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Exercise and brain function in obese & overweight people - a review

Abstract

Obesity has become a global epidemic and has almost tripled since 1975. Obesity results from an excessive accumulation of fat in the adipose tissues and has correlations with cardiovascular comorbidities. Cognition is affected by obesity mainly due to structural and functional brain changes. Exercise and physical activity for general populations have shown to have advantages at all levels in the management of obesity. This review aims to examine if exercise can improve brain function in obese and overweight people. Studies have looked at the obesity effects on factors associated with deteriorating cognitive and motor functions. Obesity has been found to have an association with a reduction in cognition and brain plasticity. There are important functions of exercise for aiding the overall health of the brain however the ways in which brain health is supported by exercise are not well understood. Therefore, it is important to explore if exercise can improve brain function and cognition along with reducing a decline in motor functions. This review also discusses how brain function can be improved with aerobic exercise. Exercise interventions that start early in life seems to have huge benefits for brain function. For long enough periods of time, moderately intense exercise has been found to be especially advantageous for young people.

Keywords: obesity, brain function, exercise, aerobic, anaerobic

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Abbreviations: WHO, World health organization; CVD, cardiovascular diseases; PA, physical activity; BMI, body mass index; IL-1, interleukin-1; BDNF, brain-derived neurotrophic factor; IGF-1, insulin-like growth factor 1; DNA, deoxyribonucleic acid; APE1, apurinic/apyrimidinic endonuclease 1; AD, Alzheimer's disease; CREB, cAMP response element binding; RCI, randomized controlled trial; APOE, apolipoprotein E; DMN, default mode network; ACC, anterior cingulate cortex; PI, pulsatility index; VBM, voxel-based morphometry; rGMV, regional grey matter volume; PBMC, peripheral blood mononuclear cell; TrkB, tropomyosin receptor kinase B

Introduction

Obesity has become a global epidemic and the World Health Organization (WHO) states that it has almost tripled since 1975.[1] In 2016, there were higher than 1.9 billion (39% of adults above 18 years of age) overweight people and over 650 million (13% adults) obese people.[1] Obesity is involved with various diseases including hypertension, diabetes, cardiovascular diseases (CVDs), dyslipidaemia and cancer.[2,3] Obesity may be caused due to a lack of physical activity (PA), an increase in energy intake or genetic susceptibility, with underlying causes such as endocrine disorders, gene mutations, psychiatric illnesses or medications.[3] People with body mass index's (BMIs) from 25kg/m^2 to 29.9kg/m^2 are usually overweight while people with BMI's of more than 30kg/m^2 are defined as obese.[1] Evidence suggests that obesity has associations with structural and functional brain alterations, cognitive deficits and altered brain plasticity.[4] Exercise can have important roles for supporting the health of the brain however the processes for brain health being supported by exercise are not well understood. This review aims to examine if exercise can improve brain function in obese and overweight people. Deficits related with obesity in motor control and cognition will additionally be examined and future implications will be discussed.

Obesity, cognition and brain plasticity

Obesity can affect brain structure, cerebrovascular function, insulin and leptin dysregulation, blood-brain barrier, oxidative stress and inflammation.[5,6] It can also cause insulin disturbances[7] and change motor performance by degrading the musculoskeletal system.[8] A previous cross-sectional study reported associations between adiposity measure and muscle quality ratios, finger tapping speed, memory performance ($p<0.01$) and peroneal nerve motor conduction velocity.[8] Brain plasticity, also known as neuroplasticity, is the ability of the brain to reorganise its structure and functions. Cytokines produced by the adipose tissue such as interleukin-1 (IL-1), can cross barriers between the blood and brain and influence cognitive function, causing neuro-inflammation.[9] The adipose tissue also produces adipokines, including brain-derived neurotrophic factors (BDNFs), alongside inflammation causing cytokines for metabolism.[9]

BDNF is a key protein which favours neuroplasticity and insulin-like growth factor 1 (IGF-1) are neurotrophins which enable obesity's effects on behaviours and cognition.[9] BDNF stimulates neuronal survival and differentiation, neurogenesis and brain plasticity and has been especially important in memory and learning.[10] An animal study reported that BDNF also stimulates repair of deoxyribonucleic acid (DNA) for protecting cerebral cortical neurons from oxidative stress by inducing the apurinic/apyrimidinic endonuclease 1 (APE1) enzyme expression.[11] Leptin, the satiety hormone, helps to regulate energy expenditure and appetite and its production becomes higher throughout obesity.[12] Leptin is also important for synaptic plasticity and plays important roles in long-term depression and potentiation regarding the hippocampal neurons.[13] It influences neural degradation, brain development, cognitive functioning and Alzheimer's disease (AD).[13]

