REVIEW

Exercise for Brain Health: An Investigation into the Underlying Mechanisms Guided by Dose

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Abstract

There is a strong link between the practice of regular physical exercise and maintenance of cognitive brain health. Animal and human studies have shown that exercise exerts positive effects on cognition through a variety of mechanisms, such as changes in brain volume and connectivity, cerebral perfusion, synaptic plasticity, neurogenesis, and regulation of trophic factors. However, much of this data has been conducted in young humans and animals, raising questions regarding the generalizability of these findings to aging adults. Furthermore, it is not clear at which doses these effects might take place, and if effects would differ with varying exercise modes (such as aerobic, resistance training, combinations, or other). The purpose of this review is to summarize the evidence on the effects of exercise interventions on various mechanisms believed to support cognitive improvements: cerebral perfusion, synaptic neuroplasticity, brain volume and connectivity, neurogenesis, and regulation of trophic factors. We synthesized the findings according to exposure to exercise (short- [1 day-16 weeks], medium- [24-40 weeks], and long-term exercise [52 weeks and beyond]) and have limited our discussion of dose effects to studies in aging adults and aged animals (when human data was not available).

Key Words Physical exercise · cognitive brain health · exercise dose · aging brain · older adults · physiological mechanisms

Introduction

Adding to the well-established benefits of physical exercise for decreasing mortality and morbidity and improving physical function, there has been a wealth of evidence generated in recent years to support a link between the practice of regular exercise and cognitive brain health in older adults. The wealth of data that supports improved cognition following the practice of regular exercise is particularly relevant given that older adults (i.e., individuals aged 65 and older) represent the fastest growing demographic worldwide. In approximately 10 years, the older population will outnumber children for the first time in United States history, reaching 20% of the overall population [1]. The maintenance of cognitive brain health is consistently cited as the top health-related concern for aging adults and a key factor for the maintenance of maximum autonomy and independence [2].

Age-related cognitive impairment mostly affects the speed of processing of mental tasks and tasks that require memory and executive functioning (which covers a broad spectrum of abilities, but in short, refers to tasks that require organizing, planning, reasoning, and problem solving) [2]. These age-related cognitive impairments largely reflect brain atrophy, most pronounced in the frontal lobe, resulting in decreased gray matter in critical areas involved in higher-order cognitive processes, such as the prefrontal, temporal lobes, and hippocampus [3, 4]. In addition, impaired conduction of neural signals arising from lesions to white matter tracts [5] and an

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unfavorable neurochemical environment caused by decreased neurotrophins and trophic factors [6], neurotransmitter imbalances [7, 8], and deposition of toxic protein aggregates such as amyloid beta (Aβ) all contribute to increased free radicals and impaired neuronal function [9].

It is encouraging that adopting a lifestyle change in the form of the practice of regular exercise constitutes an opportunity for action to promote healthy cognitive aging, but in order for exercise to be used as a "medicine" [10], it is necessary to become much more specific with the dose. Most recently, the Physical Activity Guidelines for Americans [11] was updated and mentioned the importance of exercise for brain health and emphasized generally moving more and sitting less. However, within the literature, there is great heterogeneity in the methodologies and findings across studies regarding exercise dose, which have only now begun to be addressed systematically. For example, there is no consensus on the optimal doses or mode of physical exercise to maximize cognitive benefits, but a recent large-scale systematic review and regression found that the total time spent exercising (~52 h) was the only significant correlate of improved cognition. Additionally, the same study found that most consistent improvements from physical exercise interventions occur in executive functions and processing speed, an encouraging finding given that these are among the cognitive domains that first begin to show age-related cognitive decline [12].

Although this initial examination of dose is a definite positive step in the right direction, a large proportion of the findings regarding the structural and molecular effects of exercise (hypothesized to drive cognitive improvements) have been discovered in rodent studies, and the generalizability of these results to humans is unclear. The neurobiological underpinnings linked to exercise-mediated cognitive improvements include the ability to counteract the age-related atrophy of gray and white matter [13–17]; increase the vasculature, dendritic spine density, and complexity of the hippocampus; enhance synaptic plasticity [18]; and increase the release of fundamental biochemical mediators of neuronal survival (i.e., neurotrophins, trophic factors) [19–22]. Pertinently however, it is not clear at which dose these effects take place and with which exercise modes. Adding to the complexity, fewer of the studies in animal models have been performed in aging animals, leading to questions in the generalizability to the aging process itself.

Therefore, the purpose of this present study is to summarize the evidence of the effects of participation in an interventional exercise research study on the mechanisms believed to support cognitive improvements in the aging brain: cerebral perfusion, synaptic neuroplasticity, brain volume and connectivity, neurogenesis, and regulation of trophic factors [23–26]. In addition, this study aims to synthesize these effects in function of the dose (short-, medium-, and long-term exercise). For the purposes of this review, we considered short-term exercise to be 1 day to 16 weeks, medium to be 24 to 40 weeks, and long-term to be 52 weeks and beyond. In addition, we have limited our discussion of dose effects to studies in cognitively healthy individuals at least 50 years of age and aged rodents of at least 18 months (when human data was not available). Given the effects of exercise on cognitive function domains have been addressed elsewhere [12], we herein describe cognitive functions per their broad cognitive abilities and where possible adhering to the Cattell–Horn–Carroll theory of human cognitive abilities [27].

The majority of the included articles were found in the medical database MEDLINE/PubMed and through additional manual search in reference lists of included studies and expert knowledge of relevant papers. The search strategy included terms related to the intervention (exercise), participants (older adults, aged rodents), and the main physiological outcomes hypothesized to underlie cognitive improvements in the aging brain (cerebral perfusion, synaptic neuroplasticity, brain structure, neurogenesis and synaptogenesis, and trophic factors). Searches were conducted from May 2018 to February of 2019. The complete details of the inclusion criteria and search strategy are presented as Supplemental Material.

Cerebral Perfusion

One of the mechanisms shown to support cognition following regular exercise is the maintenance and improvement of cerebral blood flow. There is a decrease of approximately 30% in global cerebral blood flow from midlife to older age [28], which has been linked to age-related atrophy and decreased metabolism [29].

Physical exercise is undoubtedly associated with not only increased cardiac output but also a redistribution of the total blood volume to meet the increased partial pressure of arterial carbon dioxide ($PaCO_2$) and the resultant increased demand of the peripheral vasculature supplying the exercising muscles. The cerebral vasculature undergoes changes as well, albeit less pronounced. The elevation in arterial cerebral blood flow seems to be less dramatic, showing progressive increases in intensities up to 60% VO_2max, reaching a plateau, and then returning to resting levels with further increases in exercise intensities [30].

In this context, exercise-mediated increases in middle cerebral artery velocity (MCAv) enable the probing of the mechanism of cerebral homeostasis. Table 1 summarizes the results regarding cerebral perfusion in the aging brain. Studies have demonstrated smaller MCAv increases at rest and during exercise but did not report differences in the proportion of exercise-mediated increase in MCAv between young and older adults [31, 32]. The age-dependent decrease in MCAv could represent a physiologic compensatory mechanism to counteract the elevation in blood pressure and global

Table 1 Summary of articles in cerebral perfusion of older adults

First author, year	Research design	n	Sex (% female)	Age, mean (S.D.)	Exercise mode	Exercise dose
Chapman, 2013	RCT	37	61	64 (3.9)	Aerobic, bike or treadmill	12 weeks, 3×/week, 60 min, 50-75% max THR
Chapman, 2016	RCT	36	61	64 (4.3)	Aerobic, bike or treadmill	12 weeks, 3×/week, 60 min, 50-75% max THR
Murrell, 2013	Open trial	10	NR	63 (5.0)	Aerobic, circuit gym-based	12 weeks, 3-4×/week, 20-30 to 40-50 min, 50-55 to 65-80% max THR
Marsdem, 2012	Open trial	14 (older)	0	71 (10)	Aerobic, maximal incremental test on a cycle ergometer	1-day acute exercise (previous actively individuals)
Fisher, 2013	Open trial	9 (older)	NR	66 (2.0)	Aerobic, submaximal test on cycle ergometer	1-day acute exercise (previous actively individuals)
Fluck, 2014	RCT	17 (older)	0	66 (4.0)	Aerobic, maximal incremental test on a cycle ergometer	Acute exercise (incremental workload)
Maass, 2015	Pseudo-RCT	40	55	68.4 (4.3)	Aerobic, walking or running on a treadmill	12-week, 3×/week, 40 min, 65-80% THR
Burdette, 2010	Trial	11	75	77.6 (5.0)	Aerobic (walking or other aerobic)	16 weeks, 5×/week, 12-14 RPE

