Exercise in Cognition and Brain Health in Aging

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Physical activity and exercise have a biologically plausible and temporal relationship with a multitude of diseases, including coronary heart disease, atherosclerosis, stroke, type 2 diabetes, some cancers, and all-cause mortality. Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. Exercise, on the other hand, is a subset of physical activity that is planned, structured and repetitive and has the improvement or maintenance of physical fitness. Regular endurance and resistance exercise training decreases age-related morbidity and mortality, improves risk factors for chronic disease, and helps maintain independent functioning.

Keywords: exercise ; cognition ; brain structure ; brain function ; brain health

1. Brain Mechanisms Associated with Exercise

Animal research suggests that exercise positively impacts brain health [1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16]. Specifically, exercise stimulates neurogenesis [1], as evidenced by increased counts of new neurons in adult animals on an exercise regimen. Exercise is also associated with enhanced neuronal survival [2], resistance to brain injury [3][4], and increased synaptic development and plasticity [5]. Exercise promotes vascularization in the brain [6][7], is associated with increased learning [1][8], mobilizes gene expression profiles predicted to benefit brain plasticity [9], and maintains cognitive function [10]. Exercise in cognitively normal older adults is associated with evidence of lower cerebral amyloid deposition (as assessed by both brain PET PIB imaging and CSF Aβ) [12][15][17]. Exercise may modulate vascular risk factors for dementia (atherosclerosis [18], heart disease [19], stroke [20], diabetes [21][22][23][24][25][26]). Studies have specifically shown that exercise decreases systemic inflammatory markers [27] and increases levels of endogenously-produced, neuroprotective proteins such as brain-derived neurotrophic factor (BDNF) that support neuronal growth and survival [28][29]. Exercise also positively affects energy balance and glucose metabolism via actions on AMP kinase and insulin signaling, processes that have been suggested to increase Aβ trafficking and clearance [30][31][32].

2. Endurance Exercise and Cognition/Brain Structure

Endurance exercise consists of prolonged physical exertion with energy requirements supplied primarily by endurance metabolism. Public health recommendations from the World Health Organization (WHO), Centers for Disease Control (CDC), American College of Sports Medicine (ACSM), as well as others, recommend that older adults do at least 150 min of moderate-intensity endurance exercise per week (46–63% of maximal oxygen consumption capacity [VO_2max]) as part of a regular exercise regimen to maintain health and fitness [33][34][35]. Endurance exercise generally consists of walking, jogging, running, swimming, and cycling, with walking being the most practiced form of endurance exercise among older adults [36]. Endurance exercise regimens produce beneficial physiologic adaptations in older adults, including increases in cardiorespiratory fitness, metabolic adaptations with benefits to glycemic control and lipids, and reduced body fat [33].

Most studies of the effect of exercise on brain health focus on endurance exercise or physical activity, reflecting predominantly endurance-type activities. Observational studies have demonstrated that self-reported physical activity is positively associated with cognitive differences at baseline or may drive longitudinal gains or slower decline over time [37][38][39][40][41][42]. Additionally, MRI studies suggest that exercise, and associated endurance fitness levels, may attenuate age- and AD-related brain changes. Higher endurance fitness levels are associated with less age-related brain volume decline [43][44][45].

Randomized controlled trials have examined the role of endurance exercise on cognition. Though the results are mixed, the overall evidence suggests that endurance exercise in healthy, older adults may have a beneficial impact on cognitive performance [46][47][48][49][50][51], promotes brain plasticity [47][52], and attenuates hippocampal atrophy while improving visual attention and memory [47]. A meta-analysis [53] examined 18 endurance intervention studies of varying quality and found a moderate effect for combined exercise programs across all cognitive outcome measures (effect size = 0.6).

Increasing age did not appear to attenuate these benefits, with evidence that individuals aged 71 to 80 had perhaps greater benefits than younger age groups.

3. Resistance Training and Cognition

Resistance training is an important component of a complete exercise program for older adults [54]. It uses muscular contraction against resistance to mitigate the effects of aging on neuromuscular function and functional capacity [55][56][57][58][59]. It can also improve muscle strength, mass, and output [60]. Older adults retain the ability to benefit from resistance exercise to a similar extent as younger adults [33]. In addition to endurance exercise, public health recommendations suggest that older adults perform resistance training at least twice weekly to maintain function, health, and fitness [61]. Physiologic benefits include increased muscle mass and power and bone mass and strength [62]. These benefits of resistance exercise are not consistently observed with endurance exercise and are critical for maintaining function and combating age-related sarcopenia [63][64]. Bioenergetic adaptations from resistance training include increasing high-energy phosphate (ATP and creatine phosphate) availability and increasing mitochondrial density and oxidative capacity [33].

