SUPPLEMENTAL MATERIAL

Effects of physical activity on post-stroke cognitive function: a meta-analysis of randomized controlled trials

Lauren E. Oberlin, M.S.,[1,2] Aashna Waiwood,[1] Toby B. Cumming, Ph.D.,[3] Anna L. Marsland, Ph.D.,[1] Julie Bernhardt, Ph.D.,[3] Kirk I. Erickson, Ph.D.[1,2]

1. Department of Psychology, University of Pittsburgh

2. Center for the Neural Basis of Cognition, University of Pittsburgh

3. The Florey Institute of Neuroscience and Mental Health, University of Melbourne

Correspondence should be addressed to Lauren E. Oberlin, Department of Psychology, University of Pittsburgh, 210 S. Bouquet St., 3211 Sennott Square, Pittsburgh, PA 15260. Phone: (412) 624-4557 Email: leo11@pitt.edu

1.0 SUPPLEMENTAL METHODS

1.1 Study Selection

Two studies included in a prior meta-analysis[1] did not meet our inclusion criteria and were excluded from the present study. Specifically, Ploughman et al. (2008)[2] involved only one 20-minute bout of PA and Bateman et al., (2001)[3] included a combination of subjects who had suffered a single-incident brain injury of any cause (i.e., stroke, TBI, other). Further, several single-group non-randomized trials were excluded from the present meta-analysis.[4-7] Thus, the exclusion of these papers makes our approach more conservative because the absence of control conditions in these trials makes it difficult to account for confounding factors such as practice effects,[8] and may also overestimate treatment effects.[9]

1.2 Data Collection and Extraction

Data extracted included: study characteristics (design, year, inclusion criteria, cohort size), participant characteristics (age, gender, time since stroke, stroke type/location, baseline physical and cognitive status), intervention characteristics (components of control and PA conditions, including the length, mode, and intensity of PA, session duration, frequency, adherence, attrition, adverse outcomes), outcome measures including physical activity data (fitness, balance, strength, walking speed), and cognitive data (screening criteria, cognitive measures, frequency of administration) and data on study quality. Study outcomes for which data were extracted include self-report estimates of cognitive function (e.g., the memory domain of the Stroke Impact Scale) and objective measures of cognitive abilities (e.g., Mini-Mental State Examination, Wisconsin Cart Sorting Test, etc.). Authors of two trials that included median and range values of cognitive outcomes in the published reports were contacted and provided mean and standard deviation values.

1.3 Calculation of Effect Sizes

Data were entered into an electronic database and analyzed using Comprehensive Meta-Analysis (CMA) software, version 2. The software employs the same computational algorithms used by the Cochrane collaborators to weight studies by inverse variance methods.[10] Only 6 trials had longitudinal follow-up after the intervention, therefore, for the purposes of consistency, effect size estimates were derived from cognitive outcome data collected immediately following the intervention.

1.4 Quantitative Data Synthesis and Analysis

We evaluated whether there were domain-specific effects of PA training on neurocognitive performance in a subgroup of studies that employed multiple neuropsychological assessments. The analysis included tests that could be classified into the following categories: attention and information processing speed, working memory, and executive function. Neuropsychological tests were categorized according to cognitive domains described by Lezak (2004).[11] Tests that were not included in this neuropsychological compendium were categorized based on 1) particular factor loadings from previous studies or 2) similar classification across a preponderance of studies. Two studies included outcome variables from neuropsychological tests that were not included

in the analysis, as they did not assess the domains specified above.[12,13]

2.0 SUPPLEMENTAL RESULTS

2.1 Characteristics of included studies

Included trials were performed in nine countries, including four in North America, two in the United Kingdom and two in China, and one in Egypt, Germany, Turkey, Sweden, Spain, and Australia. The pool of 736 participants (363 in PA training conditions) was drawn from inpatient care facilities, medical and stroke centers, multi-site stroke databases, and community advertising. All trials provided exclusionary criteria, indicating that participants were stroke survivors aged 18 or over, frequently without other neurological or psychiatric conditions. The sample size within exercise or control conditions ranged from 7 to 78. Hemiparesis was an inclusionary criterion in three studies[14-16] and an additional five studies included individuals that required an assistive device while walking due to motor impairments.[12,13,17-19] The ability to walk independently was a requirement for inclusion in two studies[20,21] and the absence of limb impairment was a requirement in one study.[22] Baseline motor status was not reported in three studies.[23-25]

