, the number of total sessions, total hours, setting, a third component besides cognitive and physical

intervention, type of control group, risk of bias, and mean age of participants.

In summary, this meta-analysis aimed to examine: (1) the efficacy of combined intervention on cognition in healthy older adults by comparing combined intervention to control group, cognitive intervention and physical exercise; (2) whether the effectiveness of combined intervention was moderated by characteristics of intervention and participants.

2. Methods

The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, <http://www.cdr.york.ac.uk/prospéro>); CRD42015026025. The work was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; Moher et al., 2009) guidelines (see PRISMA checklist, Appendix A).

2.1. Search strategy

Systematic searches were conducted in MEDLINE/PUBMED, PsycINFO and ProQuest databases using no publication date limit. Search terms were intersections of cognitive intervention terms (“cognitive training” OR “cognitive intervention” OR “memory training”), AND physical intervention terms (“exercise” OR “physical training” OR “aerobic training”), AND aging population terms (“aging” OR “aged” OR “older”) AND combined intervention terms (“combined” OR “combination” OR “multimodal”) (see Appendix B for full search terms). Reference lists of selected articles and related review articles were further screened. Additional searches in Google Scholar were also performed. The search was limited to publications written in English.

2.2. Selection criteria

Studies were identified as eligible if they met the following inclusion criteria: (1) intervention studies which combined any types of cognitive intervention and physical exercise together; (2) reporting baseline and post-intervention assessment on at least one outcome measure on cognition; (3) involving adults aged over 50 years without known cognitive impairments; (4) having at least an active/passive control group or a comparison (cognitive and/or physical intervention alone) group; (5) reporting enough information to calculate an effect size for at least one cognitive outcome measure; (6) peer-reviewed journal articles written in English. Studies were excluded if they were (1) non-intervention studies; (2) case studies; (3) review articles or theoretical articles; (4) unpublished articles, thesis, dissertations or book chapters; (5) not written in English. If more than one articles were based on a same intervention project, we only included the main article. Two reviewers (X. Zhu and M. Lang) initially selected search results based on titles and abstracts. The remaining articles were further selected by full-text assessment. Disagreements between reviewers about eligibility were resolved by discussion with S. Yin and J. Li. The procedure of study selection and numbers of included and excluded studies is shown in Fig. 1.

2.3. Data extraction and analysis

The primary outcome of interest was objective measures of cognitive function (overall cognition). Based on the classification used in a recent meta-analysis (Lampit et al., 2014), cognitive outcome measures were further grouped into the following six cognitive domains: memory, executive function, attention, processing speed, and visuospatial abilities. Table C1 (Appendix C) showed the categorization of cognitive tests. The secondary outcomes were

everyday cognition and well-being. Everyday cognition included subjective measures of everyday cognitive function. Well-being included measures of well-being, stress, depression and anxiety.

Two independent reviewers (X. Zhu and S. Yin) used a spreadsheet to extract data of each study. In most studies, the summary statistics of outcomes were means, standard deviations (SDs), and the number of participants of each group at baseline and post-intervention (and follow-ups if reported). When means and SDs were not available, mean changes from baseline and SDs or mean differences with 95% confidence interval (CI) were extracted. We employed Comprehensive Meta-Analysis (CMA) Version 2.0 (Bio-stat Inc., Englewood, NJ) to conduct a quantitative synthesis. The combined intervention group were separately compared to control group, cognitive intervention group and physical exercise group. The intervention effect was measured by the standardized mean difference (SMD) of post-intervention changes between combined group and control/single intervention group. SMDs and SDs were calculated for each study, with positive SMDs indicating better therapeutic effects of combined intervention compared to control or single intervention group. As most studies included multiple cognitive measures, we calculated one pooled SMD as the effects size of overall cognition for each study, following the method used in other meta-analyses (e.g., Lampit et al., 2014; Wykes et al., 2011). The pooled SMD was computed by averaging the available effect sizes across all individual cognitive measures in each study. When SMD was obtained for each study, a combined effect size with 95% CI was calculated to determine the efficacy of combined intervention on overall cognition. Similarly, for domain-specific analyses, SMDs of the same cognitive function were generated for each study and then pooled into a combined effect size. Because of expected heterogeneity in intervention contents and outcome measures, effect sizes were assumed as similar but not identical across studies, thus, random-effects models were performed to estimate the distribution of observed effect sizes (Borenstein et al., 2009). The variation in effect sizes across studies was assessed by the homogeneity statistic, Q . The I^2 statistic was also calculated to estimate the proportion of true heterogeneity in observed variance. The funnel plot and Egger's regression intercept test as well as fail-safe N were used to estimate publication bias (Egger et al., 1997; Rosenthal, 1979).

For moderator analysis, subgroup meta-analysis was performed for categorical moderators, and metaregression was conducted for continuous moderators. Mixed effects models were used in subgroup analysis and metaregression. Categorical moderators included the mode of combination (separate versus simultaneous), other component (whether combined intervention includes other components besides cognitive and physical intervention; yes versus no), intervention length (<16 weeks versus ≥ 16 weeks), frequency (<5 sessions per week versus ≥ 5 sessions per week), session length (within one hour versus longer than an hour), type of control group (active versus passive), setting (group-based versus individual or mixed), and risk of bias (low risk versus high risk). Continuous moderators included mean age of participants, the number of total sessions and total hours of intervention.

2.4. Study quality assessment

The quality of individual studies was rated by two independent reviewers (X. Zhu and S. Yin) using a modified Physiotherapy Evidence Database (PEDro) scale. The original PEDro scale includes 11 items to rate the study quality of non-pharmacological therapies (Maher et al., 2003). With reference to Lampit et al. (2014)'s meta-analysis, two items (the blinding of therapists and participants) were not included into our modified version, as it is usually impractical to blind therapists and participants in cognitive intervention. Thus, the maximum score of study quality study was 9. Studies which scored 7 or higher were considered as low risk of bias,

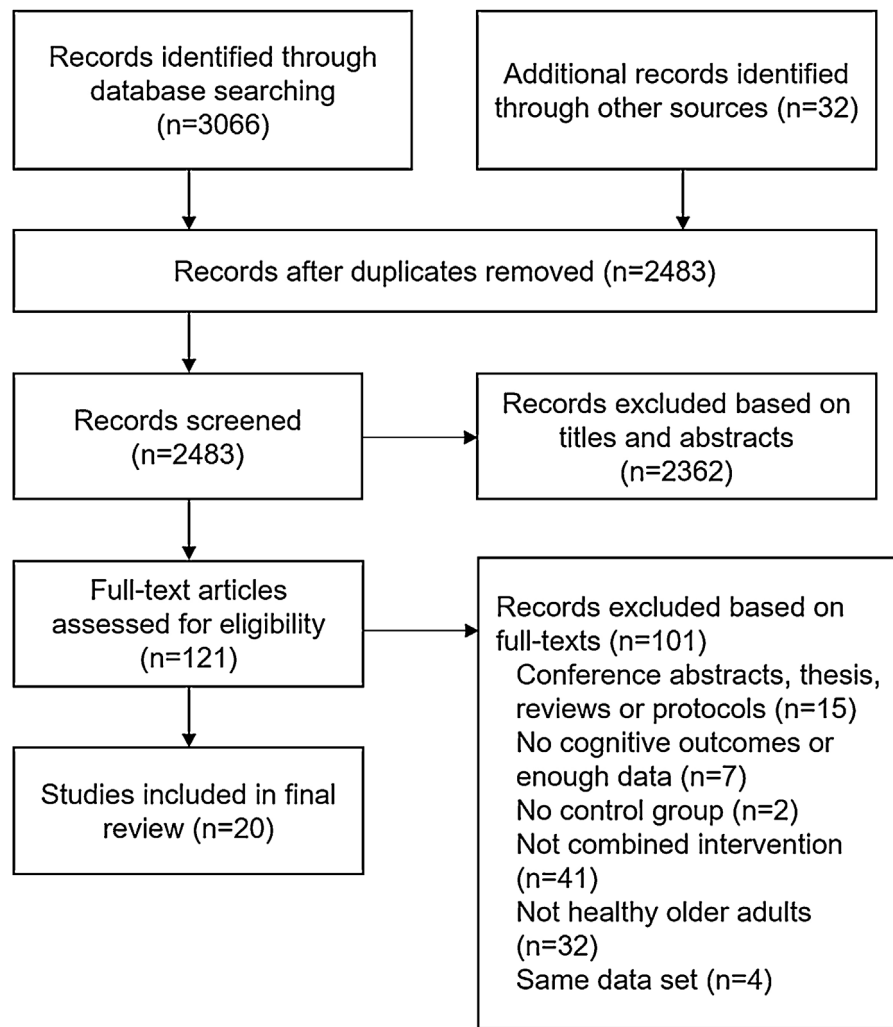


Fig. 1. Flowchart of the study selection process.

while others which scored 6 or lower were considered as high risk of bias. Two reviewers independently rated each study according to detailed guidelines (Appendix D), and disagreements on ratings were resolved by discussion with J. Li.