There are fewer large, well-designed, randomized controlled trials assessing resistance training on brain health outcomes, although the available literature has proved promising [54]. Randomized clinical trials have examined the effects of resistance training on cognitive function and have found that participation results in improvements in executive function [65], memory [66], verbal fluency [66], and global cognition [66][67][68]. However, results have been inconsistent in showing that resistance training can prevent cognitive decline and AD [69][70]. In a study of 62 older adults randomized to resistance training or a control group, resistance training (both high and low-intensity groups) was associated with improved working memory [71]. In another study of 155 older women [72], one year of resistance training was associated with the benefit of selective attention and conflict resolution performance compared to those randomized to the control group. Paradoxically, resistance training was associated with a 0.3–0.4% decline in whole brain volume compared to controls, though this effect has yet to be replicated. A recent systematic review showed that resistance training positively affected older adults' executive cognitive ability and global cognitive function. It also had a weak but positive impact on memory. There was no significant improvement in attention. The authors also concluded that tri-weekly resistance training has a better effect on general cognitive ability than biweekly [73].

4. Combined Exercise and Cognition

Despite the widespread recommendation for combined exercise, no studies have directly compared the effects of aerobic vs. resistance or combined training on cognition. However, studies have assessed the differential impact of these exercise modalities on body weight and composition [74][75][76], insulin resistance [76][77][78][79][80], inflammation [81], and functional limitations [77][78][79]. The results of these studies suggest that combining aerobic and resistance training is optimal for effects on insulin resistance [77][79] and physical function [79] but does not offer advantages for altering adiposity [82].

Resistance and endurance training elicit physiologic adaptations to cardiovascular, muscular, bioenergetic, and neuroendocrine systems [71][83][84]. Resistance training relies preferentially on anaerobic metabolism during the short but intense training bouts. This improves muscle strength and quality while increasing high energy phosphate (ATP and creatine phosphate) availability, mitochondrial density, and oxidative capacity [33], effects that are generally not observed with aerobic exercise. In contrast, aerobic exercise training increases the capacity of muscle to generate energy through increased myoglobin content in muscle and increased efficiency of oxygen extraction and carbohydrate oxidation. Despite some concern that combined aerobic and resistance training will result in an "interference effect" where the development of strength during the same period might influence the development of aerobic capacity and vice versa, several studies have found no evidence of this possible effect [81][84].

The field has not directly assessed whether public health recommendations provide independent or combined effects on cognition in older adults. Conclusions from prior work are limited by design. Specifically, there is limited literature comparing resistance or combined exercise to a non-exercise control [72][85][86][87][88][89][90][91][92]. There is also high variability in endurance exercise types: walking, circuit training, running [93], swimming/aqua endurances [93], etc. [48][69][94]. There is also variability in resistance training parameters, including modality, weekly sessions, and progression [72][86][88][89][95][96]. Finally, there is an ongoing trial to test the independent and combined effects of resistance and endurance training on brain health and physiology in old adults [97].

5. Other Forms of Exercise

Yoga. Yoga is a popular complementary health approach and form of physical activity practiced by adults and older adults. Yoga combines physical postures, rhythmic breathing, and meditative practice to offer those who do it a unique holistic mind-body experience. A recent systematic review and meta-analysis evaluated the effect of yoga-related mind-body therapies on cognitive function in older adults. For example, Bhattacharyya, Andel and Small [98] found 12 studies and 11 randomized controlled trials. The studies involved various yoga practices with a common focus on meditative postural exercises. They revealed significant beneficial effects on memory (Cohen's d = 0.38), executive function (Cohen's d = 0.40), and attention and processing speed (Cohen's d = 0.33).

Similarly, Gothe et al. [99] reviewed 11 studies examining the effects of yoga practice on brain structures, function and cerebral blood flow. The studies demonstrate a positive effect of yoga practice on the structure and/or function of the hippocampus, amygdala, prefrontal cortex, cingulate cortex, and brain networks, including the default mode network. However, there is variability in the neuroimaging findings that partially reflects different yoga styles and approaches and sample size limitations [100]. Overall, the existing body of research offers early evidence that behavioral interventions like yoga may hold promise to mitigate age-related and neurodegenerative declines, as many of the regions identified are known to demonstrate significant age-related atrophy.

Tai Chi. Tai Chi is another popular complementary health approach and form of physical activity practiced by adults and older adults. Tai Chi is a traditional Chinese martial art that includes a series of slow, gentle movements, physical postures, a meditative state of mind and controlled breathing. Research surrounding this mind-body exercise suggests it may impact older adults' cognition and brain function. For example, Liu et al. [101] recently completed a systematic review and meta-analysis to evaluate the impact of Tai Chi on cognitive function. The authors found Thirty-three randomized controlled trials and that tai chi could progress global cognition when assessed in middle-aged and elderly patients suffering from cognitive and executive function impairment. Similarly, a recent literature review to evaluate the effect of tai chi practice on brain structure and neurobehavior changes found the increased volume of cortical grey matter, improved neural activity and homogeneity, and increased neural connectivity in different brain regions, including the frontal, temporal, and occipital lobes, cerebellum, and thalamus. Furthermore, the longer one practices tai chi, these brain regions are altered [102].