2.2 Intervention characteristics

Most interventions were conducted 2-3 times per week, and the average trial duration was 12.39 (5.91) weeks. Of the 14 included studies, six studies compared an experimental group with a control group that received standard medical practice or waitlist control. [12,16,18,21,22,24] However, physical therapy and occupational therapy were considered part of standard care in a subset of participants in one trial, and therefore even participants within the control group may have received some form of PA training[21]. A majority of these studies did not explicitly state whether participants in control groups received physical or occupational therapy as part of standard care.[12,16,18,22] Two studies contained an active control condition that did not involve any form of PA (social communication, progressive muscle relaxation).[13,20] Finally, 6 studies included a control condition that involved PA without a primary aerobic component (stretching, toning, and balance).[14,15,17,19,23,25] However, in 3 studies the stretching/toning conditions were home-based, and thus training participation was not directly monitored. These trials employed daily diaries and/or regular phone check-ins to assess adherence.[14,17,23] Pooled effect size estimates stratified by type of control group are included in Table III. Among the PA training conditions, 5 studies involved stretching and toning/physiotherapy without a primary aerobic component, 3 trials consisted only of aerobic exercise training (e.g., treadmill, bicycle training), and 6 studies included a combined PA training program, involving a mixture of both aerobic exercise and stretching and toning activities. Four studies incorporated another component along with PA training into experimental conditions, including ADL training, occupational therapy, and social activities.[13,18,23,24] Six studies included a follow-up assessment after the conclusion of the intervention, which ranged from 3 to 10 months post-intervention.[14,15,18,20-22] Adherence rates were reported in 7 studies, and ranged from 80% to 100% within the exercise conditions, with an average of 89% adherence across all 7 studies. Cardiorespiratory fitness was assessed in 4

studies,[14,17,19,20] 3 of which found an increase in fitness levels following the PA intervention.[14,17,20]

2.2.1. Adverse Events

Eight studies reported on adverse events, although in most studies the criteria and methods used to define and assess adverse events were unclear and the information provided was often sparse. Four of the 8 studies reported no incidence of adverse events in PA conditions.[12,16-18] No serious adverse events were reported in any study aside from one,[15] which noted that two participants died over the course of the intervention. However, it was unclear if these participants were assigned to the exercise or control conditions, and whether these incidents were at all related to the intervention. One study found no differences in medical complications between PA and control groups aside from reported shoulder problems.[23] Mead et al.,[20] reported participant falls outside of the intervention sessions in both PA and relaxation control groups. Two studies reported falls that occurred during intervention sessions, although in both cases these falls took place during control sessions (relaxation condition and low-intensity PA condition).[19,20] Given this lack of adverse event reporting in these studies it is impossible to determine the prevalence or incidence of adverse events resulting from an exercise intervention in individuals with stroke.

2.3 Cognitive Measures

Nine studies employed a single, global measure of cognitive function, specifically the Mini-Mental Status Exam (MMSE), the Functional Independence Measure (FIM), Addenbrooke's Cognitive Examination-Revised (ACE-R), the Montreal Cognitive Assessment (MOCA), or the Stroke Impact Scale (SIS). Five of these studies used objective measures, and four used subjective cognitive assessments (e.g., SIS, FIM). Finally, five studies administered multiple neuropsychological tests that allowed for an assessment across multiple domains.

3.0 SUPPLEMENTAL TABLES

Table I. Classification of neurocognitive tests by domain.

Neurocognitive Domain		
Executive Function (# studies)	**Attention/Information Processing Speed (# studies)**	**Working Memory (# studies)**
Trail Making Test, Part B (4)	Serial Repetition Task (repeated, random) (1)	Digit Span Backward (3)
Stroop Color-Word Interference (3)	Walking While Talking Test (1)	Symbol Span Backward (1)
Go/No-go (1)	Symbol Span Forward (1)	Block Tapping Test (1)
FAS (1)	Digit Span Forward (2)	
Wisconsin Card Sort Test (1)	Trail Making Test, Part A (1)	
	Stroop Color/Word Reading (1)	
	Continuous Performance Test (1)	

Values in parentheses reflect the number of studies that employed each cognitive test.

Table II. Meta-analytic results from all random and mixed-effects models.