3. Results

3.1. Included studies

Altogether, 20 eligible studies were included in the meta-analysis, comprising 1085 participants in combined intervention groups, 249 in cognitive intervention groups, 333 in physical intervention groups and 1000 controls. Mean participant age ranged from 65 to 81.9 years old, and about 56% of participants were female. Sample sizes ranged from 13 to 1190 (median sample size=52). Four studies were conducted in United States, 4 in Germany, 3 in Japan and Germany, 2 in France, one each in South Korea, China, Italy, Spain, Switzerland, Finland and Australia. Table 1 summarized the characteristics of included studies. Ten out of 20 studies involved a two-group comparison, and 7 studies used a four-group comparison with one study involving a three-group comparison. One study (Oswald et al., 2006) used a six-group design, and two groups with psychoeducation were not included in the meta-analysis. Rahe et al. (2015a) compared combined intervention group to a cognitive training group and a combined intervention plus counseling group, and the combined intervention

plus counseling group was not included into our analysis. Control groups were included in 15 studies, cognitive intervention groups were included in 10 studies and physical exercise groups were included in 12 studies. Out of 15 studies involving control groups, 9 studies used passive control groups, and 6 studies used active controls. The active control activities included lectures, DVD watching, health education, book club and leisure activities.

Combined interventions varied in intervention components, the mode of combination, intervention frequency and length. Regarding the mode of combined intervention, 6 studies used the simultaneous mode including dual-tasks in 4 studies and exergame in 2 studies, while 14 studies conducted cognitive intervention and physical exercise separately. For physical exercise components, 12 studies included multicomponent exercises involving an aerobic component, 6 studies used aerobic exercise, 1 study included strength and balance training, and 1 study used exergames. For cognitive intervention components, 11 studies used multidomain cognitive training, 2 used single domain cognitive training, 1 used cognitive activities, 4 used cognitive tasks embedded in exercises, and 2 used exergames. Four studies included components besides cognitive and physical intervention, including nutrition programs, management of metabolic and vascular risk factors, group counseling and music stimulation (Li et al., 2014; Ngandu et al., 2015; Pieramico et al., 2012; Rahe et al., 2015b). Length of combined intervention ranged from 6 weeks to 96 weeks (median = 12 weeks), with the numbers of total sessions ranging from 12 to 672 ses-

Table 1
Study characteristics.

Study	Country	Sample	Mean Age	Study Design		Combined Intervention Design							Control Group Activity	Study Quality Score
				Randomized	Comparison	Cognitive Intervention Component	Physical Exercise Component	Mode of Combination	Other Components ^b	Setting	No. of Sessions	Frequency and Length		
Fabre et al. (2002)	France	32	65.9	Yes	CPI vs. CI vs. PE vs. CG	Multidomain cognitive training	Aerobic exercise	Separate	No	Group	24	60–90 min/session, 3 sessions/week, 8 weeks	Leisure activities	6
Oswald et al. (2006)	Germany	196	79.5	Quasi-randomized	CPI vs. CI vs. PE vs. CG	Multidomain cognitive training	Balance, coordination, flexibility, gymnastic exercises	Separate	No	Group	30	135 min/session, 1 session/week, 30 weeks	No treatment	6
You et al. (2009)	South Korea	13	68.3	No	CPI vs. PE	Cognitive tasks (memory and calculation)	Walking	Simultaneous (dual-task)	No	Mixed	18	30 min/session, 3 sessions/week, 6 weeks	N/A	2
Legault et al. (2011)	USA	68	76.4	Yes	CPI vs. CI vs. PE vs. CG	Memory training	Aerobic and flexibility training	Separate	No	Mixed	56	50–150 min/session, 3.5 sessions/week, 16 weeks	Health education	7
Hiyamizu et al. (2012)	Japan	36	72	Yes	CPI vs. CG	Cognitive tasks (calculation, visual search and verbal fluency)	Balance training (dual-task); strength training	Simultaneous (dual-task)	No	Not clear	24	60 min/session, 2 sessions/week, 12 weeks	No treatment	7
Maillot et al. (2012)	France	30	73.5	Yes	CPI vs. CG	Wii games	Wii games	Simultaneous (exergame)	No	Not clear	24	60 min/session, 2 sessions/week, 12 weeks	No treatment	6
Pieramico et al. (2012)	Italy	30	60–75	Yes	CPI vs. CG	Cognitive activities (puzzles and reading)	Walking, dancing	Separate	Music stimulation	Individual	120	120 min/session, 5 sessions/week, 24 weeks	No treatment	7
Barnes et al. (2013)	USA	126	73.4	Yes	CPI vs. CI vs. PE vs. CG	Multidomain cognitive training	Aerobic exercise	Separate	No	Mixed	72	60 min/session, 6 sessions/week, 12 weeks	Educational DVDs; stretching and toning	8
Shatil (2013)	USA	122	76.8	Yes	CPI vs. CI vs. PE vs. CG	Multidomain cognitive training	Mild aerobic, strength and flexibility training	Separate	No	Group	96	40–45 min/session, 6 sessions/week, 16 weeks	Book club	6
Kayama et al. (2014)	Japan	41	>65	No	CPI vs. PE	Sudoku (exergame)	Taichi-like exergame; aerobic, strength, flexibility and balance exercise	Simultaneous (exergame)	No	Individual	12	80 min/session, 1 session/week, 12 weeks	N/A	5
Li et al. (2014)	China	34	70.2	No	CPI vs. CG	Multidomain cognitive training	Taichi	Separate	Group counseling	Group	48	60 min/session, 6 sessions/week, 8 weeks	Lectures	5
Linde and Alfermann (2014)	Germany	55	67.1	Yes	CPI vs. CI vs. PE vs. CG	Multidomain cognitive training	Aerobic, endurance and strength training	Separate	No	Group	32	60–90 min/session, 2 sessions/week, 16 weeks	No treatment	7
McDaniel et al. (2014)	USA	79	65	Yes	CPI vs. CI vs. PE vs. CG	Multidomain cognitive training	Aerobic training	Separate	No	Group	96	60 min/session, 3–6 sessions/week, 24 weeks	Health education, low-intensity exercise	8
Shah et al. (2014)	Australia	172	67.4	No	CPI vs. CI vs. PE vs. CG	Multidomain cognitive training	Walking, strength training	Separate	No	Individual	160	60 min/session, 10 sessions/week, 16 weeks	No treatment	5
van Het Reve and de Bruin (2014)	Switzerland	182	81.9	Yes	CPI vs. PE	Attention training	Strength and balance training	Separate	No	Group	60	10–40 min/session, 5 sessions/week, 12 weeks	N/A	6
León et al. (2015)	Spain	138	71.4	Yes	CPI vs. PE vs. CG	Cognitive tasks	Strength and aerobic exercise	Simultaneous (dual-task)	No	Not clear	24	60 min/session, 2 sessions/week, 12 weeks	No treatment	6
Ngandu et al. (2015)	Finland	1190	69.3	Yes	CPI vs. CG	Multidomain cognitive training	Strength and aerobic exercises	Separate	Nutritional counseling, management of metabolic and vascular risk factors	Mixed	672	10–60 min/session, 3–11 sessions/week, 96 weeks	Regular health advice	9
Nishiguchi et al. (2015)	Japan	48	73.3	Yes	CPI vs. CG	Cognitive tasks (verbal fluency, cognitive-motor tasks)	Step exercises (dual task); stretching and strength training	Simultaneous (dual-task)	No	Group	12	90 min/session, 1 sessions/week, 12 weeks	No treatment	8
Rahe et al. (2015b)	Germany	30	66.7	No	CPI vs. CI	Multidomain cognitive training	Strength, flexibility, coordination, balance, aerobic training	Separate	Nutrition program	Group	13	110 min/session, 2 sessions/week, 6.5 weeks	N/A	5
Rahe et al. (2015a)	Germany	45	68.1	Yes	CPI vs. CI	Multidomain cognitive training	Strength, flexibility, coordination, endurance	Separate	No	Group	14	90 min/session, 2 sessions/week, 7 weeks	N/A	6

CPI: combined cognitive and physical intervention; CI: cognitive intervention; PE: physical exercise; CG: control group; N/A: not applicable.

^a N refers to the number of participants included in the analysis.^b Other components refers to intervention activities besides cognitive intervention and physical exercise.