High-Intensity Interval Training (HIIT). High-intensity interval training (HIIT) has emerged as a time-efficient strategy to improve health-related fitness compared to traditional training methods. HIIT is an interval exercise that incorporates several rounds of alternating exercises at a high intensity (i.e., 80% of heart rate max) followed by a short period of lower-intensity movements (i.e., recovery). Leahy et al. [103] recently conducted a review to explore the impact of HIIT training on cognitive function in children and adolescents. A total of 22 studies were included in the review. Acute studies showed small to moderate effects for executive function (standardized mean difference [SMD], 0.50, 95% confidence interval [CI], 0.03–0.98; p = 0.038) and affect (SMD, 0.33; 95% CI, 0.05–0.62; p = 0.020), respectively. Chronic studies also showed a small significant effect on executive function (SMD, 0.31; 95% CI, 0.15–0.76, p < 0.001), well-being (SMD, 0.22; 95% CI, 0.02–0.41; p = 0.029), and ill-being (SMD, −0.35; 95% CI, −0.68 to −0.03; p = 0.035). The review provides preliminary evidence suggesting that participation in HIIT can improve cognitive function and mental health in children and adolescents. Recent evidence also supports the contention that HIIT elicits higher fat oxidation in skeletal muscle than other forms of exercise and is an excellent stimulus to increase maximal oxygen uptake (VO_2 max). HIIT also seems to be an excellent stimulus to enhance BDNF (a protein synthesized in neurons that participates in cognitive processes as measured at the hippocampus) [104]. In addition, HIIT should be included in stroke rehabilitation for its beneficial effects on neuroplasticity processes [105]. HIIT has also enhanced cognitive flexibility in older adults [106]. The findings in older mice suggest HIIT can improve physical function and reduce frailty, decreasing the risk of disability and loss of independence with age [107][108]. However, more research on HIIT is needed before strong conclusions can be drawn.

References

1. van Praag, H.; Christie, B.R.; Sejnowski, T.J.; Gage, F.H. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc. Natl. Acad. Sci. USA 1999, 96, 13427–13431.
2. Barde, Y.A. Neurotrophins: A family of proteins supporting the survival of neurons. Prog. Clin. Biol. Res. 1994, 390, 45–56.
3. Stummer, W.; Weber, K.; Tranmer, B.; Baethmann, A.; Kempski, O. Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia. Stroke J. Cereb. Circ. 1994, 25, 1862–1869.

4. Carro, E.; Trejo, J.L.; Busiguina, S.; Torres-Aleman, I. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J. Neurosci. J. Soc. Neurosci. 2001, 21, 5678–5684.
5. Lu, B.; Chow, A. Neurotrophins and hippocampal synaptic transmission and plasticity. J. Neurosci. Res. 1999, 58, 76–87.
6. Black, J.E.; Isaacs, K.R.; Anderson, B.J.; Alcantara, A.A.; Greenough, W.T. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc. Natl. Acad. Sci. USA 1990, 87, 5568–5572.
7. Isaacs, K.R.; Anderson, B.J.; Alcantara, A.A.; Black, J.E.; Greenough, W.T. Exercise and the brain: Angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. J. Cereb. Blood Flow Metab. J. Int. Soc. Cereb. Blood Flow Metab. 1992, 12, 110–119.
8. Young, D.; Lawlor, P.A.; Leone, P.; Dragunow, M.; During, M.J. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. Nat. Med. 1999, 5, 448–453.
9. Cotman, C.W.; Berchtold, N.C. Exercise: A behavioral intervention to enhance brain health and plasticity. Trends Neurosci. 2002, 25, 295–301.
10. Escorihuela, R.M.; Tobena, A.; Fernandez-Teruel, A. Environmental enrichment and postnatal handling prevent spatial learning deficits in aged hypoemotional (Roman high-avoidance) and hyperemotional (Roman low-avoidance) rats. Learn. Mem. 1995, 2, 40–48.
11. Adlard, P.A.; Perreau, V.M.; Pop, V.; Cotman, C.W. Voluntary Exercise Decreases Amyloid Load in a Transgenic Model of Alzheimer’s Disease. J. Neurosci. 2005, 25, 4217–4221.
12. Head, D.; Bugg, J.M.; Goate, A.M.; Fagan, A.M.; Mintun, M.A.; Benzinger, T.; Holtzman, D.M.; Morris, J.C. Exercise Engagement as a Moderator of the Effects of APOE Genotype on Amyloid Deposition. Arch. Neurol. 2012, 69, 636–643.
13. Nation, D.A.; Hong, S.; Jak, A.J.; Delano-Wood, L.; Mills, P.J.; Bondi, M.W.; Dimsdale, J.E. Stress, exercise, and Alzheimer’s disease: A neurovascular pathway. Med. Hypotheses 2011, 76, 847–854.
14. Radak, Z.; Hart, N.; Sarga, L.; Koltai, E.; Atalay, M.; Ohno, H.; Boldogh, I. Exercise plays a preventive role against Alzheimer’s disease. J. Alzheimers Dis. 2010, 20, 777–783.
15. Liang, K.Y.; Mintun, M.A.; Fagan, A.M.; Goate, A.M.; Bugg, J.M.; Holtzman, D.M.; Morris, J.C.; Head, D. Exercise and Alzheimer’s disease biomarkers in cognitively normal older adults. Ann. Neurol. 2010, 68, 311–318.
16. Brown, B.M.; Peiffer, J.J.; Taddei, K.; Lui, J.K.; Laws, S.M.; Gupta, V.B.; Taddei, T.; Ward, V.K.; Rodrigues, M.A.; Burnham, S.; et al. Physical activity and amyloid-β plasma and brain levels: Results from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing. Mol. Psychiatry 2013, 18, 875–881.
17. Brown, B.M.; Peiffer, J.J.; Martins, R.N. Multiple effects of physical activity on molecular and cognitive signs of brain aging: Can exercise slow neurodegeneration and delay Alzheimer’s disease? Mol. Psychiatry 2013, 18, 864–874.
18. Lakka, T.A.; Laukkanen, J.A.; Rauramaa, R.; Salonen, R.; Lakka, H.M.; Kaplan, G.A.; Salonen, J.T. Cardiorespiratory Fitness and the Progression of Carotid Atherosclerosis in Middle-Aged Men. Ann. Intern. Med. 2001, 134, 12–20.
19. Blair, S.N.; Kampert, J.B.; Kohl, H.W., III; Barlow, C.E.; Macera, C.A.; Paffenbarger, R.S., Jr.; Gibbons, L.W. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA J. Am. Med. Assoc. 1996, 276, 205–210.
20. Kurl, S.; Laukkanen, J.A.; Rauramaa, R.; Lakka, T.A.; Sivenius, J.; Salonen, J.T. Cardiorespiratory Fitness and the Risk for Stroke in Men. Arch. Intern. Med. 2003, 163, 1682–1688.
21. Seals, D.R.; Hagberg, J.M.; Hurley, B.F.; Ehsani, A.A.; Holloszy, J.O. Effects of endurance training on glucose tolerance and plasma lipid levels in older men and women. JAMA J. Am. Med. Assoc. 1984, 252, 645–649.
22. Hughes, V.A.; Fiatarone, M.A.; Fielding, R.A.; Kahn, B.B.; Ferrara, C.M.; Shepherd, P.; Fisher, E.C.; Wolfe, R.R.; Elahi, D.; Evans, W.J. Exercise increases muscle GLUT-4 levels and insulin action in subjects with impaired glucose tolerance. Am. J. Physiol. 1993, 264, E855–E862.
23. Kirwan, J.P.; Kohrt, W.M.; Wojta, D.M.; Bourey, R.E.; Holloszy, J.O. Endurance exercise training reduces glucose-stimulated insulin levels in 60- to 70-year-old men and women. J. Gerontol. 1993, 48, M84–M90.
24. Cox, J.H.; Cortright, R.N.; Dohm, G.L.; Houmard, J.A. Effect of aging on response to exercise training in humans: Skeletal muscle GLUT-4 and insulin sensitivity. J. Appl. Physiol. 1999, 86, 2019–2025.
25. Kahn, S.E.; Larson, V.G.; Beard, J.C.; Cain, K.C.; Fellingham, G.W.; Schwartz, R.S.; Veith, R.C.; Stratton, J.R.; Cerqueira, M.D.; Abrass, I.B. Effect of exercise on insulin action, glucose tolerance, and insulin secretion in aging. Am. J. Physiol. 1990, 258, E937–E943.