Exercise & brain function

Exercise can be defined as repetitive and intentional movement that is planned and structured whereas PA is any movement that requires energy and is carried out by the muscles. While sedentary behaviour has been involved with impaired cognition, exercise on the other hand improves cognition.[14] An earlier population based study reported that during exercise, especially in older adults, brain haemodynamic changes may occur.[15] Those who exercised at least three times/week, had improved/stable cognition more frequently (95% confidence

interval (CI) 40.6 to 44.0, 42.3%) over 5 years compared to those who did not or exercised less (27.8% (95% CI 26.4-29.2)).[15] In older adults, a cross-over trial emphasized that moderate-intensity exercise improved BDNF levels and executive function or working memory.[14] An animal study found that other than increasing BDNF levels, exercise also up regulates APE1 and activates cAMP response element binding (CREB) in the hippocampus and cerebral cortex.[11] PA is a lifestyle factor which is modifiable and studies have shown that it improves both neurocognitive and physical health during a person's life.[15,16] It has been linked to both enhanced brain function and elevated cognitive performance.[15,16] PA can help both slowing and prevention of brain volume loss and help to improve functional connections for regions of the brain. Studies have shown that people who do frequent PA have lower risks of cognitive decline and larger levels of cognitive function.[15] For example, an earlier Australian randomized controlled trial (RCT) had shown that a six-month PA program improved cognitive function throughout a follow-up period of eighteen months.[17] A cohort study reported that males and females over 60 years of age, who performed more intense PA, were better at tasks that looked at cognitive function.[18] These associations were independent of gender, age, BMI, apolipoprotein E (APOE) e4 allele carriage and education.[18]

Evidence from studies of both animals and humans support PA roles for changing functional, metabolic and structural brain dimensions along with maintaining cognitive performances for older people.[19] Exercise that targets neuroprotective mechanisms and modifiable risk factors could lower reductions in cognitive performances involved with processes of normal aging along with protection against any change as a result of neurodegenerative diseases like AD as well as different dementia forms.[19] Spatial and short-term memory and learning had been assessed for male rats that had been separated randomly into four groups.[20] Amongst the four groups, exercise improved memory and spatial learning, and short-term memory through increasing neurogenesis and BDNF levels, and through stopping hippocampal dentate gyrus apoptosis for male offspring born from obese female rats.[20]

Exercise and structural changes in the brain

One meta-analysis and systematic review consisting of 14 studies examined aerobic exercise effects for structures plus functions of default mode network (DMN) brain regions throughout adulthood.[21] Aerobic exercise hugely increased right hippocampal volumes (95% CI 0.01 to 0.51, standardized mean difference (SMD)=0.26, 4 studies, I^2=7%, p=0.04) while similar changes had additionally been examined in the total, right and left anterior hippocampal volumes compared to controls.[21] Some studies mentioned that aerobic exercise could significantly decrease medial temporal lobe atrophy, increase signal activation in the ACC and cingulate gyrus, reduce anterior cingulate cortex (ACC) volume loss and enhance functional connectivity in the hippocampus.[21] A recent experimental study compared both cognitive function and CVD risk between people who have non-elevated and elevated PI.[22] They compared pulsatility index (PI) and cerebral blood flow velocity throughout exercise of moderate intensity for either older adults who had normal pulsatile flow (normal PI) or those who had elevated pulsatile flow (elevated PI).[22] The percentage PI was found to increase from resting to exercise of moderate intensities was reduced for older people with higher resting PIs. PI changes were bigger for the normal PI group (p=0.00, 535.5% versus 21.3%).[22] These results indicate that brain health could be negatively affected by higher resting PIs due to processing speed scores being slower.[22]