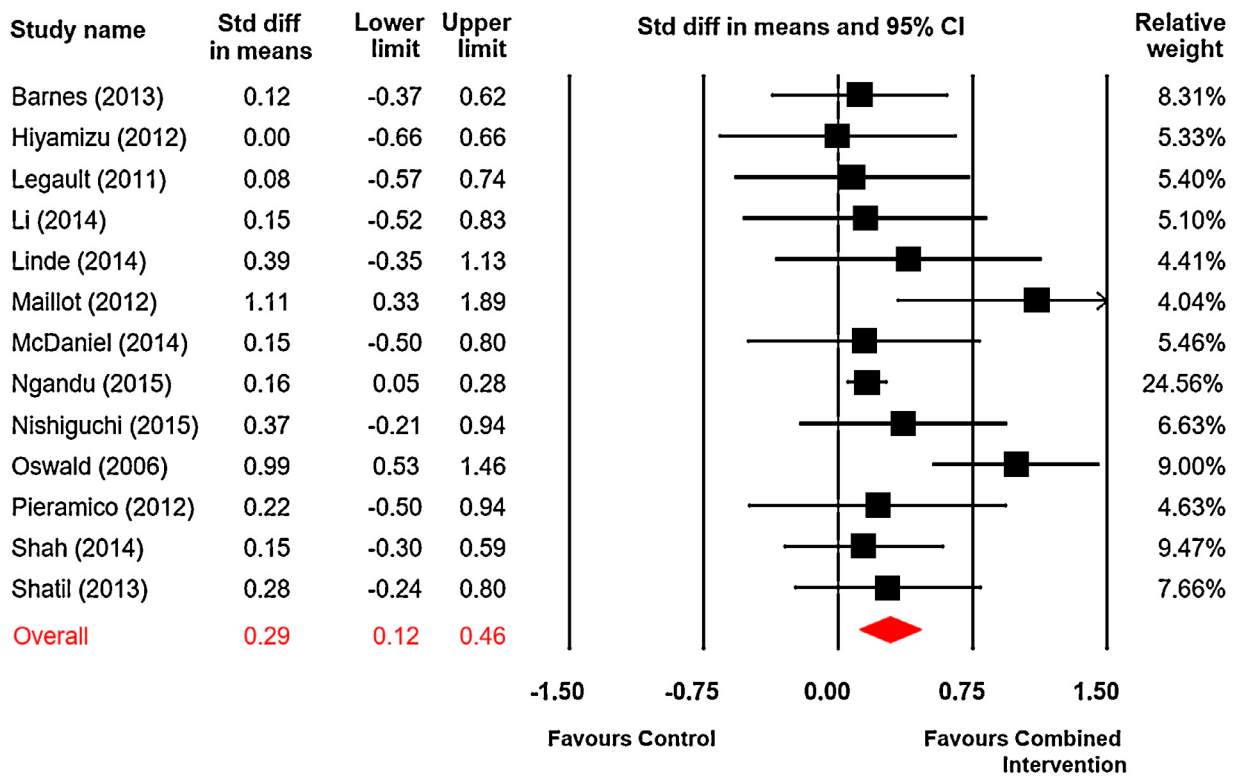


Fig. 2. Forest plot for efficacy of combined intervention compared to control group.

Table 2

Effect sizes of combined intervention on cognitive function, everyday cognition and well-being.

Comparison	Outcomes	No. of studies	SMD	95% Confidence Interval	Homogeneity Test			I ² , %
					Q	df	p	
Combined Intervention versus Control	Overall cognition	13	0.29**	0.12 to 0.46	18.06	12	0.11	33.55
	Memory	10	0.10*	0.003 to 0.20	8.14	9	0.52	0
	Executive function	12	0.13**	0.04 to 0.23	10.74	11	0.47	0
	Attention	3	0.38*	0.06 to 0.70	0.89	2	0.64	0
	Processing speed	9	0.08	-0.15 to 0.30	17.48	8	0.05	48.3
	Global Cognition	4	0.51*	0.01 to 1.01	8.32	3	0.04	63.93
	Visuospatial ability	3	0.59**	0.21 to 0.96	1.04	2	0.59	0
	Everyday cognition	2	0.08	-0.23 to 0.40	0.58	1	0.45	0
Combined Intervention versus Cognitive Intervention	Well-being	3	0.23	-0.06 to 0.51	1.28	2	0.53	0
	Overall cognition	9	0.06	-0.12 to 0.25	2.88	8	0.94	0
	Memory	8	-0.02	-0.22 to 0.18	3.71	7	0.81	0
	Executive function	8	0.05	-0.15 to 0.25	1.17	7	0.99	0
	Attention	5	-0.06	-0.51 to 0.40	11.11	4	0.03	63.99
	Processing speed	4	-0.21	-0.47 to 0.05	3.16	3	0.37	5.16
	Global Cognition	2	0.16	-0.34 to 0.65	1.66	1	0.2	39.58
	Visuospatial ability	2	0.05	-0.37 to 0.46	0.11	1	0.74	0
Combined Intervention versus Physical Exercise	Everyday cognition	2	0.01	-0.30 to 0.33	0.26	1	0.61	0
	Well-being	2	0.10	-0.22 to 0.41	0.28	1	0.60	0
	Overall cognition	10	0.22**	0.06 to 0.38	8.85	9	0.45	0
	Memory	7	0.07	-0.23 to 0.35	9.63	6	0.14	37.67
	Executive function	8	0.14	-0.03 to 0.31	2.30	7	0.94	0
	Attention	4	0.26	-0.10 to 0.62	6.78	3	0.08	55.77
	Processing speed	6	0.003	-0.18 to 0.19	5.11	5	0.40	2.12
	Global Cognition	1	0.87**	0.31 to 1.44	NA	NA	NA	NA
	Visuospatial ability	2	0.53*	0.10 to 0.94	0.44	1	0.51	0
	Everyday cognition	2	0.12	-0.21 to 0.46	0.05	1	0.82	0
	Well-being	2	0.16	-0.17 to 0.50	0.73	1	0.39	0

SMD: standardized mean difference. NA, not available.

* p < 0.05.

** p < 0.01.

sions (median = 31 sessions). Regarding intervention frequency, 13 studies conducted one to four sessions per week, and 7 studies administered five sessions or more per week. Three studies reported follow-up results, and the follow-up duration was three months (Linde and Alfermann, 2014), one year (Rahe et al., 2015b) and five years (Oswald et al., 2006), respectively.

The results of study quality were presented in Table 1 and Table D1 (Appendix D). PEDro scores ranged from 2 to 9 (mean score = 6.25, SD = 1.52). Seven (35%) studies were considered as low risk of bias, while 13 (65%) studies were rated as high risk of bias.

3.2. Post-intervention effects of combined intervention

3.2.1. Combined intervention versus control group

Two studies (Fabre et al., 2002; León et al., 2015) reported large effect sizes beyond 3 SD above the mean effect size (both SMDs > 3.5), and the funnel plot indicated significant asymmetry (Egger's regression intercept = 2.29, $p < 0.05$), so these two studies were removed from all further analyses as outliers. Fig. E1 (Appendix E) presents the funnel plot of remaining studies showing no significant asymmetry (Egger's regression intercept = 0.66, $p > 0.05$).

As shown in Fig. 2, the combined effect size of combined intervention on overall cognition was 0.29 (95% CI 0.12–0.46, $p = 0.001$). Results revealed no significant heterogeneity across studies ($Q(12) = 18.06$, $p > 0.05$, $I^2 = 33.55\%$). The fail-safe N result revealed that 54 additional studies with null findings would be needed for the efficacy to lose significance. Domain-specific analyses showed that, compared to control group, combined intervention induced significant improvements on memory, executive function, attention, global cognition and visuospatial ability but not processing speed (Table 2). Combined effect sizes were small for memory (SMD = 0.10, 95% CI 0.003–0.20, $p < 0.05$), executive function (SMD = 0.13, 95% CI 0.04–0.23, $p < 0.01$), and attention (SMD = 0.38, 95% CI 0.06–0.70, $p < 0.05$). Combined effect sizes for global cognition (SMD = 0.51, 95% CI 0.01–1.01, $p = 0.04$) and visuospatial ability (SMD = 0.59, 95% CI 0.21–0.96, $p < 0.01$) were within the range of moderate effects. There was no significant difference between two groups on measures of everyday cognition and well-being.

3.2.2. Combined intervention versus cognitive intervention

As shown in Table 2, results revealed no significant difference between combined intervention and cognitive intervention in overall cognition and all cognitive domains (Fig. 3). There was also no significant difference between two groups on everyday cognition and well-being.

3.2.3. Combined intervention versus physical exercise

Results showed significant difference in overall cognition between combined intervention and physical exercise (SMD = 0.22, 95% CI 0.06–0.38, $p < 0.01$; Fig. 4). No significant heterogeneity across studies was found ($Q(9) = 18.06$, $p > 0.05$, $I^2 = 0\%$). The fail-safe N calculation suggested that it would need to include 12 additional negative studies for the efficacy to be nullified. Domain-specific analyses revealed significant differences on global cognition (SMD = 0.87, 95% CI 0.31–1.44, $p < 0.01$) and visuospatial ability (SMD = 0.53, 95% CI 0.10–0.94, $p < 0.05$), but the combined effect sizes were respectively based on only one and two studies, respectively (Table 2). There was no significant difference between two groups on measures of everyday cognition and well-being.

3.3. Long-term effects of combined intervention

Because of limited studies with follow-up data, analyses were only conducted for overall cognition (Table 3). Results revealed

a moderate effect size (SMD = 0.61, 95% CI 0.16–1.05, $p < 0.01$) at follow-up for the comparison between combined intervention and control group. Combined intervention did not show maintenance effect when compared with cognitive intervention (SMD = 0.38, 95% CI –0.02 to 0.78, $p = 0.06$) or physical exercise (SMD = 0.69, 95% CI –0.02 to 1.41, $p = 0.06$), though both p values approached significant level.

3.4. Moderator analysis

Impacts of potential moderator variables were calculated for overall cognition. Because significant group difference was not found between combined intervention and cognitive intervention, moderator analyses were only performed for the other two comparisons. Table 4 summarizes the results of categorical and continuous moderator analysis for combined intervention versus control group.