First author, year	Exercise min/week	Control/comparison group	Cerebral perfusion outcomes	Main findings
Chapman, 2013	180 min/week	Waitlist control	rCBF	↑ rCBF in the bilateral ACC
Chapman, 2016	180 min/week	Cognitive training	rCBF	No differences between groups in cerebrovascular reactivity to hypercapnia; No changes in global or regional CBF
Murrell, 2013	3×/week: 60-90 to 120-150 min/week 4×/week: 80-120 to 160-200 min/week	NA	Cerebral blood flow	↑ Middle cerebral artery velocity; ↑ Cerebrovascular reactivity to hypercapnia
Marsdem, 2012	NA	Young adults	MCA velocity	↑ MCA velocity
Fisher, 2013	NA	Young adults	Cerebral metabolism and hemodynamics	↑ Middle cerebral artery velocity; No difference between the groups
Fluck, 2014	NA	Young adults, control trial, CO_2 supplemental	MCA velocity	↑ Middle cerebral artery velocity; No difference between the groups
Maass, 2015	120 min/week	Indoor progressive-muscle relaxation/stretching	Resting brain (hippocampus) blood flow	No improvements in hippocampal regional CBF compared to control
Burdette, 2010	150 min/week	Education and light stretching	Resting brain (hippocampus) blood flow	↑ CBF in the bilateral hippocampus

n = number of subjects; S.D. = standard deviation; RCT = randomized controlled trials; NR = not reported; NA = not applied; THR = target heart rate; RPE = rate of perceived exertion; rCBF = resting cerebral blood flow; ACC = anterior cingulate cortex; MCA = middle cerebral artery; ↑ = significant increase

decreased elasticity of blood vessels in older age. In addition, improvement in cerebrovascular reactivity to hypercapnia (i.e., cerebrovascular reactivity or the ability of blood vessels to vasodilate) associated with exposure to short-term (i.e., 12 weeks) moderate- to high-intensity aerobic exercise has been found to be similar between young and older adults [33].

Studies have examined the effect of short-term (ranging from 12-16 weeks) moderate-intensity aerobic exercise on regional or whole-brain cerebral perfusion and have found mixed results. Following one 12-week intervention, there was increased cerebral blood flow (CBF) in the bilateral anterior cingulate cortex (ACC) when compared with a waitlist control [34], but a subsequent study utilizing the same exercise dose found no changes in global or regional CBF when making comparisons with a cognitive training group [35]. One 12-week intervention was not sufficient to improve hippocampal regional CBF, when compared with muscle relaxation/stretching [17], but a 16-week intervention in an older sample (~+ 10 years) who had subjective memory complaints found improvements in bilateral hippocampal CBF when compared with a comparison group of education and light stretching [36].

Synaptic Neuroplasticity

Synaptic neuroplasticity is defined as long-lasting changes in efficacy of synaptic connections (i.e., long-term potentiation (LTP) or long-term depression (LTD). Synaptic neuroplasticity was first described following repetitive electrical stimulation of hippocampal neurons, and when measured with electrodes placed directly in hippocampal tissue, evidence for the role of LTP and LTD in memory consolidation was shown [37, 38]. LTP is currently the strongest candidate to explain brain-wide synaptic activity implicated in cognitive processes and learning (both cognitive and motor), and there is a documented decreased LTP associated with aging in experimental rodent models [18, 39]. In experimental studies with young rodent models, robust improvement in visuospatial ability after regular exercise is observed and correlated with enhanced LTP of synaptic activity in hippocampal cells [18, 40]. Furthermore, exercise rescues LTP ability and promotes cognitive gains in different young rodent models of impaired LTP [41–44].

Only 2 studies have examined the influence of exercise on LTP in aged rodent models and have found improved synaptic plasticity following exposure to long-term exercise interventions. Kumar et al. [45] assessed short-term exercise exposure in the form of a 12-week intervention and found increased LTP and improved performance on the cue discrimination task of the water Morris maze and object recognition memory. O'Callaghan et al. [46] assessed LTP in aged rats following long-term exercise exposure (8-month-long aerobic exercise

intervention) initiated in middle age. The authors found that the long-term exercise prevented age-related decreases in LTP and spatial learning.

Brain Structure

Volume

The aging brain undergoes selective atrophy, mainly in the prefrontal cortices and medial temporal lobes [47, 48]. For instance, it has been reported that beginning at approximately age 50, the hippocampus shrinks 1 to 2% every year in healthy older adults [47]. These decrements in volume have been linked to age-related decreases in memory and executive function [49, 50]. Decreased age-related atrophy has historically been implicated in explaining exercise-mediated improvements in cognitive performance for the older adult population [13].

Table 2 summarizes the results of studies that investigated the effects of exercise on brain volume. The 2 studies that examined the influence of short-term (12-week) moderate-intensity aerobic interventions on brain structure failed to find differences in whole-brain gray matter volume, either when exercise was compared to a waitlist control [51] or a stretching/muscle relaxation comparison [17]. Although no between-group differences were found, a subanalysis in the Maass et al. [17] study demonstrated regional increases in the volume of the hippocampal head exclusively in those who exhibited improvements in fitness and hippocampal perfusion [17]. Taken together, these results suggest that perhaps certain individuals who show mediatory gains in secondary outcome measures (such as cardiorespiratory fitness and hippocampal perfusion) may also exhibit benefits in exercise-induced changes in brain structure.

Medium length interventions may have greater impact in the regional brain structure however. Kleemeyer et al. [52] found that 26 weeks (i.e., 6 months) of both low and high aerobic exercise was associated with increased neuron density and volume in the hippocampus, and these 2 outcomes were correlated [52]. Ruscheweyh et al. [15] found that both high-intensity exercise in the form of Nordic walking and low-intensity exercise in the form of gymnastics improved gray matter volume, mainly in prefrontal and cingulate cortices, when compared with a no-intervention control [15]. In addition, a low- to moderate-intensity aerobic exercise was associated with increased regional brain volume in both gray and white matter areas relevant to the processing of attentional control and memory processes and shown to be implicated in age-related atrophy, when compared with stretching and toning [13]. Namely, the most prominent increases in volume were found in the ACC, right superior temporal gyrus, right middle frontal gyrus, and anterior white matter. However, a