26. Houmard, J.A.; Tyndall, G.L.; Midyette, J.B.; Hickey, M.S.; Dolan, P.L.; Gavigan, K.E.; Weidner, M.L.; Dohm, G.L. Effect of reduced training and training cessation on insulin action and muscle GLUT-4. J. Appl. Physiol. 1996, 81, 1162–1168.

27. Ford, E.S. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology 2002, 13, 561–568.

28. Nichol, K.; Deeny, S.P.; Seif, J.; Camaclang, K.; Cotman, C.W. Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. Alzheimers Dement. 2009, 5, 287–294.

29. García-Mesa, Y.; López-Ramos, J.C.; Giménez-Llort, L.; Revilla, S.; Guerra, R.; Gruart, A.; Laferla, F.M.; Cristòfol, R.; Delgado-García, J.M.; Sanfeliu, C. Physical exercise protects against Alzheimer’s disease in 3xTg-AD mice. J. Alzheimers Dis. 2011, 24, 421–454.

30. Vingtdeux, V.; Chandakkar, P.; Zhao, H.; d’Abramo, C.; Davies, P.; Marambaud, P. Novel synthetic small-molecule activators of AMPK as enhancers of autophagy and amyloid-β peptide degradation. FASEB J. 2011, 25, 219–231.

31. De Felice, F.G.; Vieira, M.N.; Bomfim, T.R.; Decker, H.; Velasco, P.T.; Lambert, M.P.; Viola, K.L.; Zhao, W.Q.; Ferreira, S.T.; Klein, W.L. Protection of synapses against Alzheimer’s-linked toxins: Insulin signaling prevents the pathogenic binding of Abeta oligomers. Proc. Natl. Acad. Sci. USA 2009, 106, 1971–1976.

32. Gasparini, L.; Gouras, G.K.; Wang, R.; Gross, R.S.; Beal, M.F.; Greengard, P.; Xu, H. Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. J. Neurosci. 2001, 21, 2561–2570.

33. Chodzko-Zajko, W.J.; Proctor, D.N.; Fiatarone Singh, M.A.; Minson, C.T.; Nigg, C.R.; Salem, G.J.; Skinner, J.S. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med. Sci. Sports Exerc. 2009, 41, 1510–1530.

34. 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.; et al. 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. 2011, 59, 704–716.