Effects of combined intervention were influenced by intervention frequency and setting. Regarding intervention frequency, the heterogeneity between groups was significant ($Q(1) = 7.12$, $p = 0.008$), with an effect size of 0.17 (95% CI 0.06–0.27, $p = 0.001$) for intervention administered five or more sessions per week and an effect size of 0.54 (95% CI 0.28–0.79, $p < 0.001$) for intervention administered less than five times per week. There was also a significant effect for intervention setting (group versus individual or mixed; $Q(1) = 5.11$, $p = 0.02$). The effect size for group-based intervention was 0.46 (95% CI 0.22–0.70, $p < 0.001$), and the effect size for individual or mixed intervention was 0.16 (95% CI 0.06–0.27, $p = 0.003$). For the mode of combined intervention, the effect size for separate intervention is 0.27 (95% CI 0.08–0.46, $p = 0.006$), and the effect size for simultaneous intervention is 0.43 (95% CI 0.01–0.86, $p = 0.048$), but the heterogeneity between groups was not significant ($Q(1) = 0.48$, $p = 0.49$). There was also no significant effect for other component, type of cognitive intervention, intervention length, session length, or control group.

Regarding continuous potential moderators, metaregression revealed a significant effect for age ($\beta = 0.045$, 95% CI 0.012–0.078, $p < 0.01$), indicating participants in older age getting greater improvement from combined intervention. No moderator effect was observed for the number of total sessions and total hours (both $ps > 0.5$). Considering intervention duration in one study (Ngandu et al., 2015) was much longer than others, additional analyses were performed after excluding this study, resulting no moderator effects for the number of total sessions and total hours (both $ps > 0.5$).

For the comparison between combined intervention and physical exercise, none of the potential moderators was associated with intervention effects (Table F1, Appendix F).

4. Discussion

To our knowledge, this is the first meta-analysis about effects of combined physical and cognitive intervention on cognitive function of healthy older adults. By synthesizing twenty studies with cognitively healthy older adults, we compared the effects of combined physical and cognitive intervention on cognitive function to control group and single cognitive/physical intervention. A small effect size on cognition was found for combined intervention versus control group. Combined intervention also led to positive effects compared to single physical intervention, while no significant difference was found when comparing combined intervention with single cognitive intervention. Thus, our results only partially supported the hypothesized superiority of combined intervention. Moreover, effects of combined intervention were moderated by age of participants, intervention frequency and setting. Larger cognitive

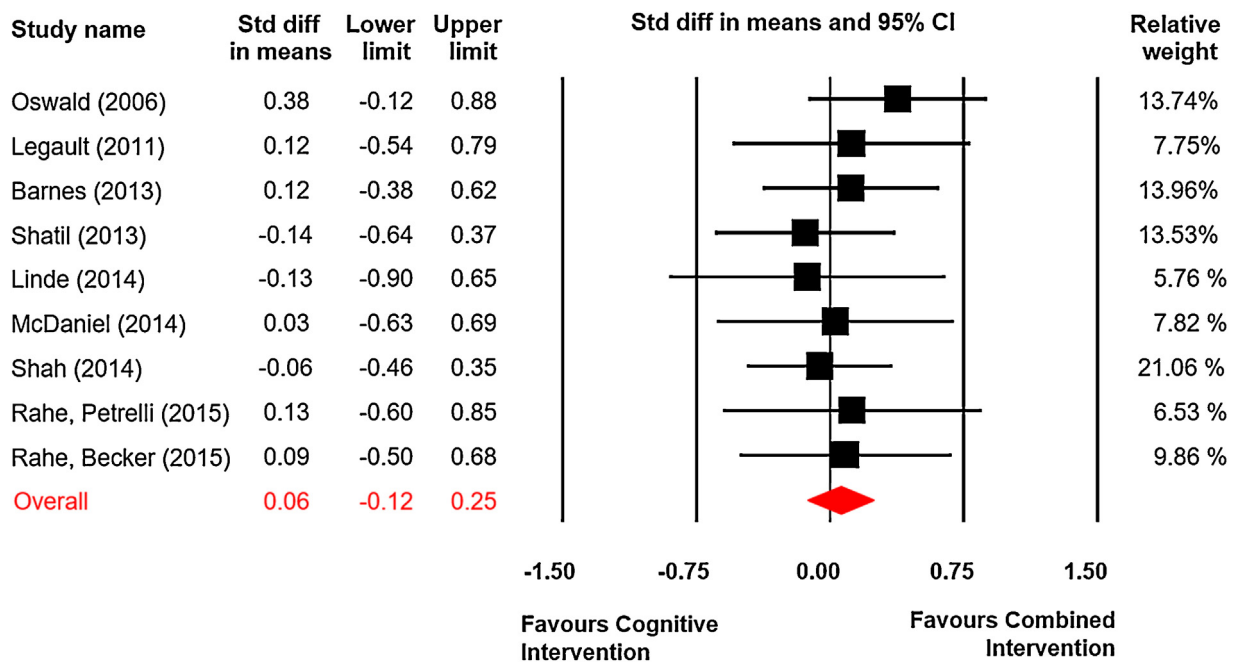


Fig. 3. Forest plot for efficacy of combined intervention compared to cognitive intervention.

Table 3

Effect sizes of combined intervention on overall cognition based on the follow-up data.

Comparison	No. of studies	SMD	95% Confidence Interval	Homogeneity Test			I ² , %
				Q	df	p	
Combined Intervention versus Control	2	0.61**	0.16 to 1.05	0.28	1	0.60	0
Combined Intervention versus Cognitive Intervention	3	0.38	−0.02 to 0.78	0.90	2	0.63	0
Combined Intervention versus Physical Exercise	2	0.69	−0.02 to 1.41	1.91	1	0.17	47.76

SMD: standardized mean difference.

** p < 0.01.

gains are to be expected for participants with older age, and combined intervention administered in group and less than five times per week.

4.1. Immediate effects of combined intervention

Results for combined intervention versus control suggest that combined intervention is effective in improving cognitive function in healthy older adults while intervention effects vary across cognitive domains. Combined intervention produced small effects on memory, executive function and attention, and a moderate effect on global cognition. Notably, the analysis of visuospatial ability revealed a moderate to large effect size. This finding is promising because visuospatial ability is an important type of cognitive ability greatly affecting daily functioning. The rate of decline in visuospatial ability accelerates with the progression of dementia (Marcos et al., 2006; Yin et al., 2015). The result suggests the potential value of combined intervention in improving visuospatial ability for patients with mild cognitive impairment and dementia. Nevertheless, it should be noted that the analysis of visuospatial ability was based on only three studies, so further research is needed to verify the efficacy.

When comparing combined intervention with single cognitive/physical intervention, the hypothesized superiority of combined intervention has only been partially supported. Although combined intervention produced positive effects compared to physical exercise, null results for comparison with cognitive inter-

vention queried the assumption of therapeutic additive effects. In addition, the effect size for combined intervention versus control was within the range of small effects (SMD = 0.29). The magnitude was close to those of effect sizes for cognitive training (0.33, Hindin and Zelinski, 2012; 0.22, Lampit et al., 2014) and physical exercise alone (0.33, Hindin and Zelinski, 2012; 0.24, Colcombe and Kramer, 2003) reported in previous meta-analytic studies. Negative findings were also reported in a multi-armed interventional study for older adults with MCI (Fiatarone Singh et al., 2014). In this study, after six months of intervention, combined group did not outperform single cognitive training group, and performed worse than single resistance training group at both post-intervention and twelve month follow-up. Reasons for the conflicting results on the superiority of combined intervention are still not known. One possible explanation might be the mode of cognitive and physical intervention combination (Fissler et al., 2013), which will be discussed in the next section (section 4.2). High intensity and challenging tasks of combined intervention might also have negative impacts on efficacy. Combined intervention requires both mental and physical exertion of older adults, and possibly leads to cognitive fatigue (Holtzer et al., 2010; Lampit et al., 2014), excessive stress and less engagement in intervention activities (Fiatarone Singh et al., 2014), which might interfere with intervention gains and neural plasticity. In line with this speculation, our moderator analysis showed that high frequency intervention produced less efficacy, about one third of the effect size produced by more spaced intervention.

Table 4

Moderator analysis for combined intervention versus control group.