Table 2 Summary of articles in brain volume in older adults

First author, year	Research design	n	Sex (% female)	Age, mean (S.D.)	Exercise mode	Exercise dose
Mass, 2015	Pseudo-RCT	40	55	68.4 (4.3)	Aerobic, walking or running on a treadmill	12 weeks, 3×/week, 40 min, 65-80% THR
Matura, 2017	RCT	53	43.4	75.3 (7.2)	Aerobic (cycle ergometer training)	12 weeks, 3×/week, 30 min, progressive workload based on first VAT ($64 \pm 9\%$ VO$_2$max)
Colcombe, 2006	RCT	59	55	66.5	Aerobic	26 weeks, 3×/week, 60 min, 40-50 to 60-70% THR
Ruscheweyh, 2011	RCT	62	69.3	60.2 (6.6)	G1: aerobic, Nordic walking; G2: aerobic, gymnastics	26 weeks, 5×/week, 50 min, G1: 50-60%, G2: 30-40% THR
Jonasson, 2017	RCT	60	52	68.4 (2.54)	Aerobic, walking or jogging, cycling, cross-trainers	26 weeks, 3×/week, 30-60 min, 40-80% THR
Kleemeyer, 2016	RCT	52	61.5	66 (4.36)	Aerobic, stationary biking (high vs low intensity)	26 weeks, 3×/week, 55 min, high (80-110% VAT), low (constant resistance of 10 W)
Rehfeld, 2018	RCT	38	50	63-80	Dancing	26 weeks, 2×/week, 90 min, new dance routines every second week
Mortimer, 2012	RCT	120	63.3	67.3 (5.3)	Tai chi or walking or social interaction	40 weeks, 3×/week, 50-60 min
Best, 2015	RCT	83	100	69.4 (3.0)	Resistance	52 weeks, 1-2×/week, 60 min, progressive high intensity
Erickson, 2011	RCT	120	73	67.6 (5.81)	Aerobic, walking	52 weeks, 3×/week, 40 min, 50-60 to 60-75% THR
Liu-Ambrose, 2010	RCT	155	100	69.6 (2.9)	Resistance	52 weeks, 1-2×/week, 60 min, progressive high intensity
Voss, 2012	RCT	70	64.2	64.87 (4.46)	Aerobic, walking	52 weeks, 3×/week, 10-40 min, 50-60 to 60-75% THR
Niemann, 2014	RCT	49	65	68.92 (3.75)	G1: aerobic, Nordic walking, G2: coordination	52 weeks, 3×/week, 45-60 min, intensity based on self HR responses
Rosano, 2017	RCT	26	80.8	74.9	Combined Physical activity	104 weeks, 187 sessions (self-reported), moderate intensity

First author, year	Exercise min/week	Control/comparison group	Brain volume outcomes	Main findings
Mass, 2015	120 min/week	Indoor progressive-muscle relaxation/stretching	Resting brain (hippocampus) blood flow and connectivity	No differences between groups in whole-brain gray matter volume; ↑ Hippocampal head volume when ↑ hippocampal perfusion
Matura, 2017	90 min/week	Waiting control	GM volume	No differences between groups in whole-brain gray matter volume
Colcombe, 2006	180 min/week	1) Toning and stretching; 2) nonexercise young adults	Gray and white matter volume	↑ Brain volume in ACC, rtSTG, rtMFG, and AWM
Ruscheweyh, 2011	G1: 141 (30) G2: 138 (27) min/week	No intervention control group	WBV	↑ Gray matter volume, mainly in the PFC and cingulate cortices
Jonasson, 2017	90-180min/week	Stretching and toning control training	Cortical thickness in frontal regions and hippocampus volume	No differences found in whole-brain volume or cortical thickness when compared with a stretching/toning group
Kleemeyer, 2016	165 min/week	Low-intensity group	Hippocampal microstructure and hippocampal volume	↑ Neuron density and volume in the hippocampus
Rehfeld, 2018	180 min/week		Gray and white matter volumes	Dance group:

Table 2 (continued)

Study	Control/comparison	Dose	Brain measure	Results
	Sport group (endurance, strength–endurance and flexibility)			↑ Multiple frontal and temporal cortices areas (ACC, MCC, lSMA, lGPre, the lGFM, left insula, lGTS, and lGPo) compared to the sport group ↑ CC-T and CC-S, right and left frontal and right parietal WM Sport group: ↑ Occipital and cerebellar regions (V1, lGL, rGF, rTP, and right lobe of the cerebellum) compared to the dance group ↑ rTWS and rOWS white matter
Mortimer, 2012	No intervention control	150-180 min/week	Brain volume	↑ Whole-brain volume in the tai chi and social interaction groups There were no differences between aerobic exercise and the control group
Best, 2015	Balance and toning	60-120 min/week	Brain volume (cortical WM volume, cortical GM, and hippocampal volume)	↓ Cortical white matter atrophy on in the 2×/week resistance group Neither group (resistance training frequencies (1×/week and 2×/week)) showed changes in whole-brain gray matter or hippocampal volume
Erickson, 2011	Stretching control group	120 min/week	Hippocampal volume	↑ Bilateral hippocampal volume (great in dentate gyrus)
Liu-Ambrose, 2010	Balance and toning	60-120 min/week	WBV	↓ Whole-brain volume in the resistance training, either delivered 1×/week or 2×/week, compared with a balance and toning group even though ↑ increased executive function
Voss, 2012	Flexibility, toning and balance	30-120 min/week	Cerebral white matter integrity	No differences in white matter integrity (frontal or temporal lobes) ↑ White matter integrity when high ↑ fitness level
Niemann, 2014	Stretching and relaxation training	135-180 min/week	Hippocampal volume	↑ Bilateral hippocampal volume Aerobic ↑ left hippocampus Coordination ↑ right hippocampus
Rosano, 2017	Healthy education and UE stretching	NR	Hippocampal, dentate gyrus, and CA volume; WM hyperintensities; brain atrophy	↑ Bilateral hippocampal and left CA volume

n = number of subjects; $S.D.$ = standard deviation; RCT = randomized controlled trials; NR = not reported; NA = not applied; THR = target heart rate; RPE = rate of perceived exertion; $1RM$ = one-repetition maximum; $VT1$ = first ventilatory threshold; VO_2max = maximum rate of oxygen consumption; WBV = whole-brain volume; ACC = anterior cingulate cortex; $rtSTG$ = right superior temporal gyrus; $rtMFG$ = right middle frontal gyrus; AWM = anterior white matter; PFC = prefrontal cortex; MCC = medial cingulate cortex; $lSMA$ = left supplementary motor area; $lGPre$ = left gyrus precentralis; $lGFM$ = left gyrus frontalis medius; $lGTS$ = left gyrus temporalis superior; $lGPo$ = left gyrus postcentralis; $CC-T$ = truncus of corpus callosum; WM = white matter; GM = gray matter; $V1$ = primary visual cortex; lGL = left gyrus lingualis; rGF = right gyrus fusiformis; rTP = right temporalpol; $rTWS$ = right temporal white matter; $rOWS$ = occipital white matter; CA = cornus ammonis; ↑ = significantly increase; ↓ = significantly decrease

more recent intervention delivered with similar dose and exercise mode (differing in total time per week 90-180 *vs* 180 min) did not find differences in frontal and hippocampus cortical thickness when compared with a stretching/toning group, despite an improvement in a composite cognitive score (episodic memory, processing speed, updating, task-switching, visuospatial reasoning) in the aerobic exercise group [53]. The author discussed 2 possible reasons for these controversial findings, especially regarding brain volume. First, it is possible that an exercise intervention longer than 6 months may be required to achieve greater changes in brain volume. Second, the myriad cognitive improvements following a 6-month exercise intervention may be driven by other physiological processes, apart from macrostructural changes.

Furthermore, there is evidence suggesting differential structural effects according to exercise mode. For instance, individuals demonstrated increased brain volume in various frontal and temporal cortical areas following a 26-week dancing intervention, whereas individuals participating in a resistance training and flexibility group demonstrated increased brain volume in occipital and cerebellar regions [54]. Interestingly, both groups had similar increased aerobic fitness and small changes in attention and visuospatial memory. It was hypothesized that the constant novelty and greater demand in attention and memory posed by the choreography in the dancing group created a greater challenge than the repetitive routine in the resistance training and flexibility group, possibly accounting for the larger improvements in brain volume.

The only study we found proposing moderate–high exposure to exercise (40 weeks) incorporated 2 distinct nonaerobic modalities, tai chi and social interaction, and made comparisons to light aerobic exercise and a no-exercise control group [55]. Interestingly, only tai chi and social interaction were associated with increased whole-brain volume and improved processing speed and short-term memory. Contrary to previous findings in the literature, there were no differences between the light aerobic exercise and the control. We believe that this is possibly due to the fact that unlike the other studies that used light exercise interventions [15, 52], there was not a preferred intensity or a target zone, allowing the participants to walk at their self-selected pace. Although walking interventions are common in the literature, support for a potential floor effect in the aerobic exercise group comes from a subanalysis which revealed that faster walkers exhibited greater processing speed and short-term memory and lower brain tissue loss than slower walkers. Although there was no target intensity for the tai chi, this intervention requires a higher level of intellectual involvement and sustained attention compared to walking, which may have contributed to the results. Taken together, it is possible that aerobic exercise needs to be dosed at a minimum intensity and session time to achieve a threshold for structural gains, whereas other interventions such as tai

chi, gymnastics, or social interaction may enlist distinct mechanisms due to the fact that they are more cognitively challenging.