Model	N	Hedge's g	95%CI	P-value	Heterogeneity (Q)	I^2	Q P-value	Q_B	Q_B P-value
Overall	14	0.304**	(0.14; 0.47)	< .001	15.36	15.36	0.29	-	-
Exercise Mode	14							1.35	0.508
Combined	6	0.43*	(0.09; 0.77)	0.012	10.23	51.44	0.069		
Aerobic	3	0.16	(-0.15; 0.47)	0.314	1.21	0	0.546		
Stretching/Toning	5	0.28*	(0.05; 0.52)	0.017	2.97	0	0.563		
Cognitive assessment	14							1.93	0.165
Objective Outcomes	10	0.39**	(0.18; 0.59)	< .001	11.17	19.39	0.27		
Subjective Outcomes	4	0.16	(-0.09; 0.40)	0.21	2.61	0	0.46		
Control conditions	14							0.49	0.48
PA-controls	9	0.25**	(0.08; 0.42)	0.005	7.19	0	0.52		
non-PA controls	5	0.4*	(0.03; 0.77)	0.036	7.72	48.19	0.1		
Length of Intervention	14							0.82	0.367
< 3 months	7	0.39**	(0.14; 0.63)	0.002	7.97	24.7	0.24		
≥ 3 months	7	0.23*	(0.01; 0.46)	0.045	6.8	11.77	0.34		
Time from stroke to intervention	14							2.89	0.089
≤ 3 months	4	0.16	(-0.04; 0.36)	0.11	2.11	0	0.549		
> 3 months	10	0.43**	(0.20; 0.65)	< .001	10.35	13.02	0.323		
Motor Limitations	8	0.33	(0.10; 0.56)	0.006	4.36	0	0.74	-	-
Cognitive Domains	24							2.18	0.336
Executive Function	10	0.11	(-0.11; 0.33)	0.319	4.87	0	0.85		
Processing Speed	9	0.37**	(0.10; 0.63)	0.007	10.64	24.84	0.22		
Working Memory	5	0.27	(-0.13; 0.67)	0.18	5.68	29.6	0.22		
Type of Control Condition	14								
Standard Care	6	0.27	(0.02; 0.53)	0.036					
Non-PA Controls	2	0.21	(-0.30; 0.71)	0.42					
PA component	6	0.39	(0.13; 0.66)	0.004					

- $p < 0.05$; $^{**}p < 0.01$ CI = Confidence interval; PA = physical activity

Table III. Characteristics of included studies.