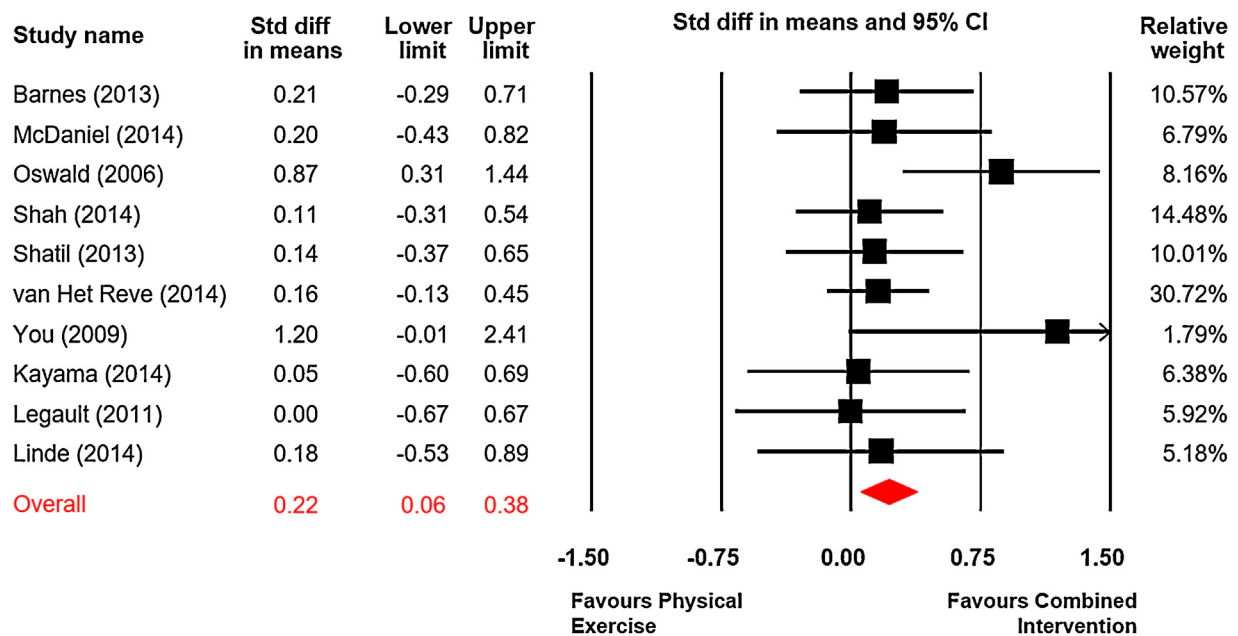
Moderator variable (categorical)	Level	No. of studies	SMD	95% Confidence Interval	I ² , %	Test for between-group heterogeneity		
						Q	df	p
Mode of combination	Separate	10	0.27**	0.08 to 0.46	26.66	0.48	1	0.49
	Simultaneous	3	0.43*	0.01 to 0.86	56.68			
Third component	Yes	3	0.17	−0.12 to 0.47	0	1.00	1	0.32
	No	10	0.36**	0.15 to 0.57	39.37			
Intervention length	<16 weeks	5	0.30	−0.03 to 0.63	29.37	0	1	0.99
	≥16 weeks	8	0.30**	0.08 to 0.51	42.33			
Frequency	<5 sessions/week	6	0.54***	0.28 to 0.79	53.22	7.12	1	0.008
	≥5 sessions/week	7	0.17**	0.06 to 0.27	0			
Session length	Within 1 h	8	0.20*	0.03 to 0.36	0	3.34	1	0.07
	Longer than 1 h	5	0.50**	0.22 to 0.79	40.76			
Control group	Active	5	0.16*	−0.15 to 0.48	0	1.07	1	0.30
	Passive	8	0.37**	0.14 to 0.59	60.22			
Setting ^a	Group	6	0.46***	0.22 to 0.70	31.92	5.11	1	0.02
	Individual or mixed	5	0.16**	0.06 to 0.27	0			
Study quality	Low risk	6	0.19	−0.10 to 0.47	0	1.08	1	0.30
	High risk	7	0.38**	0.14 to 0.63	72.23			
Moderator variable (continuous)	No. of studies	β	95% Confidence Interval	Q	df	p		
Age ^b	12	0.045**	0.012 to 0.078	7.19	1	0.007		
Number of total sessions	13	−0.0003	−0.001 to 0.000	3.34	1	0.07		
Number of total sessions ^c	12	−0.003	−0.007 to 0.001	2.69	1	0.10		
Total hours	13	−0.0005	−0.001 to 0.000	3.28	1	0.07		
Total hours ^c	11	−0.002	−0.005 to 0.002	0.96	1	0.32		

SMD: standardized mean difference.

* p < 0.05.

** p < 0.01.

*** p < 0.001.

^a Settings could not be determined for 2 studies (Maillot et al., 2012; Hiyamizu et al., 2012).^b One study (Pieramico et al., 2012) was excluded because mean participant age was not reported.^c Results after excluding the study of Ngandu et al. (2015).**Fig. 4.** Forest plot for efficacy of combined intervention compared to physical exercise.

4.2. Simultaneous versus separate combination

Fissler et al. (2013) proposed that simultaneous conduct of cognitive and physical activities might be crucial for interactions effects between cognitive and physical components. Our subgroup analysis revealed that, both separate and simultaneous intervention produced significant gains. Though the magnitude of

simultaneous combination (SMD = 0.43) seemed larger than that of separate combination (SMD = 0.27), the heterogeneity test did not reach significance. It should be noted that, in some dual-task interventions (Hiyamizu et al., 2012; You et al., 2009), cognitive assessments were limited to a single domain or very similar with training tasks, so it remains unclear whether gains in dual-task intervention would generalize to more global cognitive func-

tion. However, some simultaneous combined interventions with encouraging results were not included into meta-analysis, as they did not meet inclusion criteria. Eggenberger et al. (2015) found that, two simultaneous combined intervention group outperformed single physical training group on executive function, and improvements were maintained at one-year follow-up. In Anderson-Hanley et al. (2012)'s study, cybercycling, which could provide cognitive stimulation by virtual reality during cycling, produced a medium effect ($d = 0.5$) over traditional cycling. Moreover, fitness and exercise effect were comparable in two groups, while the cybercycling group showed a greater increase in peripheral BDNF level than the traditional cycling group. Interestingly, a study of separate combined intervention reported different results (Rahe et al., 2015a). In this study, two combined groups did not produce larger improvements than single cognitive training group in cognition as well as in peripheral BDNF. Results from these two studies (Anderson-Hanley et al., 2012; Rahe et al., 2015a) may provide some support to Fissler et al.'s assumption of restricted time window for physical-cognitive interactions, and the underlying mechanism may associate with neurotrophic growth factors. More studies are needed to verify the efficacy of simultaneous combined intervention and to systematically explore the potential physical-cognitive interaction and underlying mechanism.

4.3. Long-term effects and generalization

Maintenance effects of combined intervention were calculated for studies with follow-up data. Because of very limited available data, we cannot draw any conclusion, but the preliminary analysis helped to extrapolate a trend for long-term effects of combined intervention. For the comparison between combined intervention and control, the analysis of follow-up data revealed a much larger effect ($SMD = 0.61$) than immediate effect at post-intervention ($SMD = 0.29$). For the comparison between combined intervention and single cognitive/physical intervention, results revealed marginal trends toward significant (both $ps = 0.06$). Specially, superior effects of combined intervention sustained for five years after intervention in one study (Oswald et al., 2006). In another study, the advantage of combined intervention was not displayed until the one-year follow-up (Rahe et al., 2015b). Combined intervention and single cognitive training induced paralleled improvements from pre- to post-intervention, but at the follow-up, combined intervention showed further increase on attention while the performance of cognitive training group dropped to baseline level. Similarly, a recent review showed that physical exercise intervention with longer follow-ups reported more consistent positive results on cognitive function (Kelly et al., 2014b). Taken together, the results highlight that combined intervention may have particular advantages in long-term maintenance. The results were preliminary but rather encouraging because maintenance effect is a key evaluation indicator for intervention efficacy. Future studies with follow-ups are needed to confirm the long-term effects of combined intervention.

Outcomes related to everyday functioning were rarely assessed in combined intervention studies, and our results found no significant result. The generalization to everyday-like situations reflects benefits beyond laboratory scenarios and applicability of intervention in clinical and everyday context. It is important to include measurements on everyday cognition and daily activities to evaluate real life benefits and practical values of combined intervention.

4.4. Moderators: age, intervention setting and frequency

The positive association between age and intervention gains suggests greater benefits for participants with older age. The result is consistent with two meta-analytic studies of video game train-

ing (Powers et al., 2013; Toril et al., 2014). The favorable effects for advanced age might partially relate to lower baseline performance of older old relative to their younger counterparts.

The moderator analyses suggest that intervention effects would be impacted by intervention characteristics. The favorable effect of group setting was in line with evidence from meta-analyses of cognitive training (Lampit et al., 2014; Verhaeghen et al., 1992) and physical exercise (Karr et al., 2014). Efficacy of group intervention may be facilitated by social engagement, which closely associates with neurogenesis and better cognitive function (Amieva et al., 2010). Other possible advantages of group intervention may involve effective strategy practice with training partners (Rebok et al., 2007), and direct guidance and enhanced compliance provided by group trainers (Lampit et al., 2014).

Intervention administrated five or more sessions per week showed less efficacy than intervention conducted less than five times per week. Lampit et al. (2014)'s meta-analysis also found relative inefficacy of high frequency training. Two working memory training studies (Penner et al., 2012; Wang et al., 2014) reported larger gains and transfer from more distributed training schedule than high frequency schedule. As discussed earlier (section 4.1), tightly scheduled intervention might cause cognitive fatigue, less adherence and excessive stress (Fiatarone Singh et al., 2014). In addition, a negative correlation between total intervention hours and efficacy was revealed by metaregression, although the correlation lost significance after removal of one outlier. This result is a little surprising but not unique, as two meta-analyses of cognitive training linked longer duration with weaker effects (Au et al., 2015; Li et al., 2011). Taken all together, a maximal dosage possibly exists for both duration and frequency. These findings emphasize the significance to design an appropriate schedule for combined intervention, providing sufficient and challenging but not overwhelming amount of training.