35. Garber, C.E.; Blissmer, B.; Deschenes, M.R.; Franklin, B.A.; Lamonte, M.J.; Lee, I.M.; Nieman, D.C.; Swain, D.P. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. Med. Sci. Sports Exerc. 2011, 43, 1334–1359.

36. Gao, Y.; Zhu, W. Identifying group-sensitive physical activities: A differential item functioning analysis of NHANES data. Med. Sci. Sports Exerc. 2011, 43, 922–929.

37. Yaffe, K.; Barnes, D.; Nevitt, M.; Lui, L.Y.; Covinsky, K. A Prospective Study of Physical Activity and Cognitive Decline in Elderly Women: Women Who Walk. Arch. Intern. Med. 2001, 161, 1703–1708.

38. Pignatti, F.; Rozzini, R.; Trabucchi, M.; Yaffe, K. Physical Activity and Cognitive Decline in Elderly Persons. Arch. Intern. Med. 2002, 162, 361–362.

39. Laurin, D.; Verreault, R.; Lindsay, J.; MacPherson, K.; Rockwood, K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch. Neurol. 2001, 58, 498–504.

40. Albert, M.S.; Jones, K.; Savage, C.R.; Berkman, L.; Seeman, T.; Blazer, D.; Rowe, J.W. Predictors of cognitive change in older persons: MacArthur studies of successful aging. Psychol. Aging 1995, 10, 578–589.

41. Larson, E.B.; Wang, L.; Bowen, J.D.; McCormick, W.C.; Teri, L.; Crane, P.; Kukull, W. Exercise Is Associated with Reduced Risk for Incident Dementia among Persons 65 Years of Age and Older. Ann. Intern. Med. 2006, 144, 73–81.

42. Buchman, A.S.; Boyle, P.A.; Yu, L.; Shah, R.C.; Wilson, R.S.; Bennett, D.A. Total daily physical activity and the risk of AD and cognitive decline in older adults. Neurology 2012, 78, 1323–1329.

43. Colcombe, S.J.; Erickson, K.I.; Raz, N.; Webb, A.G.; Cohen, N.J.; McAuley, E.; Kramer, A.F. Aerobic Fitness Reduces Brain Tissue Loss in Aging Humans. J. Gerontol. Ser. A Biol. Sci. Med. Sci. 2003, 58, M176–M180.

44. Burns, J.M.; Mayo, M.S.; Anderson, H.S.; Smith, H.; Donnelly, J.E. Cardiorespiratory Fitness in Early-Stage Alzheimer’s Disease. Alzheimer Dis. Assoc. Disord. 2008, 22, 39–46.

45. Honea, R.A.; Thomas, G.P.; Harsha, A.; Anderson, H.S.; Donnelly, J.E.; Brooks, W.M.; Burns, J.M. Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer’s Disease. Alzheimer Dis. Assoc. Disord. 2009, 23, 188–197.

46. Kramer, A.F.; Hahn, S.; Cohen, N.J.; Banich, M.T.; McAuley, E.; Harrison, C.R.; Chason, J.; Vakil, E.; Bardell, L.; Boileau, R.A.; et al. Ageing, fitness and neurocognitive function. Nature 1999, 400, 418–419.

47. Erickson, K.I.; Voss, M.W.; Prakash, R.S.; Basak, C.; Szabo, A.; Chaddock, L.; Kim, J.S.; Heo, S.; Alves, H.; White, S.M.; et al. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. USA 2011, 108, 3017–3022.

48. Dustman, R.E.; Ruhling, R.O.; Russell, E.M.; Shearer, D.E.; Bonekat, H.W.; Shigeoka, J.W.; Wood, J.S.; Bradford, D.C. Aerobic Exercise Training and Improved Neuropsychological Function of Older Individuals. Neurobiol. Aging 1984, 5, 35–42.

49. Hassmen, P.; Koivula, N. Mood, physical working capacity and cognitive performance in the elderly as related to physical activity. Aging-Clin. Exp. Res. 1997, 9, 136–142.

50. Williams, P.; Lord, S.R. Effects of group exercise on cognitive functioning and mood in older women. Aust. N. Z. J. Public Health 1997, 21, 45–52.

51. Hill, R.D.; Storandt, M.; Malley, M. The impact of long-term exercise training on psychological function in older adults. J. Gerontol. 1993, 48, 12–17.

52. Colcombe, S.J.; Kramer, A.F.; Erickson, K.I.; Scalf, P.; McAuley, E.; Cohen, N.J.; Webb, A.; Jerome, G.J.; Marquez, D.X.; Elavsky, S. Cardiovascular fitness, cortical plasticity, and aging. Proc. Natl. Acad. Sci. USA 2004, 101, 3316–3321.

53. Heyn, P.C.; Johnson, K.E.; Kramer, A.F. Endurance and strength training outcomes on cognitively impaired and cognitively intact older adults: A meta-analysis. J. Nutr. Health Aging 2008, 12, 401–409.

54. Fragala, M.S.; Cadore, E.L.; Dorgo, S.; Izquierdo, M.; Kraemer, W.J.; Peterson, M.D.; Ryan, E.D. Resistance Training for Older Adults: Position Statement from the National Strength and Conditioning Association. J. Strength Cond. Res. 2019, 33, 2019–2052.