Study (Year)	N	Age (Mean)	Time from Stroke to Int.	Length of Intervention	Type of PA	PA Session Duration	PA Frequency	Control Type	Cognitive Outcomes
Chen, 2006	Ex: 25; Con: 20	Ex: 66.2; Con: 67.3	<6 mon (13); 6-12 mon (8); >12 mon (4)	12 weeks	Combined	-	2x week	Standard Care	MMSE
El-Tamawy, 2014	Ex: 15; Con: 15	Ex: 48.4; Con: 49.7	3-18 months	8 weeks	Combined	75 min/day	3x week	Stretching, gait, strength training	ACE-R
Fang, 2003	Ex: 78; Con: 78	Ex: 65.6; Con: 61.8	Within first week	4 weeks	Physiotherapy	45 min/day	5x week	Routine Therapy	MMSE
Fernandez-Gonzalo, 2016	Ex: 16; Con: 16	Ex: 61.2; Con: 65.7	Mean years: 3.91	12 weeks	Resistance Training	4 sets of 7 repetitions	2x week	Standard Care	CPT, Digit Span, FAS, RAVLT, Spatial Span, Stroop, Trail Making Test, WWTT
Immink, 2014	Ex: 11; Con: 11	Ex: 56.1; Con: 63.2	Mean months: 52.5	10 weeks	Yoga	40-90 min	90 min/1x week supervised, 40 min/day home-based	Waitlist Control	SIS – memory domain
Liu-Ambrose, 2015	Ex: 11; Con: 14	Ex: 62.9; Con: 66.9	Mean years: Ex: 2.4; Con: 2.9	24 weeks	Combined	60 min/day	2x week	Standard Care	Stroop, Trail Making Test, Digit Span
Mead, 2007	Ex:32; Con: 34	Median age: Ex: 72; Con: 71.7	Median days: Ex: 178; Con:162	12 weeks	Combined	75 min/day	3x week	PMR	FIM memory, problem solving questions
Moore, 2014	Ex: 20; Con: 20	Ex: 68; Con: 70	Mean months: Ex: 21; Con: 16	19 weeks	Combined	45-60 min/day	3x week	Stretching	ACE-R
Nilsson, 2001	Ex: 36; Con: 37	Median age: Ex: 54; Con: 56	Median days: Ex: 22; Con: 17	9.5 weeks	Aerobic treadmill walking	30 min/day	5x week	Track walking with physiotherapist	FIM-Cognitive
Ozdemir, 2001	Ex: 30; Con: 30	Ex: 59.1; Con: 61.8	Mean days: Ex: 41; Con: 36	9 weeks	Stretching, toning, neuromuscular facilitation exercises	120 min/day	5x week	Conventional PA at home	MMSE
Quaney, 2009	Ex: 19; Con; 19	Ex: 64.1; Con: 59	Mean years: Ex: 4.6; Con: 5.1	8 weeks	Aerobic	45 min/day	3x week	Home-based stretching exercises	WCST, Trail Making Test, Serial Reaction Time Test, Stroop,
Schachten, 2015	Ex: 7; Con: 7	Ex: 55.1; Con: 53.1	Mean years: Ex: 3.43; Con: 3.86	10 weeks	Golf training (coordinative exercises)	60 min/day	2x week	Social Communication	Block Tapping Test, Go/No-go, Mental Rotation Test
Studenski, 2005	Ex: 44; Con: 49	Ex: 68.5; Con: 70.4	Mean Days: Ex: 77.5; Con: 74.1	12 weeks	Combined	NR	3x week	Standard Care (some received PT/OT as part of standard care)	FIM-Cognitive
Tang, 2016	Ex: 22; Con: 25	Ex: 65.9; Con: 66.9	Mean years: Ex: 3.5; Con: 2.3	24 weeks	High intensity aerobic PA (40 – 80% HR reserve)	60 min/day	3x week	Stretching, balance, strength training (< 40% HR reserve)	Digit Span Forward, Digit Span Backward, Stroop Color-Word Interference Test, Trail Making Test Part B

WWTT = Walking While Talking Test; RAVLT = Rey Auditory Verbal Learning Test; CPT = Conners Continuous Performance Test-II; PMR = Progressive Muscle Relaxation ACE-R = Addenbrooke's Cognitive Examination-Revised; FIM = Functional Independence Measure; HR= Heart Rate; MMSE = Mini-Mental State Examination; OT = Occupational Therapy; PT = Physical Therapy; SIS = Stroke Impact Scale

4.0 SUPPLEMENTAL REFERENCES

1. Cumming, T. B., Tyedin, K., Churilov, L., Morris, M. E., & Bernhardt, J. The effect of physical activity on cognitive function after stroke: a systematic review. *International Psychogeriatrics,* 2012;24:557-567.
2. Ploughman, M., McCarthy, J., Bossé, M., Sullivan, H. J., & Corbett, D. Does treadmill exercise improve performance of cognitive or upper-extremity tasks in people with chronic stroke? A randomized cross-over trial. *Archives of physical medicine and rehabilitation,* 2008;89:2041-2047.
3. Bateman, A., Culpan, F. J., Pickering, A. D., Powell, J. H., Scott, O. M., & Greenwood, R. J. The effect of aerobic training on rehabilitation outcomes after recent severe brain injury: a randomized controlled evaluation. *Archives of physical medicine and rehabilitation,* 2001;82:174-182.
4. Kluding, P. M., Tseng, B. Y., & Billinger, S. A. Exercise and executive function in individuals with chronic stroke: a pilot study. *Journal of neurologic physical therapy: JNPT,* 2011;35:11.
5. Marzolini, S., Oh, P., McIlroy, W., & Brooks, D. The effects of an aerobic and resistance exercise training program on cognition following stroke. *Neurorehabilitation and neural repair,* 2013;27:392-402.
6. Rand, D., Eng, J. J., Liu-Ambrose, T., & Tawashy, A. E. Feasibility of a 6-month exercise and recreation program to improve executive functioning and memory in individuals with chronic stroke. *Neurorehabilitation and neural repair,* 2010;8:722-729.
7. Blanchet, S., Richards, C. L., Leblond, J., Olivier, C., & Maltais, D. B. Cardiorespiratory fitness and cognitive functioning following short-term interventions in chronic stroke survivors with cognitive impairment: a pilot study. *International Journal of Rehabilitation Research,* 2016;39:153-159.
8. Campbell, D. T., & Stanley, J. C. Experimental and quasi-experimental designs for research. 1st Ed. Boston, Massacheussettes: Houghton Mifflin Company; 1963.
9. Schulz, K. F., Chalmers, I., Hayes, R. J., & Altman, D. G. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Jama,* 1995;273:408-412.
10. Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. Comprehensive meta-analysis: Version 2. Englewood, NJ: Biostat;2005.
11. Lezak, M. D. Neuropsychological assessment. 4th Ed. New York, New York:Oxford University Press, Inc; 2004.
12. Fernandez-Gonzalo, R., Fernandez-Gonzalo, S., Turon, M., Prieto, C., Tesch, P. A., & del Carmen García-Carreira, M. Muscle, functional and cognitive adaptations after flywheel resistance training in stroke patients: a pilot randomized controlled trial. *Journal of neuroengineering and rehabilitation,* 2016;13:1.
13. Schachten, T., & Jansen, P. The effects of golf training in patients with stroke: a pilot study. *International Psychogeriatrics,* 2015;27:865-873.
14. Quaney, B. M., Boyd, L. A., McDowd, J. M., Zahner, L. H., He, J., Mayo, M. S., et al. Aerobic exercise improves cognition and motor function poststroke. *Neurorehabilitation and neural repair,* 2009;23:879-885.