4.5. Control group and comparison design

To investigate the unique contribution of an intervention, proper design of comparison conditions is needed. Passive control group helps to control practice effects on cognitive assessments, and active control could further control expectancy effects, social contact, and other unspecific effects induced by control activities. Previous meta-analyses shows that trials with active controls usually yielded smaller effects than those with passive controls. Our subgroup analysis of control type revealed similar trend, although the heterogeneity test did not reach significant.

Out of 20 included studies, eight used a multi-arm comparison group design. The strength of the multi-armed design is to distinguish the specific contribution of combined intervention from effects of single cognitive/physical exercise and unspecific common components of control group at the same time (Law et al., 2014). However, a fact that cannot be ignored is the large variation in intervention dosage across conditions. In most multi-armed trials using separate combined intervention (Fabre et al., 2002; Legault et al., 2011; Oswald et al., 2006; Shah et al., 2014; Shatil, 2013; van Het Reve and de Bruin, 2014), the combined group exposed to intervention almost twice as long as the single intervention group did, so the confounding effects of discrepant intervention duration could not be excluded. Two exceptions (Barnes et al., 2013; McDaniel et al., 2014) used low-intensity exercise and low cognitively simulating activities as sham activities, making intervention frequency and duration completely matched across all four conditions (combined group, cognitive training group, physical exercise group, active control). Barnes et al. (2013) found cognitive performance increased after intervention but the improvements did not differ across four groups. In McDaniel et al. (2014)'s study, gains in memory were produced only by cognitive training component but

not aerobic exercise component. In the cases of trials using simultaneous combined intervention, the problem of discrepant dose could be avoided.

4.6. Implication for future research and limitations

The meta-analysis highlights the need for multi-armed trials to clarify the specific effects of combined cognitive and physical intervention compared to single intervention. Future studies need to be rigorously designed, with careful consideration of combination mode, dosage, setting, comparison groups, outcome selection and long-term follow-ups. Group intervention and more distributed schedule are recommended, but the optimal frequency and duration remains to be explored to maximize intervention effects. Combined intervention in simultaneous mode seems promising but the effectiveness is needed to be cautiously examined by more studies.

Several limitations of this meta-analysis should be addressed. First, heterogeneity and limited number of included studies confine the ability to analyze impacts of specific cognitive/physical components in combined intervention, that is, how the various combination of different types of cognitive and physical activities would affect intervention effectiveness. The small number of reviewed studies may also limit the power to detect significant heterogeneity. Second, due to very limited data of follow-ups, we could only track the trend of long-term effects of combined intervention rather than draw any conclusion. Third, as merely trials for healthy older adults were included, the results may not generalize to populations with cognitive impairment. Fourth, removal of two outliers with extremely large effect sizes (Fabre et al., 2002; León et al., 2015) may possibly underestimate the synthesized effect size of combined intervention.

5. Conclusion

In summary, the meta-analysis suggests that combined cognitive and physical intervention was effective at improving cognitive function in healthy older adults while intervention effects varied across cognitive domains. Combined intervention demonstrated potential superiority over single physical exercise, while no convincing evidence supported the superiority of combined intervention in comparison with single cognitive intervention. Importantly, combined intervention might have particular advantages in long-term maintenance. Efficacy of combined intervention was moderated by age of participants, intervention frequency and setting. Results should be cautiously interpreted because of differences in intervention methodologies. Well-designed studies with long follow-ups are needed to clarify the potential unique efficacy and underlying mechanism of combined intervention for older adults.

Conflict of interest

The authors declare no conflict of interests.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (31070916, 31271108 and 31470998), the CAS/SAFEA International Partnership Program for Creative Research Team (Y2CX131003), Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences (KLMH2014ZK02), and the funding from State Key Laboratory of Brain and Cognitive Science.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.arr.2016.07.003>.

References

- Amieva, H., Stoykova, R., Matharan, F., Helmer, C., Antonucci, T.C., Dartigues, J.-F., 2010. What aspects of social network are protective for dementia? not the quantity but the quality of social interactions is protective up to 15 years later. *Psychosom. Med.* 72, 905–911, <http://dx.doi.org/10.1097/PSY.0b013e3181f5e121>.
- Anderson-Hanley, C., Arciero, P.J., Brickman, A.M., Nimmon, J.P., Okuma, N., Westen, S.C., Merz, M.E., Pence, B.D., Woods, J.A., Kramer, A.F., Zimmerman, E.A., 2012. Exergaming and older adult cognition: a cluster randomized clinical trial. *Am. J. Prev. Med.* 42, 109–119, <http://dx.doi.org/10.1016/j.amepre.2011.10.016>.
- Au, J., Sheehan, E., Tsai, N., Duncan, G.J., Buschkuhl, M., Jaeggi, S.M., 2015. Improving fluid intelligence with training on working memory: a meta-analysis. *Psychon. Bull. Rev.* 22, 366–377.
- Bamidis, P.D., Vivas, A.B., Styliadis, C., Frantzidis, C., Klados, M., Schlee, W., Siountas, A., Papageorgiou, S.G., 2014. A review of physical and cognitive interventions in aging. *Neurosci. Biobehav. Rev.* 44, 206–220, <http://dx.doi.org/10.1016/j.neubiorev.2014.03.019>.
- Barnes, D.E., Yaffe, K., 2011. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol.* 10, 819–828, [http://dx.doi.org/10.1016/S1474-4422\(11\)70072-2](http://dx.doi.org/10.1016/S1474-4422(11)70072-2).
- Barnes, D.E., Santos-Modesitt, W., Poelke, G., Kramer, A.F., Castro, C., Middleton, L.E., Yaffe, K., 2013. The mental activity and exercise (max) trial: a randomized controlled trial to enhance cognitive function in older adults. *JAMA Intern. Med.* 173, 797–804, <http://dx.doi.org/10.1001/jamainternmed.2013.189>.
- Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2009. Fixed-Effect versus random-effects models. In: *Introduction to Meta-Analysis*. John Wiley & Sons, Ltd, Chichester, UK, <http://dx.doi.org/10.1002/9780470743386.ch13>.
- Buchman, A.S., Boyle, P.A., Yu, L., Shah, R.C., Wilson, R.S., Bennett, D.A., 2012. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology* 78, 1323–1329, <http://dx.doi.org/10.1212/WNL.0b013e3182535d35>.
- Chang, Y.-K., Pan, C.-Y., Chen, F.-T., Tsai, C.-L., Huang, C.-C., 2012. Effect of resistance exercise training on cognitive function in healthy older adults: a review. *J. Aging Phys. Act.* 20, 497–517.
- Cheng, S.T., Chow, P.K., Song, Y.Q., Yu, E.C., Chan, A.C., Lee, T.M., Lam, J.H., 2014. Mental and physical activities delay cognitive decline in older persons with dementia. *Am. J. Geriatr. Psychiatry* 22, 63–74, <http://dx.doi.org/10.1016/j.jagp.2013.01.060>.
- Colcombe, S., Kramer, A.F., 2003. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol. Sci.* 14, 125–130.
- Curlik, D.M., Shors, T.J., 2013. Training your brain: do mental and physical (MAP) training enhance cognition through the process of neurogenesis in the hippocampus? *Neuropharmacology* 64, 506–514, <http://dx.doi.org/10.1016/j.neuropharm.2012.07.027>.
- Eggenberger, P., Schumacher, V., Angst, M., Theill, N., de Bruin, E.D., 2015. Does multicomponent physical exercise with simultaneous cognitive training boost cognitive performance in older adults? A 6-month randomized controlled trial with a 1-year follow-up. *Clin. Interv. Aging* 10, 1335–1349, <http://dx.doi.org/10.2147/CIA.S87732>.
- Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315, 629–634.
- Fabel, K., Wolf, S., Ehninger, D., Babu, H., Galicia, P., Kempermann, G., 2009. Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. *Front. Neurosci.* 3, <http://dx.doi.org/10.3389/neuro.22.002.2009>.
- Fabre, C., Chamari, K., Mucci, P., Masse-Biron, J., Prefaut, C., 2002. Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. *Int. J. Sports Med.* 23, 415–421.
- Fiatarone Singh, M.A., Gates, N., Saigal, N., Wilson, G.C., Meiklejohn, J., Brodaty, H., Wen, W., Singh, N., Baune, B.T., Suo, C., Baker, M.K., Foroughi, N., Wang, Y., Sachdev, P.S., Valenzuela, M., 2014. The Study of Mental and Resistance Training (SMART) Study—resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. *J. Am. Med. Dir. Assoc.* 15, 873–880, <http://dx.doi.org/10.1016/j.jamda.2014.09.010>.
- Fissler, P., Küster, O., Schlee, W., Kolassa, I.-T., 2013. Novelty interventions to enhance broad cognitive abilities and prevent dementia: synergistic approaches for the facilitation of positive plastic change. *Prog. Brain Res.* 207, 403–434, <http://dx.doi.org/10.1016/B978-0-444-63327-9.00017-5>.
- Green, C.S., Strobach, T., Schubert, T., 2014. On methodological standards in training and transfer experiments. *Psychol. Res.* 1–17, <http://dx.doi.org/10.1007/s00426-013-0535-3>.
- Hindin, S.B., Zelinski, E.M., 2012. Extended practice and aerobic exercise interventions benefit untrained cognitive outcomes in older adults: a meta-analysis. *J. Am. Geriatr. Soc.* 60, 136–141, <http://dx.doi.org/10.1111/j.1532-5415.2011.03761.x>.
- Hiyamizu, M., Morioka, S., Shomoto, K., Shimada, T., 2012. Effects of dual task balance training on dual task performance in elderly people: a randomized