55. Borde, R.; Hortobágyi, T.; Granacher, U. Dose-Response Relationships of Resistance Training in Healthy Old Adults: A Systematic Review and Meta-Analysis. Sports Med. 2015, 45, 1693–1720.

56. Cadore, E.L.; Casas-Herrero, A.; Zambom-Ferraresi, F.; Idoate, F.; Millor, N.; Gómez, M.; Rodriguez-Mañas, L.; Izquierdo, M. Multicomponent exercises including muscle power training enhance muscle mass, power output, and functional outcomes in institutionalized frail nonagenarians. Age 2014, 36, 773–785.

57. Cadore, E.L.; Izquierdo, M.; Pinto, S.S.; Alberton, C.L.; Pinto, R.S.; Baroni, B.M.; Vaz, M.A.; Lanferdini, F.J.; Radaelli, R.; González-Izal, M.; et al. Neuromuscular adaptations to concurrent training in the elderly: Effects of intrasession exercise sequence. Age 2013, 35, 891–903.

58. Peterson, M.D.; Rhea, M.R.; Sen, A.; Gordon, P.M. Resistance exercise for muscular strength in older adults: A meta-analysis. Ageing Res. Rev. 2010, 9, 226–237.

59. Steib, S.; Schoene, D.; Pfeifer, K. Dose-response relationship of resistance training in older adults: A meta-analysis. Med. Sci. Sports Exerc. 2010, 42, 902–914.

60. Häkkinen, K.; Newton, R.U.; Gordon, S.E.; McCormick, M.; Volek, J.S.; Nindl, B.C.; Gotshalk, L.A.; Campbell, W.W.; Evans, W.J.; Häkkinen, A.; et al. Changes in muscle morphology, electromyographic activity, and force production characteristics during progressive strength training in young and older men. J. Gerontol. A Biol. Sci. Med. Sci. 1998, 53, B415–B423.

61. Elsawy, B.; Higgins, K.E. Physical activity guidelines for older adults. Am. Fam. Physician 2010, 81, 55–59.

62. Dalsky, G.P.; Stocke, K.S.; Ehsani, A.A.; Slatopolsky, E.; Lee, W.C.; Birge, S.J., Jr. Weight-bearing exercise training and lumbar bone mineral content in postmenopausal women. Ann. Intern. Med. 1988, 108, 824–828.

63. Borst, S.E.; De Hoyos, D.V.; Garzarella, L.; Vincent, K.; Pollock, B.H.; Lowenthal, D.T.; Pollock, M.L. Effects of resistance training on insulin-like growth factor-I and IGF binding proteins. Med. Sci. Sports Exerc. 2001, 33, 648–653.

64. Liu, C.J.; Latham, N.K. Progressive resistance strength training for improving physical function in older adults. Cochrane Database Syst. Rev. 2009, 2009, Cd002759.

65. Liu-Ambrose, T.; Donaldson, M.G.; Ahamed, Y.; Graf, P.; Cook, W.L.; Close, J.; Lord, S.R.; Khan, K.M. Otago home-based strength and balance retraining improves executive functioning in older fallers: A randomized controlled trial. J. Am. Geriatr. Soc. 2008, 56, 1821–1830.

66. Suzuki, T.; Shimada, H.; Makizako, H.; Doi, T.; Yoshida, D.; Tsutsumimoto, K.; Anan, Y.; Uemura, K.; Lee, S.; Park, H. Effects of multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: A randomized controlled trial. BMC Neurol. 2012, 12, 128.

67. Fiatarone Singh, M.A.; Gates, N.; Saigal, N.; Wilson, G.C.; Meiklejohn, J.; Brodaty, H.; Wen, W.; Singh, N.; Baune, B.T.; Suo, C.; et al. 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. 2014, 15, 873–880.