The remainder of human studies examined high exercise exposure in yearlong interventions. Liu-Ambrose [56] assessed the effects of resistance training, either delivered 1×/week or 2×/week, and made comparisons with a balance and toning group delivered 2×/week. Interestingly, the authors found *decreased* whole-brain volume and increased executive function in the resistance groups when compared with the balance and toning group. The decreased whole-brain volume was unexpected but consistent with a mean of about 0.5% decreased annual whole-brain volume reported in healthy aging [57, 58]. A latter follow-up study performed 1 year after intervention demonstrated that neither group showed changes in whole-brain gray matter or hippocampal volume, but the 2×/week did show reduced cortical white matter atrophy [59]. Additionally, both resistance training frequencies (1×/week and 2×/week) maintained their increased processing speed and attention, but the 2×/week group additionally demonstrated improved short-term memory [59]. Thus, further research is needed to examine the relationship between structural brain changes and resistance training, especially given the improvements in certain cognitive abilities noted.

Both light to moderate aerobic exercise and a flexibility/toning/balance interventions were found to be associated with similar levels of white matter integrity in the frontal and temporal lobes, executive control, and short-term memory [60]. A subanalysis revealed that individuals who made greater improvements in cardiovascular fitness made greater improvements in white matter integrity and short-term memory. An average increase in cardiovascular fitness of 8% following a moderate aerobic exercise intervention was associated with an average 2% increase in hippocampal volume, when compared with a yearlong stretching intervention [14]. Similar increases in hippocampal volume have been reported with a coordination intervention [61]. Interestingly however, aerobic exercise increased volume in the left hippocampus and the coordination group increased the volume of the right hippocampus. The authors attributed the differential effects to distinct demands posed by the 2 interventions; the right hippocampus is more highly engaged in spatial memory processes and, thus, theoretically more active during coordination exercises, whereas the left hippocampus is more engaged in verbal memory and highly associated with the increase in fitness level [62].

In the study proposing the highest exposure to exercise (2 years), a multimodal intervention consisting of moderate-intensity physical activity (walking, lower extremity resistance training, balance, stretching, and behavioral counseling) was associated with improved bilateral hippocampal and left cornu ammonis volumes, when compared with a control group consisting of healthy education and stretching. In

addition, the authors reported that greater self-reported adherence to the intervention was associated with greater hippocampal volume [63].

Connectivity

In addition to structural changes, age-related cognitive decline is associated with impaired functional activation of neural networks. For example, older individuals with age-related cognitive decline have exhibited impaired neural interhemispheric communication between the frontal and posterior cortices [64] and disrupted frontotemporal activation during memory-related tasks [65–67]. The studies described herein measure the degree of connectivity (i.e., degree of simultaneous cortical activation) between spatially distant cortical areas either during resting state (when the individual is not engaged in a specific thought or task) or during the performance of a specific task.

Table 3 summarizes the results of studies that investigated changes in brain connectivity after exercise intervention. Short-term exposure (12 weeks) to moderate-intensity exercise has been associated with a reduction in the number of cortical areas active during the performance of a memory semantic task, which was attributed to a potential increase in the efficiency of neural networks [68]. In addition, the same intervention delivered at a slightly higher dose (16 weeks) was associated with connectivity of the hippocampi and increased interconnectivity between the hippocampi and ACC, when compared with education and light stretching [36]. The interconnections with the ACC are relevant as this structure has reciprocal connections with the prefrontal cortex and is active during tasks that require executive control [69].

Medium-term exposure (6 months) to light to moderate aerobic interventions (6 months) was also associated with improved connectivity. The authors found decreased activation of the ACC, which was associated with improved executive control. The authors attributed the improved executive control to a task-related increase in various areas in the attentional circuitry network (middle frontal gyrus, superior frontal gyrus, and superior parietal lobules) which in theory decreased the demand of the ACC during the task [70]. The authors attributed these findings to an increase in cardiovascular fitness, not exhibited by the stretching/toning group. Taken together, these results suggest that a global increase in connectivity and increased focal connectivity in areas pertinent to executive control and memory are possible with approximately 3 to 6 months of moderate aerobic exercise.

Similar to these previously reported findings, long-term exposure to exercise was also shown to improve connectivity and executive control, but with differing patterns according to exercise mode [71]. Specifically, 1 year of light to moderate aerobic exercise was associated with an improvement in the connectivity between areas within the default mode network and within the frontal executive network. On the other hand, the stretching/toning/balance intervention was associated with increased connectivity within areas of the DMN at 6 months and within the frontoparietal network. However, neither group showed differences in task-switching ability or spatial working memory [71]. The default mode network, frontal executive network, and frontoparietal network are highly engaged during the performance of executive control and spatial memory tasks, and connectivity between these areas is impaired in age-related cognitive decline [72, 73].

Voelker-Rehage et al. [74] also found improved perceptual speed and executive functioning with different exercise modes and differential patterns of improved connectivity. The authors found that both moderate to high aerobic exercise and coordination: 1) improved neural efficiency during the performance of an executive control task and 2) improvements in executive attentional control and perceptual speed, albeit with differential patterns of connectivity. The aerobic group showed a decreased activation of left superior and middle frontal, bilateral medial frontal gyrus, the left ACC, the left parahippocampal gyrus, and the right superior and middle temporal gyrus. The coordination group showed increased activation of inferior frontal gyrus, superior parietal cortex, and thalamus and caudate. In addition to the differential connectivity patterns between the 2 intervention groups, the authors also found that the improved perceptual speed and executive functioning in the aerobic exercise was driven by an improvement in cardiovascular fitness. Taken together, these studies suggest that long-term exposure to different modes of exercise may be associated with certain cognitive benefits via distinct patterns of functional connectivity.

Neurogenesis and Synaptogenesis

Animal models enable the study of the microscopic changes in brain structure that support exercise-mediated cognitive benefits, such as the formation of new neurons (neurogenesis) and synapses (synaptogenesis) in the hippocampus. One of the strongest and earliest links between exercise and cognition was found on neurogenesis [75–77], which was 1 of the first hypotheses used to explain the neurobiological underpinnings of exercise-mediated cognitive performance benefits. However, when considering the generalizability of these microscopic findings to translational research in aging humans, it is pertinent to also consider how age might impact processes such as neurogenesis and synaptogenesis. For instance, older rodents (9 months) show hippocampal neurogenesis at half the rate of young adult rodents (6 weeks), and that by 24 months, the rate of neurogenesis is further decreased to 17% [78].

Despite the age-related decrease in hippocampal neurogenesis, it is encouraging that neurogenesis can be enhanced with exercise in aged rodents. For example, 1 month and half of voluntary wheel-running (VWR) was shown to