- controlled trial. *Clin. Rehabil.* 26, 58–67, <http://dx.doi.org/10.1177/0269215510394222>.
- Holtzer, R., Shuman, M., Mahoney, J.R., Lipton, R., Verghese, J., 2010. Cognitive fatigue defined in the context of attention networks. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol.* 18, 108–128, <http://dx.doi.org/10.1080/13825585.2010.517826>.
- Karr, J.E., Areshenkoff, C.N., Rast, P., Garcia-Barrera, M.A., 2014. An empirical comparison of the therapeutic benefits of physical exercise and cognitive training on the executive functions of older adults: a meta-analysis of controlled trials. *Neuropsychology* 28, 829–845, <http://dx.doi.org/10.1037/neu0000101>.
- Kayama, H., Okamoto, K., Nishiguchi, S., Yamada, M., Kuroda, T., Aoyama, T., 2014. Effect of a Kinect-based exercise game on improving executive cognitive performance in community-dwelling elderly: case control study. *J. Med. Internet. Res.* 16, e61, <http://dx.doi.org/10.2196/jmir.3108>.
- Kelly, M.E., Loughrey, D., Lawlor, B.A., Robertson, I.H., Walsh, C., Brennan, S., 2014a. The impact of cognitive training and mental stimulation on cognitive and everyday functioning of healthy older adults: a systematic review and meta-analysis. *Ageing Res. Rev.* 15, 28–43, <http://dx.doi.org/10.1016/j.arr.2014.02.004>.
- Kelly, M.E., Loughrey, D., Lawlor, B.A., Robertson, I.H., Walsh, C., Brennan, S., 2014b. The impact of exercise on the cognitive functioning of healthy older adults: a systematic review and meta-analysis. *Ageing Res. Rev.* 16, 12–31, <http://dx.doi.org/10.1016/j.arr.2014.05.002>.
- Klusmann, V., Evers, A., Schwarzer, R., Schlattmann, P., Reischies, F.M., Heuser, I., Dimeo, F.C., 2010. Complex mental and physical activity in older women and cognitive performance: a 6-month randomized controlled trial. *J. Gerontol. A Biol. Sci. Med. Sci.* 65, 680–688, <http://dx.doi.org/10.1093/gerona/gdq053>.
- Knaepen, K., Goekint, M., Heyman, E.M., Meeusen, R., 2010. Neuroplasticity—exercise-induced response of peripheral brain-derived neurotrophic factor. *Sports Med.* 40, 765–801.
- Kraft, E., 2012. Cognitive function, physical activity, and aging: possible biological links and implications for multimodal interventions. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 19, 248–263, <http://dx.doi.org/10.1080/13825585.2011.645010>.
- Lampit, A., Hallock, H., Valenzuela, M., 2014. Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. *PLoS Med.* 11, e1001756, <http://dx.doi.org/10.1371/journal.pmed.1001756>.
- Landau, S.M., Marks, S.M., Mormino, E.C., Rabinovici, G.D., Oh, H., O'Neil, J.P., Wilson, R.S., Jagust, W.J., 2012. Association of lifetime cognitive engagement and low β -amyloid deposition. *Arch. Neurol.* 69, 623–629, <http://dx.doi.org/10.1001/archneurol.2011.2748>.
- Langdon, K.D., Corbett, D., 2012. Improved working memory following novel combinations of physical and cognitive activity. *Neurorehabil. Neural Repair* 26, 523–532, <http://dx.doi.org/10.1177/1545968311425919>.
- Law, L.L.F., Barnett, F., Yau, M.K., Gray, M.A., 2014. Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: a systematic review. *Ageing Res. Rev.* 15, 61–75, <http://dx.doi.org/10.1016/j.arr.2014.02.008>.
- Legault, C., Jennings, J., Katula, J., Dagenbach, D., Gaussoin, S., Sink, K., Rapp, S., Rejeski, W.J., Shumaker, S., Espeland, M., the SHARP-P Study Group, 2011. Designing clinical trials for assessing the effects of cognitive training and physical activity interventions on cognitive outcomes: the Seniors Health and Activity Research Program Pilot (SHARP-P) Study, a randomized controlled trial. *BMC Geriatr.* 11, 27.
- León, J., Urena, A., Bolanos, M.J., Bilbao, A., Ona, A., 2015. A combination of physical and cognitive exercise improves reaction time in persons 61–84 years old. *J. Aging Phys. Act.* 23, 72–77, <http://dx.doi.org/10.1123/japa.2012-0313>.
- Li, H., Li, J., Li, N., Li, B., Wang, P., Zhou, T., 2011. Cognitive intervention for persons with mild cognitive impairment: a meta-analysis. *Ageing Res. Rev.* 10, 285–296, <http://dx.doi.org/10.1016/j.arr.2010.11.003>.
- Li, R., Zhu, X., Yin, S., Niu, Y., Zheng, Z., Huang, X., Wang, B., Li, J., 2014. Multimodal intervention in older adults improves resting-state functional connectivity between the medial prefrontal cortex and medial temporal lobe. *Front. Aging Neurosci.* 6, 39, <http://dx.doi.org/10.3389/fnagi.2014.00039>.
- Linde, K., Alfermann, D., 2014. Single versus combined cognitive and physical activity effects on fluid cognitive abilities of healthy older adults: a 4-month randomized controlled trial with follow-up. *J. Aging Phys. Act.* 22, 302–313, <http://dx.doi.org/10.1123/japa.2012-0149>.
- MacDonald, S.W.S., Hultsch, D.F., Dixon, R.A., 2011. Aging and the shape of cognitive change before death: terminal decline or terminal drop? *J. Gerontol. B Psychol. Sci. Soc. Sci.* 66, 292–301, <http://dx.doi.org/10.1093/geronb/gbr001>.
- Maher, C.G., Sherrington, C., Herbert, R.D., Moseley, A.M., Elkins, M., 2003. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys. Ther.* 83, 713–721.
- Maillot, P., Perrot, A., Hartley, A., 2012. Effects of interactive physical-activity video-game training on physical and cognitive function in older adults. *Psychol. Aging* 27, 589.
- Marcos, A., Gil, P., Barabash, A., Rodriguez, R., Encinas, M., Fernández, C., Cabranes, J.A., 2006. Neuropsychological markers of progression from mild cognitive impairment to Alzheimer's disease. *Am. J. Alzheimers Dis. Other Dement.* 21, 189–196.
- McDaniel, M.A., Binder, E.F., Bugg, J.M., Waldum, E.R., Dufault, C., Meyer, A., Johanning, J., Zheng, J., Schechtman, K.B., Kudejka, C., 2014. Effects of cognitive training with and without aerobic exercise on cognitively demanding everyday activities. *Psychol. Aging* 29, 717–730, <http://dx.doi.org/10.1037/a0037363>.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., The PRISMA Group, 2009. Preferred reporting items for systematic reviews and meta-Analyses: the PRISMA statement. *PLoS Med.* 6, e1000097, <http://dx.doi.org/10.1371/journal.pmed.1000097>.
- Ngandu, T., Lehtisalo, J., Solomon, A., Levalahti, E., Ahtiluoto, S., Antikainen, R., Backman, L., Hanninen, T., Jula, A., Laatikainen, T., Mangialasche, F., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T., Tuomilehto, J., Soininen, H., Kivipelto, M., 2015. 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. *Lancet* 385, 2255–2263, [http://dx.doi.org/10.1016/S0140-6736\(15\)60461-5](http://dx.doi.org/10.1016/S0140-6736(15)60461-5).
- Nishiguchi, S., Yamada, M., Tanigawa, T., Sekiyama, K., Kawagoe, T., Suzuki, M., Yoshikawa, S., Abe, N., Otsuka, Y., Nakai, R., Aoyama, T., Tsuboyama, T., 2015. A 12-week physical and cognitive exercise program can improve cognitive function and neural efficiency in community-dwelling older adults: a randomized controlled trial. *J. Am. Geriatr. Soc.* 63, 1355–1363, <http://dx.doi.org/10.1111/jgs.13481>.
- Noack, H., Lövdén, M., Schmiedek, F., 2014. On the validity and generality of transfer effects in cognitive training research. *Psychol. Res.* 78, 1–17, <http://dx.doi.org/10.1007/s00426-014-0564-6>.
- Oswald, W., Gunzelmann, T., Rupprecht, R., Hagen, B., 2006. Differential effects of single versus combined cognitive and physical training with older adults: the SimA study in a 5-year perspective. *Eur. J. Ageing* 3, 179–192.
- Park, D.C., Lodi-Smith, J., Drew, L., Haber, S., Hebrank, A., Bischof, G.N., Aamodt, W., 2014. The impact of sustained engagement on cognitive function in older adults: the Synapse Project. *Psychol. Sci.* 25, 103–112, <http://dx.doi.org/10.1177/0956797613499592>.
- Penner, I.-K., Vogt, A., Stöcklin, M., Gschwind, L., Opwis, K., Calabrese, P., 2012. Computerised working memory training in healthy adults: a comparison of two different training schedules. *Neuropsychol. Rehabil.* 22, 716–733, <http://dx.doi.org/10.1080/09602011.2012.686883>.
- Pieramico, V., Esposito, R., Sensi, F., Cilli, F., Mantini, D., Mattei, P.A., Frazzini, V., Ciavarella, D., Gatta, V., Ferretti, A., Romani, G.L., Sensi, S.L., 2012. Combination training in aging individuals modifies functional connectivity and cognition, and is potentially affected by dopamine-related genes. *PLoS One* 7, e43901, <http://dx.doi.org/10.1371/journal.pone.0043901>.
- Powers, K., Brooks, P., Aldrich, N., Palladino, M., Alfieri, L., 2013. Effects of video-game play on information processing: a meta-analytic investigation. *Psychon. Bull. Rev.* 20, 1055–1079, <http://dx.doi.org/10.3758/s13423-013-0418-z>.
- Rahe, J., Becker, J., Fink, G.R., Kessler, J., Kukulja, J., Rahn, A., Rosen, J.B., Szabados, F., Wirth, B., Kalbe, E., 2015a. Cognitive training with and without additional physical activity in healthy older adults: cognitive effects, neurobiological mechanisms, and prediction of training success. *Front. Aging Neurosci.* 7, <http://dx.doi.org/10.3389/fnagi.2015.00187>.
- Rahe, J., Petrelli, A., Kaesberg, S., Fink, G.R., Kessler, J., Kalbe, E., 2015b. Effects of cognitive training with additional physical activity compared to pure cognitive training in healthy older adults. *Clin. Interv. Aging* 10, 297–310, <http://dx.doi.org/10.2147/CIA.S74071>.
- Read, J., Shortell, S.M., 2011. Interactive games to promote behavior change in prevention and treatment. *JAMA* 305 (16), 1704–1705, <http://dx.doi.org/10.1001/jama.2011.408>.
- Rebok, G.W., Carlson, M.C., Langbaum, J.B.S., 2007. Training and maintaining memory abilities in healthy older adults: traditional and novel approaches. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 62, 53–61.
- Reijnders, J., van Heugten, C., van Bortel, M., 2013. Cognitive interventions in healthy older adults and people with mild cognitive impairment: a systematic review. *Ageing Res. Rev.* 12, 263–275, <http://dx.doi.org/10.1016/j.arr.2012.07.003>.
- Rosenthal, R., 1979. The file drawer problem and tolerance for null results. *Psychol. Bull.* 86, 638–664, <http://dx.doi.org/10.1037/0033-2909.86.3.638>.
- Rovio, S., Kareholt, I., Helkala, E.L., Viitanen, M., Winblad, B., Tuomilehto, J., Soininen, H., Nissinen, A., Kivipelto, M., 2005. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol.* 4, 705–711.
- Scarmeas, N., Luchsinger, J.A., Schupf, N., Brickman, A.M., Cosentino, S., Tang, M.X., Stern, Y., 2009. Physical activity diet, and risk of Alzheimer disease. *JAMA* 302, 627–637.
- Shah, T., Verdile, G., Sohrabi, H., Campbell, A., Putland, E., Cheetham, C., Dhaliwal, S., Maruff, P., Darby, D., Martins, R.N., 2014. A combination of physical activity and computerized brain training improves verbal memory and increases cerebral glucose metabolism in the elderly. *Transl. Psychiatry* 4, e487, <http://dx.doi.org/10.1038/tp.2014.122>.
- Shatil, E., 2013. Does combined cognitive training and physical activity training enhance cognitive abilities more than either alone? A four-condition randomized controlled trial among healthy older adults. *Front. Aging Neurosci.* 5, <http://dx.doi.org/10.3389/fnagi.2013.00008>.
- Smith, A.M., Spiegler, K.M., Sauce, B., Wass, C.D., Sturzo, T., Matzel, L.D., 2013. Voluntary aerobic exercise increases the cognitive enhancing effects of working memory training. *Behav. Brain Res.* 256, 626–635, <http://dx.doi.org/10.1016/j.bbr.2013.09.012>.
- Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Cooper, H., Strauman, T.A., Welsh-Bohmer, K., Browndyke, J.N., Sherwood, A., 2010. Aerobic exercise and

- neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom. Med.* 72, 239–252, <http://dx.doi.org/10.1097/PSY.0b013e3181d14633>.
- Snowden, M., Steinman, L., Mochan, K., Grodstein, F., Prohaska, T.R., Thurman, D.J., Brown, D.R., Laditka, J.N., Soares, J., Zweiback, D.J., Little, D., Anderson, L.A., 2011. Effect of exercise on cognitive performance in community-dwelling older adults: review of intervention trials and recommendations for public health practice and research. *J. Am. Geriatr. Soc.* 59, 704–716, <http://dx.doi.org/10.1111/j.1532-5415.2011.03323.x>.
- Toril, P., Reales, J.M., Ballesteros, S., 2014. Video game training enhances cognition of older adults: a meta-analytic study. *Psychol. Aging* 29, 706–716, <http://dx.doi.org/10.1037/a0037507>.
- Valenzuela, M.J., Matthews, F.E., Brayne, C., Ince, P., Halliday, G., Kril, J.J., Dalton, M.A., Richardson, K., Forster, G., Sachdev, P.S., The Medical Research Council Cognitive Function and Ageing Study, 2012. Multiple biological pathways link cognitive lifestyle to protection from dementia. *Biol. Psychiatry* 71, 783–791, <http://dx.doi.org/10.1016/j.biopsych.2011.07.036>.
- Valenzuela, M.J., Sachdev, P., Wen, W., Chen, X., Brodaty, H., 2008. Lifespan mental activity predicts diminished rate of hippocampal atrophy. *PLoS One* 3, e2598, <http://dx.doi.org/10.1371/journal.pone.0002598>.
- van Het Reve, E., de Bruin, E.D., 2014. Strength-balance supplemented with computerized cognitive training to improve dual task gait and divided attention in older adults: a multicenter randomized-controlled trial. *BMC Geriatr.* 14 (1), 134, <http://dx.doi.org/10.1186/1471-2318-14-134>.
- Verghese, J., Lipton, R.B., Katz, M.J., Hall, C.B., Derby, C.A., Kuslansky, G., Ambrose, A.F., Sliwinski, M., Buschke, H., 2003. *Leisure activities and the risk of dementia in the elderly*. *N. Engl. J. Med.* 348, 2508–2516.
- Verhaeghen, P., Marcoen, A., Goossens, L., 1992. Improving memory performance in the aged through mnemonic training: a meta-analytic study. *Psychol. Aging* 7 (2), 242–251.
- Wang, Z., Zhou, R., Shah, P., 2014. Spaced cognitive training promotes training transfer. *Front. Hum. Neurosci.* 8, <http://dx.doi.org/10.3389/fnhum.2014.00217>.
- Wayne, P.M., Walsh, J.N., Taylor-Piliae, R.E., Wells, R.E., Papp, K.V., Donovan, N.J., Yeh, G.Y., 2014. Effect of Tai Chi on cognitive performance in older adults: systematic review and meta-analysis. *J. Am. Geriatr. Soc.* 62, 25–39, <http://dx.doi.org/10.1111/jgs.12611>.
- Wilson, R.S., Boyle, P.A., Segawa, E., Yu, L., Begeny, C.T., Anagnos, S.E., Bennett, D.A., 2013. The influence of cognitive decline on well-being in old age. *Psychol. Aging* 28, 304–313, <http://dx.doi.org/10.1037/a0031196>.
- Wilson, R.S., Segawa, E., Boyle, P.A., Bennett, D.A., 2012. Influence of late-life cognitive activity on cognitive health. *Neurology* 78, 1123–1129, <http://dx.doi.org/10.1212/WNL.0b013e31824f8c03>.
- Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am. J. Psychiatry* 168, 472–485, <http://dx.doi.org/10.1176/appi.ajp.2010.10060855>.
- Yin, S., Zhu, X., Huang, X., Li, J., 2015. Visuospatial characteristics of an elderly Chinese population: results from the WAIS-R block design test. *Front. Aging Neurosci.* 7, <http://dx.doi.org/10.3389/fnagi.2015.00017>.
- You, J.H., Shetty, A., Jones, T., Shields, K., Belay, Y., Brown, D., 2009. Effects of dual-task cognitive-gait intervention on memory and gait dynamics in older adults with a history of falls: a preliminary investigation. *NeuroRehabilitation* 24, 193–198.
- Zelinski, E.M., 2009. Far transfer in cognitive training of older adults. *Restor. Neurol. Neurosci.* 27, 455–471, <http://dx.doi.org/10.3233/rnn-2009-0495>.