68. Tarazona-Santabalbina, F.J.; Gómez-Cabrera, M.C.; Pérez-Ros, P.; Martínez-Arnau, F.M.; Cabo, H.; Tsaparas, K.; Salvador-Pascual, A.; Rodriguez-Mañas, L.; Viña, J. A Multicomponent Exercise Intervention that Reverses Frailty and Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail Elderly: A Randomized Clinical Trial. J. Am. Med. Dir. Assoc. 2016, 17, 426–433.
69. Colcombe, S.; Kramer, A.F. Fitness effects on the cognitive function of older adults: A meta-analytic study. Psychol. Sci. 2003, 14, 125–130.
70. Kane, R.L.; Butler, M.; Fink, H.A.; Brasure, M.; Davila, H.; Desai, P.; Jutkowitz, E.; McCreedy, E.; Nelson, V.A.; McCarten, J.R.; et al. AHRQ Comparative Effectiveness Reviews. In Interventions to Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia; Agency for Healthcare Research and Quality: Rockville, MD, USA, 2017.
71. Cassilhas, R.C.; Viana, V.A.; Grassmann, V.; Santos, R.T.; Santos, R.F.; Tufik, S.; Mello, M.T. The impact of resistance exercise on the cognitive function of the elderly. Med. Sci. Sports Exerc. 2007, 39, 1401–1407.
72. Liu-Ambrose, T.; Nagamatsu, L.S.; Graf, P.; Beattie, B.L.; Ashe, M.C.; Handy, T.C. Resistance training and executive functions: A 12-month randomized controlled trial. Arch. Intern. Med. 2010, 170, 170–178.
73. Li, Z.; Peng, X.; Xiang, W.; Han, J.; Li, K. The effect of resistance training on cognitive function in the older adults: A systematic review of randomized clinical trials. Aging Clin. Exp. Res. 2018, 30, 1259–1273.
74. Willis, L.H.; Slentz, C.A.; Bateman, L.A.; Shields, A.T.; Piner, L.W.; Bales, C.W.; Houmard, J.A.; Kraus, W.E. Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. J. Appl. Physiol. 2012, 113, 1831–1837.
75. Slentz, C.A.; Bateman, L.A.; Willis, L.H.; Shields, A.T.; Tanner, C.J.; Piner, L.W.; Hawk, V.H.; Muehlbauer, M.J.; Samsa, G.P.; Nelson, R.C.; et al. Effects of aerobic vs. resistance training on visceral and liver fat stores, liver enzymes, and insulin resistance by HOMA in overweight adults from STRRIDE AT/RT. Am. J. Physiol. Endocrinol. Metab. 2011, 301, E1033–E1039.
76. Donges, C.E.; Duffield, R.; Guelfi, K.J.; Smith, G.C.; Adams, D.R.; Edge, J.A. Comparative effects of single-mode vs. duration-matched concurrent exercise training on body composition, low-grade inflammation, and glucose regulation in sedentary, overweight, middle-aged men. Appl. Physiol. Nutr. Metab. 2013, 38, 779–788.
77. Church, T.S.; Blair, S.N.; Cocreham, S.; Johannsen, N.; Johnson, W.; Kramer, K.; Mikus, C.R.; Myers, V.; Nauta, M.; Rodarte, R.Q.; et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: A randomized controlled trial. JAMA 2010, 304, 2253–2262.
78. Sigal, R.J.; Kenny, G.P.; Boulé, N.G.; Wells, G.A.; Prud'homme, D.; Fortier, M.; Reid, R.D.; Tulloch, H.; Coyle, D.; Phillips, P.; et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: A randomized trial. Ann. Intern. Med. 2007, 147, 357–369.
79. Davidson, L.E.; Hudson, R.; Kilpatrick, K.; Kuk, J.L.; McMillan, K.; Janiszewski, P.M.; Lee, S.; Lam, M.; Ross, R. Effects of exercise modality on insulin resistance and functional limitation in older adults: A randomized controlled trial. Arch. Intern. Med. 2009, 169, 122–131.
80. Sillanpää, E.; Häkkinen, A.; Punnonen, K.; Häkkinen, K.; Laaksonen, D.E. Effects of strength and endurance training on metabolic risk factors in healthy 40-65-year-old men. Scand. J. Med. Sci. Sports 2009, 19, 885–895.
81. Libardi, C.A.; De Souza, G.V.; Cavaglieri, C.R.; Madruga, V.A.; Chacon-Mikahil, M.P. Effect of resistance, endurance, and concurrent training on TNF-α, IL-6, and CRP. Med. Sci. Sports Exerc. 2012, 44, 50–56.
82. Ismail, I.; Keating, S.E.; Baker, M.K.; Johnson, N.A. A systematic review and meta-analysis of the effect of aerobic vs. resistance exercise training on visceral fat. Obes. Rev. 2012, 13, 68–91.
83. Liu-Ambrose, T.; Donaldson, M.G. Exercise and cognition in older adults: Is there a role for resistance training programmes? Br. J. Sports Med. 2009, 43, 25–27.
84. Glowacki, S.P.; Martin, S.E.; Maurer, A.; Baek, W.; Green, J.S.; Crouse, S.F. Effects of resistance, endurance, and concurrent exercise on training outcomes in men. Med. Sci. Sports Exerc. 2004, 36, 2119–2127.
85. Ansai, J.H.; Rebelatto, J.R. Effect of two physical exercise protocols on cognition and depressive symptoms in oldest-old people: A randomized controlled trial. Geriatr. Gerontol. Int. 2015, 15, 1127–1134.
86. Coetsee, C.; Terblanche, E. The effect of three different exercise training modalities on cognitive and physical function in a healthy older population. Eur. Rev. Aging Phys. Act. 2017, 14, 13.