Table 3 Summary of articles in brain connectivity in older adults

First author, year	Research design	n	Sex (% female)	Age, mean (S.D.)	Exercise mode	Exercise dose	Exercise min/week	Control/comparison group	Brain connectivity outcomes	Main findings
Smith, 2013	Open trial	35	71.4	76 (7.3)	Aerobic, walking	12 weeks, 4×/week, 30 min, 50-60%	120 min/week	Aerobic active control	Whole-brain activation	↑ Efficiency of neural networks
Burdette, 2010	Trial	11	75	77.6 (5.0)	Aerobic (walking or other aerobic)	16 weeks, 5×/week, 12-14 RPE	150 min/week	Education and light stretching	Resting brain (hippocampus) blood flow and connectivity	↑ Hippocampal connectivity; ↑ Interconnectivity hippocampi and ACC
Colcombe, 2004	Open trial	29	62	65.6 (5.66)	Aerobic, walking	26 weeks, 3×/week, 10-15 to 40-45 min, 40-50 to 60-70% THR	45-135 min/week	Stretching and tone	Cerebral area activation in a cognitive task; GM density	↑ Attentional circuitry in the MFG, SFG, and SPL and ↓ ACC activation
Voss, 2010	RCT	97	73	65.37	Aerobic, walking	52 weeks, 3×/week, 10-40 min, 50-60 to 60-75% THR	30-120 min/week	Stretching and toning group and young control	Plasticity of brain networks	↑ Connectivity in areas relevant to age-related cognitive decline; ↑ Connectivity between areas within the DMN and within the FE (aerobic at 1 year); ↑ Connectivity between areas within the DMN (6 months) and within the FE (1 year) control group
Voelcker-Rehage, 2011	RCT	44	63.6	69.64 (3.84)	G1: aerobic, walking, G2: coordination	52 weeks, 3×/week, 35-50 min, individual HR intensity zone, AerTGE (but below AnTG	105-150 min/week	Relaxation and stretching	Brain activation patterns	Both aerobic and coordination ↑ neural efficiency in the PFC. Aerobic group: ↓ Activation of lsFG, MFG, bilateral mFG, the left ACC, the left parahippocampal gyrus, rtSTG, and mTP. Coordination group: ↑ activation of iFG, sPC, thalamus, and caudate

n = number of subjects; S.D. = standard deviation; RCT = randomized controlled trials; NR = not reported; NA = not applied; THR = target heart rate; RPE = rate of perceived exertion; 1RM = one-repetition maximum; ACC = anterior cingulate cortex; MFG = middle frontal gyrus; SFG = superior frontal gyrus; SPL = superior parietal lobules; DMN = default mode network; FE = frontal executive network; PFC = prefrontal cortex; lsFG = left superior frontal gyrus; bilateral mFG = bilateral middle frontal gyrus; rtSTG = right superior temporal gyrus; mTG = middle temporal gyrus; iFG = inferior frontal gyrus; sPC = superior parietal cortex; ↑ = significant increase; ↓ = significant decrease

revert the decline in neurogenesis in 19-month-old rodents by 50% and increase gliogenesis by 20%, an improvement that was paralleled with improved spatial learning, when compared with sedentary control rodents [79]. Interestingly, the authors found no difference in the number of new cells or in fine morphology between older exercised and young mice, suggesting that exercise may have enhanced the capacity for conversion of precursor cells into neurons. The aged exercised mice showed increased rate of conversion by 3-fold when compared with the sedentary aged mice (25.6 vs 9.5%, respectively). Regarding the exercise dose necessary to induce such benefits, there is evidence to support that 10 to 28 days of VWR was sufficient to induce increases in precursor cell divisions associated with hippocampal neurogenesis [78, 80, 81]. However, 1 study found that 14 days of VWR in 22-month-old mice was associated with lower neurogenesis [82].

Neural stem cells (NSC), considered to support the regenerative function of the brain, are decreased to about 70% in 18-month-old mice and 90% in 24-month-old mice [83]. Interestingly, 21 days of VWR exercise attenuated the age-dependent decrease in NSC proliferation in endogenous extrahippocampal areas by 67% in 18-month-old mice but failed to do so in 24-month-old mice [83]. One study did find increased proliferation of hippocampal NSC in 24-month aged mice after 3 days of VWR [84]. Taken together, it is possible that aerobic exercise may have differential effects in different types of NSC.

Other studies have shown that exercise may influence neurogenesis through different pathways. For instance, evidence suggests that exercise rescues the levels of enzymes TET1 and TET2 (Ten-eleven translocation 1 and 2), shown to be decreased in aging animals and act to regulate hippocampal neurogenesis [85]. In addition, exercise has been shown to revert the toxic effect of lipopolysaccharide, a bacterial endotoxin shown to reduce hippocampal neurogenesis levels when expressed in 21-month-old mice [86]. Furthermore, exercise decreased new microglia, immune cells linked to low-grade neuroinflammation that may contribute to decreased plasticity and increased new neuron survival [87].

Similarly, to neurogenesis, synaptogenesis is also decreased in aged rodents. For example, the number of presynaptic receptors in the hippocampus is decreased [88]. Unfortunately, we could not find evidence of the impact of exercise in aged rodents, but studies suggest improvements in synaptogenesis in young exercised rodents. For instance, VWR is associated with increased synaptophysin, a marker of synaptogenesis in young rodents [89]. In addition, nonaerobic exercise (walking through an obstacle course) was also associated with new synapses in other areas of the brain, mostly related with the control of motor activity [90].

As mentioned previously, animal studies show that the capacity for neurogenesis can be positively influenced by exercise. However, the generalizability of decreased neurogenesis found in aged mice needs to be carefully interpreted when applied to older adults. A recent cross-sectional study in post-mortem healthy individuals from 14 to 79 years found that adult hippocampal neurogenesis may persist throughout the life span, including the 8th decade of life, despite the common clinical finding of age-related cognitive decline [91]. Neurogenesis (measured by levels of intermediate neural progenitors, immature neurons, glia, and mature granule in the dentate gyrus) was found to be at similar levels in individuals from 14 to 80 years of age. The authors attributed the aspects of preserved cognitive performance in older adults to the maintenance of those levels of neurogenesis. However, in the comparison between young adults and older adults, the authors did find decreased angiogenesis, neuroplasticity markers of PSA-NCAM+ (polysialylated neural cell adhesion molecule) cells of different morphologies, and capacity for neurogenesis (assessed by the number of quiescent NSC), potentially implicated in the aspects of cognition that show decreases in the aging brain [91].

Trophic Factors

Several trophic factors have been identified to support cognition in aging adults. The most commonly discussed factors that are supportive of cognition include brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and insulin-like growth factor-1 (IGF-1). These trophic factors work in concerted fashion to modulate exercise-induced cognitive improvements [23]. IGF-1 is important for vascular maintenance and remodeling. Both IGF-1 and VEGF are thought to mediate neurogenesis and angiogenesis and influence the induction of hippocampal BDNF.

BDNF supports neuronal development and has been demonstrated to be crucial for exercise-related improvements in cognitive function. Blocking BDNF annuls the cognitive improvements induced by exercise [92], demonstrating its significance for cognitive change. Additionally, running increases IGF-1 and VEGF in the hippocampus [93, 94], both of which are crucial to exercise-induced plasticity and cognitive improvements. IGF-1 is increased in the hippocampus following exercise, and blocking IGF-1 receptors reduces exercise-induced BDNF and inhibits exercise-related cognitive improvements [93]. Similarly, blocking VEGF reverses running-induced hippocampal neurogenesis [95].

In aged animals (24 months), treadmill running has been shown to increase BDNF and IGF-1 after 4 weeks of intervention, and these changes were associated with improved spatial learning and memory [96]. However, another study in aged animals showed that there was a transient increase in BDNF levels after 1 week of a wheel running that returned to baseline levels in subsequent weeks (2-4 weeks). In this study, it was found that aged animals did not increase their running distance each week whereas the other study utilized a

treadmill which standardized the exercise exposure, which may account for the transient increase found in voluntary wheel-running. Furthermore, improvements in memory and increases in BDNF have been shown after 8 weeks of aerobic and strength training, showing possible benefits beyond aerobic exercise [97]. Table 4 summarizes the results of studies investigating the effects of exercise on trophic factors in humans.

BDNF

Three studies that utilized short-term exercise interventions (between 4 and 10 weeks) proposed moderate-load resistance training, either in isolation [98, 99] or combined with aerobic exercise [100]. Moderate-load resistance training increased BDNF levels when compared with baseline [99], but not when compared with a control [98]. The combined intervention also did not improve BDNF levels [100]. These studies suggest that short-term exposure to resistance training may not be associated with increases in BDNF.