15. Nilsson, L., Carlsson, J., Danielsson, A., Fugl-Meyer, A., Hellström, K., Kristensen, L., et al. Walking training of patients with hemiparesis at an early stage after stroke: a comparison of walking training on a treadmill with body weight support and walking training on the ground. *Clinical rehabilitation,* 2001;15:515-527.
16. Immink, M. A., Hillier, S., & Petkov, J. Randomized controlled trial of yoga for chronic poststroke hemiparesis: motor function, mental health, and quality of life outcomes. *Topics in stroke rehabilitation,* 2014;21:256-271.
17. Moore, S. A., Hallsworth, K., Jakovljevic, D. G., Blamire, A. M., He, J., Ford, G. A., et al. Effects of Community Exercise Therapy on Metabolic, Brain, Physical, and Cognitive Function Following Stroke A Randomized Controlled Pilot Trial. *Neurorehabilitation and neural repair,* 2014:1545968314562116.
18. Liu-Ambrose, T., & Eng, J. J. Exercise training and recreational activities to promote executive functions in chronic stroke: A proof-of-concept study. *Journal of Stroke and Cerebrovascular Diseases,* 2015;24:130-137.
19. Tang, A., Eng, J. J., Krassioukov, A. V., Tsang, T. S., & Liu-Ambrose, T. High-and low-intensity exercise do not improve cognitive function after stroke: A randomized controlled trial. *Journal of rehabilitation medicine,* 2016;48:841.
20. Mead, G. E., Greig, C. A., Cunningham, I., Lewis, S. J., Dinan, S., Saunders, D. H., et al. Stroke: a randomized trial of exercise or relaxation. *Journal of the American Geriatrics Society,* 2007;55:892-899.
21. Studenski, S., Duncan, P. W., Perera, S., Reker, D., Lai, S. M., & Richards, L. Daily functioning and quality of life in a randomized controlled trial of therapeutic exercise for subacute stroke survivors. *Stroke,* 2005;36:1764-1770.
22. Fang, Y., Chen, X., Li, H., Lin, J., & Huang, R. A study on additional early physiotherapy after stroke and factors affecting functional recovery. *Clinical rehabilitation,* 2003;17:608-617.
23. Özdemir, F., Birtane, M., Tabatabaei, R., Kokino, S., & Ekuklu, G. Comparing stroke rehabilitation outcomes between acute inpatient and nonintense home settings. *Archives of physical medicine and rehabilitation,* 2001;82:1375-1379.
24. Chen, X. Effect of community-based-rehabilitation on activities of daily life and cognitive function in stroke patients. *Chinese Journal of Clinical Rehabilitation,* 2006;10:4-6.
25. El-Tamawy, M. S., Abd-Allah, F., Ahmed, S. M., Darwish, M. H., & Khalifa, H. A. Aerobic exercises enhance cognitive functions and brain derived neurotrophic factor in ischemic stroke patients. *NeuroRehabilitation,* 2014;34:209-213.