87. Iuliano, E.; di Cagno, A.; Aquino, G.; Fiorilli, G.; Mignogna, P.; Calcagno, G.; Di Costanzo, A. Effects of different types of physical activity on the cognitive functions and attention in older people: A randomized controlled study. Exp. Gerontol. 2015, 70, 105–110.
88. Kimura, K.; Obuchi, S.; Arai, T.; Nagasawa, H.; Shiba, Y.; Watanabe, S.; Kojima, M. The influence of short-term strength training on health-related quality of life and executive cognitive function. J. Physiol. Anthropol. 2010, 29, 95–101.
89. Liu-Ambrose, T.; Nagamatsu, L.S.; Voss, M.W.; Khan, K.M.; Handy, T.C. Resistance training and functional plasticity of the aging brain: A 12-month randomized controlled trial. Neurobiol. Aging 2012, 33, 1690–1698.
90. Nouchi, R.; Taki, Y.; Takeuchi, H.; Sekiguchi, A.; Hashizume, H.; Nozawa, T.; Nouchi, H.; Kawashima, R. Four weeks of combination exercise training improved executive functions, episodic memory, and processing speed in healthy elderly people: Evidence from a randomized controlled trial. Age 2014, 36, 787–799.
91. Shatil, E. 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. 2013, 5, 8.
92. Vedovelli, K.; Giacobbo, B.L.; Corrêa, M.S.; Wieck, A.; Argimon, I.I.d.L.; Bromberg, E. Multimodal physical activity increases brain-derived neurotrophic factor levels and improves cognition in institutionalized older women. GeroScience 2017, 39, 407–417.
93. Albinet, C.T.; Abou-Dest, A.; André, N.; Audiffren, M. Executive functions improvement following a 5-month aquaerobics program in older adults: Role of cardiac vagal control in inhibition performance. Biol Psychol 2016, 115, 69–77.
94. Ruscheweyh, R.; Willemer, C.; Krüger, K.; Duning, T.; Warnecke, T.; Sommer, J.; Völker, K.; Ho, H.V.; Mooren, F.; Knecht, S.; et al. Physical activity and memory functions: An interventional study. Neurobiol. Aging 2011, 32, 1304–1319.
95. Best, J.R.; Chiu, B.K.; Liang Hsu, C.; Nagamatsu, L.S.; Liu-Ambrose, T. Long-Term Effects of Resistance Exercise Training on Cognition and Brain Volume in Older Women: Results from a Randomized Controlled Trial. J. Int. Neuropsychol. Soc. 2015, 21, 745–756.
96. Dao, E.; Hsiung, G.-Y.R.; Liu-Ambrose, T. The role of exercise in mitigating subcortical ischemic vascular cognitive impairment. J. Neurochem. 2018, 144, 582–594.
97. Szabo-Reed, A.; Clutton, J.; White, S.; Van Sciver, A.; White, D.; Morris, J.; Martin, L.; Lepping, R.; Shaw, A.; Puchalt, J.P.; et al. COMbined Exercise Trial (COMET) to improve cognition in older adults: Rationale and methods. Contemp. Clin. Trials 2022, 118, 106805.
98. Bhattacharyya, K.K.; Andel, R.; Small, B.J. Effects of yoga-related mind-body therapies on cognitive function in older adults: A systematic review with meta-analysis. Arch. Gerontol. Geriatr. 2021, 93, 104319.
99. Gothe, N.P.; Khan, I.; Hayes, J.; Erlenbach, E.; Damoiseaux, J.S. Yoga Effects on Brain Health: A Systematic Review of the Current Literature. Brain Plast. 2019, 5, 105–122.
100. van Aalst, J.; Ceccarini, J.; Demyttenaere, K.; Sunaert, S.; Van Laere, K. What Has Neuroimaging Taught Us on the Neurobiology of Yoga? A Review. Front. Integr. Neurosci. 2020, 14, 34.
101. Liu, F.; Chen, X.; Nie, P.; Lin, S.; Guo, J.; Chen, J.; Yu, L. Can Tai Chi Improve Cognitive Function? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J. Altern. Complement. Med. 2021, 27, 1070–1083.
102. Howe, L.; Yasser, S.; Eric, A.; Hao, L. Brain Structural Response and Neurobehavior Changes in the Elderly after Tai Chi Practice—A Literature Review. Tradit. Integr. Med. 2023, 2023, 86–96.
103. Leahy, A.A.; Mavilidi, M.F.; Smith, J.J.; Hillman, C.H.; Eather, N.; Barker, D.; Lubans, D.R. Review of high-intensity interval training for cognitive and mental health in youth. Med. Sci. Sport. Exerc. 2020, 52, 2224–2234.
104. Jiménez-Maldonado, A.; Rentería, I.; García-Suárez, P.C.; Moncada-Jiménez, J.; Freire-Royes, L.F. The Impact of High-Intensity Interval Training on Brain Derived Neurotrophic Factor in Brain: A Mini-Review. Front. Neurosci. 2018, 12, 839.
105. Hugues, N.; Pellegrino, C.; Rivera, C.; Berton, E.; Pin-Barre, C.; Laurin, J. Is High-Intensity Interval Training Suitable to Promote Neuroplasticity and Cognitive Functions after Stroke? Int. J. Mol. Sci. 2021, 22, 3003.
106. Mekari, S.; Neyedli, H.F.; Fraser, S.; O'Brien, M.W.; Martins, R.; Evans, K.; Earle, M.; Aucoin, R.; Chiekwe, J.; Hollohan, Q.; et al. High-Intensity Interval Training Improves Cognitive Flexibility in Older Adults. Brain Sci. 2020, 10, 796.
107. Seldeen, K.L.; Lasky, G.; Leiker, M.M.; Pang, M.; Personius, K.E.; Troen, B.R. High Intensity Interval Training Improves Physical Performance and Frailty in Aged Mice. J. Gerontol. Ser. A 2017, 73, 429–437.
108. Seldeen, K.L.; Redae, Y.Z.; Thiyagarajan, R.; Berman, R.N.; Leiker, M.M.; Troen, B.R. High intensity interval training improves physical performance in aged female mice: A comparison of mouse frailty assessment tools. Mech. Ageing Dev. 2019, 180, 49–62.