Many studies assessed the effects of various isolated modes of short-duration (12 or 16 weeks) exercise. None of the following moderate-intensity aerobic activities modulated BDNF levels: walking or running [19] and cycling [51] and light and moderate-load resistance training [101–103]. Four studies employed combined exercise programs that contained resistance training: high-intensity aerobic cycling followed by moderate level coordination/strength [104], high-intensity aerobic cycling followed by moderate level coordination/strength [105], moderate-load resistance training followed by moderate- to high-intensity aerobic training [106], and combined aerobic/strength/coordination [107]. Of these, only the moderate-load resistance training followed by moderate- to high-intensity aerobic training and the combined aerobic/strength/coordination reported increased BDNF levels, and both reported improvements in short-term memory and processing speed [106, 107]. Taken together, these studies suggest that medium exposure to aerobic or resistance training delivered in isolation might not be sufficient to influence BDNF levels. In addition, the only 2 studies that demonstrated BDNF increases employed a combined intervention of approximately 2000 total intervention minutes (i.e., 32 h), and therefore, the additional load posed by a second intervention and the greater exposure to exercise could have contributed to the results.

Three studies investigated medium-duration exercise (6 months), employing various modes of exercise: high-intensity aerobic, moderate-intensity aerobic, and a dance-based intervention [15, 54, 108]. The studies that utilized moderate- or high-intensity aerobic exercise in isolation found no changes in BDNF levels [15, 108]. Rehfeld et al. [54] found that a dance-based intervention was associated with increased BDNF levels, when compared to an endurance/

strength/flexibility group. The dance intervention required subjects to memorize routines, perform complex choreography, and was regularly changed throughout the study, whereas the comparison group utilized an unchanging exercise regimen, which may have been related to the increases in BDNF found in the intervention group. However, despite the discrepancies in BDNF findings, all studies demonstrated improvements in a range of cognitive abilities (processing speed, visuospatial memory, and episodic memory).

Three studies evaluated the effects of long-duration exercise in a 12-month moderate aerobic walking intervention compared to a stretching and toning group. It appears that these studies are from 1 larger sample, with each study reporting on a subset of the total sample: 92 subjects [21], 120 subjects [14], and 65 subjects [109]. There were no changes in BDNF levels from before to after in the intervention groups in any of the cohorts. A secondary analysis performed by Leckie et al. [21] showed that when dividing the sample by age, younger and older than 65 years of age, the intervention group had an increase in BDNF levels, whereas the control group had a decrease in BDNF levels in individuals older than 65 years old. Both Erickson et al. [14] and Leckie et al. [21] assessed and reported improvements in spatial memory function and task-switching after the intervention. These findings are consistent with the previous results that suggest that only aerobic activity may not be sufficient to modulate BDNF levels. However, it is possible that in individuals over 65 who are susceptible to decreases in BDNF [110], that the prolonged effects of a year-long aerobic intervention may have a positive influence on BDNF levels whereas shorter duration interventions are potentially unable to have the same effect.

IGF and VEGF

Six studies utilized short-duration exercise (10-12 weeks) of various modes: moderate aerobic exercise [19, 111, 112], combined moderate- and high-intensity aerobic and resistance training [111, 113], and low or moderate resistance training [112, 114, 115]. The moderate-intensity aerobic exercise interventions had no effect on IGF-1 levels [19, 111, 112] or VEGF levels [19]. In 2 studies utilizing combined aerobic and resistance training, 1 found within-group increases in IGF-1, regardless of intervention order [113], whereas the other found no changes when compared to a control group. In the studies utilizing resistance training, only 1 study utilizing moderate-intensity exercise found increases in IGF-1 [112], whereas the other 2 found no changes. Both studies that found increased IGF-1 after the intervention (combined or resistance) were in participants in their late 60s, whereas the studies that found no changes were in people 80 years old [114, 115] or 50 years old [111]. These findings may suggest that short exposure to both a combined approach and moderate-intensity resistance

Table 4 Summary of articles in trophic factors in older adults

First author, year	Research design	n	Sex (% female)	Age, mean (S.D.)	Exercise mode	Exercise dose
Ruiz, 2015	RCT	40	80	92.3 (2.3)	Aerobic, cycle erg + resistance	8 weeks, 3×/week, 40-45 min, 2-3 sets of 8-10 reps, RPE of 10-12, 30% of 1RM at start to 70% of 1RM
Kim, 2015	RCT	13	100	81 (2.6)	Exercise + MFGM supplementation, resistance, balance and gait training	12 weeks, 2×/week, 60 min, RPE Borg 12-14
Levinger, 2008	RCT	49	49	50.9 (6.2)	Resistance training, HiMF training	10 weeks, 3×/week, 7 exercises, 15-20 reps at 40-50% 1RM, weeks 2-10 3 sets of 8-20 reps at 50-85% 1RM
Coelho, 2012	Quasi-experimental	48	100	70.5 (4.6)	Resistance training (physical therapy)	10 weeks, 3×/week, 60 min, 2 weeks 50% of 1 RM, weeks 2-10 75% of 1RM
Vedovelli, 2017	Open trial	29	100	83 (6.53)	Aerobic, walking + resistance training	12 weeks, 3×/week, 60 min, 2 weeks resistance-50% of 1RM increased to >/= 75% of 1RM by 3rd week, aerobic: 75-85% of HR max
Forti, 2014	Non-RCT	40	45	65.69	Resistance training	12 weeks, 3×/week, 60 min, 50% of 1RM up to 70-80% of 1RM
Forti, 2015	RCT	49	54	68 (5)	Resistance training, high intensity	12 weeks, 3×/week, HIGH: 2 sets, 10-15 reps of 80% 1RM; LOW: 1 set of 80-100 reps at 20% of RM, LOX MIXED: 60 reps at 20% of 1RM and immediately after (no rest) resistance increased to 40% of 1RM for 10-20 reps
Matura, 2017	RCT	53	43.4	75.3 (7.2)	Aerobic, cycle ergometer	12 weeks, 3×/week, 30 min, progressive workload based on VT1 ($64 \pm 9\%$ VO_2max)
Hvid, 2017	RCT	47	55	82.7 (5.4)	High-intensity power	12 weeks, 2×/week, 3 sets 70% of 1RM (10 reps for weeks 1-7) 80% 1RM (weeks 8-12, 8 reps)
Prestes, 2014	Open trial	49	100	65.52 (4.72)/69.2 (6.05)	Resistance training with periodization (linear or undulating)	16 weeks, 2×/week, 40-50 min, 3 sets to concentric failure, 12-14 RM to 6-8 RM)
Vaughan, 2014	RCT	49	100	69 (3.1)	Aerobic, resistance, and motor fitness,	16 weeks, 2×/week, 60 min
Maass, 2015	Pseudo-RCT	40	55	68.4 (4.3)	Aerobic, walking or running on a treadmill	12 weeks, 3×/week, 40 min, 65-80% THR
Baker, 2010	RCT	28	50	71 (7.5)	Aerobic, treadmill, bike, or elliptical	26 weeks, 4×/week, 45-60 min, 75-85% of HR reserve
Rehfeld, 2018	RCT	38	50	63-80	Dancing	26 weeks, 2×/week, 90 min, new dance routines every second week
Ruscheweyh, 2011	RCT	62	69.3	60.2 (6.6)	G1: aerobic, Nordic walking; G2: aerobic, gymnastics	26 weeks, 3-5×/week, 50 min, G1: 50-60%, G2: 30-40% THR
Leckie, 2014	RCT	92	64.1	66.82 (5.59)	Aerobic, walking	52 weeks, 3×/week, 10-40 min (10 min, increased to 40 by week 7), 50-60 to 60-75% THR
Erickson, 2011	RCT	120	73	67.6 (5.81)	Aerobic, walking	52 weeks, 3×/week, 10-40 min (10 min, increased to 40 by week 7), 50-60 to 60-75% THR
Voss, 2013	RCT	65	73	66.3	Aerobic, indoor walking	52 weeks, 3×/week, 10-40 min (10 min, increased to 40 by week 7), 50-60 to 60-75% THR

Table 4 (continued)

First author, year	Design	Exercise min/week	n	% female	Age	Control/comparison group	Trophic factors outcomes	Intervention	Main findings
Vale, 2009	Open trial		35	100	68.08 (3.37)/68.69 (4.7)	Resistance or aerobic, aquatic exercise		12 weeks, 3×/week, 50 min, moderate to high, 50% to 75-85% 1RM (resistance); light to moderate RPE (aerobic)	
Banitalebi, 2018	RCT		40	100	67.35 (1.4)	G1: resistance + aerobic; G2: aerobic + resistance; G3: interval resistance–aerobic		12 weeks, 3×/week, 50 min, moderate- to high-intensity (aerobic) and moderate resistance training	
Cassilhas, 2007	RCT		62	0	69.01 (1.1)/68.4 (67)	Resistance, moderate or high intensity		24 weeks, 3×/week, 60 min, moderate (50% 1RM) and high intensity (80% 1RM)	
Hofmann, 2016	RCT		91	100	83.6	Progressive resistance training with bands		26 weeks, 2×/week, 60 min, yellow and then red and black resistance band	
Mason, 2013	RCT		35	100	58	Diet, exercise, diet + exercise		52 weeks, 5×/week (3x supervised +2x home), 45 min, moderate to vigorous 70-85% THR	
Tsai, 2015	RCT		48	0	71.4 (3.79)	Resistance		52 weeks, 3×/week 60 min, high-intensity resistance training (75-80% of 1RM, 3 sets × 20 reps)	
Ogawa, 2010	Before and after trial		21	100	85 (4.5)	Resistance		12 weeks, at least 1×/week, 40 min, low intensity progressed by participant request	
Seo, 2012	RCT		22	100	55	Aerobic, walking or combined (aerobic–resistance)		12 weeks, 3×/week 60 min, moderate aerobic intensity (60-80% of HR reserve) and resistance (50-70% of 1RM)	
Ruiz, 2015		120-135 min/week				Usual care	Serum levels of BDNF		No effect on BDNF serum levels
Kim, 2015		120 min/week				Exercise + placebo; MFGM supplementation; or only placebo group	BDNF and IGF-1 serum levels		No change in BDNF or IGF-1
Levinger, 2008		NA				HiMF control; or LoMF training; or LoMF control	BDNF levels		No changes in BDNF before to after in any group
Coelho, 2012		180 min/week				Nonfrail vs prefrail	BDNF levels, plasma		↑ BDNF levels
Vedovelli, 2017		180 min/week				No exercise	BDNF serum levels		↑ in BDNF levels for the intervention group
Forti, 2014		180 min/week				No exercise	BDNF serum, basal levels		No change in BDNF
Forti, 2015		NA				Resistance training, low intensity or mixed low resistance	BDNF, serum levels		No time x group interaction
Matura, 2017		90 min/week				Waiting list control group	BDNF, venous blood sample		No change in BDNF serum levels
Hvid, 2017		NA				No intervention	BDNF (mature BDNF, precursor proBDNF, total BDNF), serum levels at fasting		No change in BDNF serum levels
Prestes, 2014		80-100 min/week				Control group	BDNF, serum levels		↑ Percent in BDNF serum concentration in high responders compared to medium and low responders; ↑ Serum concentrations of BDNF in the high and medium responders after intervention and ↓ in low responders
Vaughan, 2014		120 min/week				Waiting list control group	BDNF, plasma levels		↑ BDNF levels in the intervention group from 4.5 to 5.2; ↓ BDNF levels in the control group 5.6 to 4.7

Table 4 (continued)

Study	Dose	Comparison group	Measure	Results
Maass, 2015	120 min/week	Indoor progressive-muscle relaxation/stretching	IGF-1, VEGF, and BDNF level	No changes in VEGF, IGF-1, and BDNF (no main or interaction effects)
Baker, 2010	180–240 min/week	Stretching and balance group	BDNF, IGF, plasma levels	↑ BDNF for the stretching group; ↓ BDNF for the aerobic group
Rehfeld, 2018	180 min/week	Sport group (endurance, resistance–endurance, and flexibility)	Serum and plasma BDNF	↑ BDNF plasma levels (not serum) in the dance group only plasma
Ruscheweyh, 2011	G1: 141 (30) G2: 138 (27) min/week	No intervention control group	BDNF, serum blood levels	No changes in BDNF
Leckie, 2014	120 min/week	Stretching and toning group	BDNF serum levels (fasting)	↑ BDNF levels for the intervention group individuals > 65 years; ↓ BDNF for the control group > 65 years
Erickson, 2011	120 min/week	Stretching control group	BDNF, serum levels	No changes in BDNF levels (no time x group interaction)
Voss, 2013	120 min/week	Flexibility, toning, and balance group	BDNF, IGF, and VEGF serum blood levels	No changes in BDNF, IGF, and VEGF
Vale, 2009	150 min/week	Regular activity	IGF-1, blood serum levels	↑ IGF-1 in strength training only; No changes in aquatic or control
Banitalebi, 2018	150 min/week	Control group	IGF-1, blood levels fasting state	No between-group differences in IGF-1; ↑ IGF-1 within-group differences for aerobic + resistance and resistance + aerobic groups
Cassilhas, 2007	180 min/week	Warm-up and stretching without overload 1×/week	IGF-1, blood serum levels	↑ IGF-1 in both experimental groups related to the control
Hofmann, 2016	180 min/week	Cognitive training	IGF-1, blood serum levels	No changes in IGF-1
Mason, 2013	125 min/week + 90 min/week	Control no intervention	IGF-1, blood serum levels at fasting	No changes in IGF-1 comparing exercisers to control
Tsai, 2015	180 min/week	Nonspecific exercise intervention or group activity	IGF-1, blood serum levels	↑ IGF-1 in the exercise group
Ogawa, 2010	At least 40 min/week	No control group	IGF-1 and VEGF, blood serum levels at fasting	No changes in IGF-1 or VEGF
Seo, 2012	180 min/week	Stretching control group	IGF-1, blood serum levels	No main effects for IGF-1

n = number of subjects; *S.D.* = standard deviation; *RCT* = randomized controlled trials; *NR* = not reported; *NA* = not applied; *THR* = target heart rate; *RPE* = rate of perceived exertion; *BDNF* = brain-derived neurotrophic factor; *IGF-1* = insulin-like growth factor; *VEGF* = vascular endothelial growth factor; *HiMF* = high number of metabolic risk factors; *LoMF* = low number of metabolic risk factors; *1RM* = one-repetition maximum; *VT1* = first ventilatory threshold; *VO₂max* = maximum rate of oxygen consumption; ↑ = significant increase; ↓ = significant decrease

training may increase IGF-1 levels, but there may be an optimal window with regard to age range (at approximately 60 years of age).

Three studies utilized medium-duration exercise (24 weeks) including moderate- to high-intensity aerobic [108] and moderate to high resistance training [116, 117]. The aerobic exercise showed no changes in IGF-1 [108], but the cognitive assessment revealed improvements in executive function (task-switching and visuospatial processing speed). Only 1 of 2 studies found moderate- and high-intensity resistance training to increase IGF-1 levels [116]. A possible reason for the difference in findings is that Cassilhas et al. [116] achieved 72 h of total intervention compared to 48 h [117]. Additionally, Cassilhas et al. [116] showed that the intervention group had improvements in visual processing and short-term memory. As such, in the medium term, resistance training, but not aerobic, associated with memory and attention improvements, possibly due to longer intervention duration, may lead to increases in IGF-1.

Three studies used long-duration exercise (52 weeks), employing moderate to vigorous aerobic [109, 118] and high-load resistance training [119]. Neither aerobic exercise intervention demonstrated a change in IGF-1 when compared to a control or comparison group. Voss et al. [109] also looked at the effects of aerobic intervention on VEGF, finding no changes [109]. High-load resistance training compared to a control group was found to increase IGF-1 and improve processing speed [119]. Overall, these studies provide evidence that short, medium, and long exposure to moderate- to high-intensity resistance training may increase IGF-1 levels in aging adults; however, no consistent effects from aerobic exercise have been evidenced.

The Takeaway: Dose Effects of Exercise in Aging Adults

In this review, we have summarized the evidence on the effects of different intervals of exposure to exercise (short- [1 day-16 weeks], medium- [24-40 weeks], and long-term exercise [52 weeks and beyond]) on the most well-accepted mechanisms used to explain the link between the practice of regular exercise and the improvement in cognitive performance. Due to the heterogeneity in studies, it was not possible to report on domain-specific mechanistic changes. However, evidence from a large-scale systematic review and regression indicates that the most stable and consistent improvements in cognition following exercise occur in executive functions and processing speed [12]. Therefore, we discussed changes in cerebral perfusion, synaptic neuroplasticity, brain structure (volume and connectivity), neurogenesis and synaptogenesis, and trophic factors (BDNF, IGF-1, and VEGF) following participation of exercise in older adults or aged rodents (if no

human data was available), that would underlie these improvements in cognitive abilities. We refer to Fig. 1 for a time-guided discussion of the exercise-mediated improvements in mechanisms related to brain health in humans.

Short Term (1 Day to 16 Weeks)

Even with very short aerobic exercise interventions (i.e., just a few minutes as part of an incremental cycling test), there were increases in resting regional CBF and MCA velocity. Short-duration aerobic was the only exercise mode found to be effective at changing connectivity, primarily increasing neural efficiency in frontal and temporal areas, relevant to the processing of cognitive information. The finding of increased connectivity allied to increased brain perfusion is consistent with animal studies that have found that increased connectivity is among the first of exercise-mediated improvements at the brain level, which in turn promotes an increase in angiogenesis to support increased metabolism, ultimately leading to neurogenesis [76, 79]. The only other structural improvement also associated with aerobic exercise was increased hippocampal volume, which was associated with increased cerebral blood flow to the hippocampus. Despite all of the aforementioned beneficial structural brain changes, aerobic exercise did not seem to change neurobiological factors, as increases in BDNF and IGF-1 were only found with resistance training or combined aerobic and resistance training. Therefore, for the most global benefits from exercise, a combined approach utilizing both aerobic and resistance exercises with at least moderate intensity will contribute best to improved brain structure, cerebral blood flow, as well as improvements in neurobiological factors such as BDNF and IGF-1, in the short-term.

Medium Term (24 to 40 Weeks)

As the intervention time increased to medium exposure, there continued to be findings of increased connectivity with aerobic exercise. In addition, there were more consistent and diverse structural changes found in terms of increased white and gray matter and volumetric increases mainly in the in frontal and temporal areas (such as the hippocampus, cingulate, and frontal cortices). BDNF was only increased when individuals engaged in an aerobic dance intervention and IGF-1 was only increased when individuals engaged in moderate to high resistance training. We also found some patterns in the studies and identified 3 isolated characteristics that seemed to be associated with the greater likelihood of finding a benefit: including a progressive intervention that increased the exercise intensity from moderate to high, an exercise intervention with at least 150 weekly minutes, and constant novelty (a choreography or the combination of exercise modes).
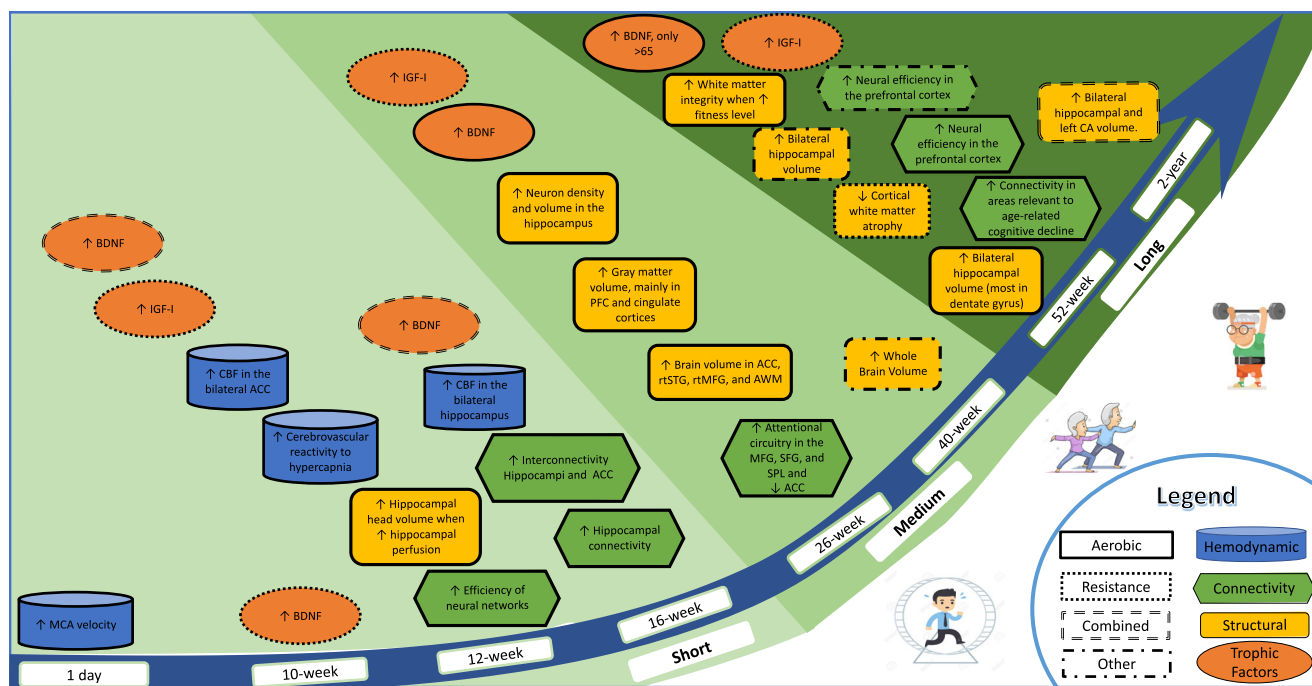
Fig. 1 The significant changes in cerebral perfusion, brain structure, and connectivity and trophic factors with short-, medium-, and long-term exercise. The findings are characterized by the type of exercise performed: aerobic, resistance, combined, or other (i.e., tai chi). MCA = middle cerebral artery; CBF= cerebral blood flow; BDNF = brain-derived neurotrophic factor; IGF-1 = insulin-like growth factor-1; VEGF = vascular endothelial growth factor; ACC= anterior cingulate cortex; PFC = prefrontal cortex; rtSTG = right superior temporal gyrus; rtMFG = right medial frontal gyrus; AWM = anterior white matter; MFG = medial frontal gyrus; SFG = superior frontal gyrus; SPL = superior parietal lobules; CA = cornus ammonis

Although the present review synthesizes results from healthy aging individuals, it is pertinent to also consider the role of commonly seen cardiovascular risk factors on the baseline level of risk for cognitive decline. Cardiovascular risk factors are also risk factors for cognitive impairment [120]. Hypertension (present in 65% of adults older than 60) [121], diabetes mellitus (present in 25% of adults older than 65) [122], obesity (present in 40% of adults older than 60), smoking (present in 8% of adults 65 and over), and insufficient activity (present in 60% of adults older than 65) are all associated with poor cognitive health [123]. Notably, age-related cognitive changes associated with vascular risk factors are likely mediated through small vessel disease, including white matter pathology. For example, in a sample of 113 aging adults, 67% of individuals who had white matter lesions also had cardiovascular diseases, which in turn was linked to greater impaired visual functions, mental flexibility, and attention [120]. Favorably however, maintaining a regular exercise regimen for approximately 3 to 6 months can improve maximal aerobic capacity (the gold standard for cardiorespiratory fitness) in older adults [124]. The increased cardiovascular fitness can have a role in modifying these risk factors, thus contributing to potential improvements in cognitive brain health and, additionally, enlisting neurohumoral processes controlling the cardiovascular and endothelial systems [123, 125].

Long Term (52 Weeks and Beyond)

Studies in long-term exercise included exercise modes beyond aerobic interventions. Aerobic, coordination, and combined exercise interventions were linked to increases in white matter integrity and increased hippocampal volume, which seemed to be driven by an improvement in cardiovascular fitness through moderate to high exercise intensities. In addition, these interventions were associated with increased neural efficiency. Resistance training was shown to be effective at increasing IGF-1. These studies have also provided evidence that different exercise modes exert benefits via distinct mechanisms, which further supports the suggestion that engaging in physical exercise of different modes will lead to the greatest benefits on brain health.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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