Structural brain changes are normally influenced by exercise and regularity.[23] The amount of exercise per week was found to have a significant correlation with the right hippocampus volume in adults.[23] An animal study also provided more understandings for adult animal's structural brain plasticity.[24] In the exercise group, longitudinal voxel-based morphometry (VBM) analysis showed huge increases for regional grey matter volume (rGMV) in the somato sensory, motor, visual and association cortices.[24] A positive correlation was also found with rGMV motor cortex changes and distance runs in the 1-week exercise.[24] A randomised controlled trial (RCT) demonstrated aerobic training improving the aging brain's resting functional efficiencies for cognitive networks of higher levels.[25] Functional connectivity was increased within a year of walking between aspects of the temporal, posterior and frontal cortices in two brain networks that were vital in brain dysfunction of the aged.[25] Training length is another important factor. Exercise interventions for seven days in an animal study had higher grey matter volumes for motor, visual and somato sensory cortices[24] while year-long walking had more working connections for the default mode networks frontal and executive networks.[25] After 12 months of training, effects favouring the walking group had been examined in comparison with trends without any significance after 6 months.[25] In aged animals, regular PA reduced pro-inflammatory signalling, increased anti-inflammatory signalling and reduced oxidative stress.[26] A daily moderate intensity exercise for a period of 15 weeks resulted reduced ROS levels due to lower protein carbonyl amounts for the hippocampus in physically trained rats in comparison with sedentary controls.[26] Peripheral risk factors, including diabetes and CVD that were involved with neurodegeneration were also reduced by exercise.[27] Furthermore, changes in vasculature were observed after exercise. The surface area and total cortical capillary lengths were increased for middle-aged rats after running.[28] However, the surface area and total length of the cortex capillaries for running in female rats of middle age were higher.[28] The presence of gender differences in running exercise's effects on the cortex capillaries were revealed by the results.[28]

In trained adolescents, IGF-1 and BDNF levels were largely increased than in sedentary people.[29] However, no effect of training was found in the activation of CREB in peripheral blood mononuclear cells (PBMCs).[29] PA increased neuroadaptation, neuroprotection and neurogenesis, through neurotrophic factor actions.[30] It restored hippocampal function by increasing expressions of neurotrophic factors for encouraging synaptic plasticity, angiogenesis and neurogenesis.[29] BDNF levels for example, increased with PA and regular exercise.[31] Interestingly, studies with more females have shown less BDNF change due to exercise. A meta-analysis showed moderate effect sizes for increased BDNF after one exercise session (p<0.001, Hedges' g=0.46) and regular exercise increased those effects (p=0.02, Hedges' g=0.59).[31] The researchers observed that gender significantly moderated exercise effects on BDNF levels.[31] For obese adolescents, training during exercise promoted metabolic health and increased BDNF.[32] In aged rats, short bouts of exercise lasting 5 weeks improved spatial learning and long-term memory related with hippocampal BDNF levels.[33] Short exercise bouts enabled CREB pro-survival signalling and threonine/serine protein kinase (AKT), which increased BDNF protein levels and mRNA expressions for the hippocampus in aging rats.[33] Dentate gyrus hippocampal BDNF levels and tropomyosin receptor kinase B (TrkB) receptor activation were increased after PA.[34] In this study, the researchers demonstrated that PA enabled T-type voltage-dependent Ca^{2+} currents and synaptogenesis for immature neuron.[34] Exercise which lasted a week increased tissue type plasminogen activator activities for enabling cleavages of precursor stage of (proBDNF) to mature form of BDNF (mBDNF).[35] Exercise also prevented neurodegeneration and increased mitochondrial biogenesis.[36] These improvements induced

prevention of signs of neurodegeneration, mitochondrial biogenesis stimulation, sirtuin 1 up regulation and AMP-activated protein kinase (AMPK) activation.[36] These results are consistent with different studies demonstrating exercise's positive effects for hormesis.[36]

Biological and psychological benefits of exercise

Evidence suggests that PA can affect brain plasticity, influencing wellbeing and cognition.[37] Academic lessons that are physically active could mean bigger instant academic along with cognitive advantages among obese and overweight children than normal-weight children.[38] If academic lessons are physically active, it could enhance attentiveness along with inhibition, especially for overweight adolescents. PA which is frequent could be successful in improving neurological, achievement and cognitive results in youth who are either obese or overweight.[38] For example, growing evidence has demonstrated that it controls memory processes and neuroplasticity. Moderate-intensity exercise which occurred in the morning was shown to improve serum BDNF and executive function or working memory for older people, especially if succeeding resting was additionally disrupted by irregular light intensity walking.[14] Epigenetics has been founded through conceptual models accounting for genes interacting in their environments for producing phenotypes.[39] Psychological and biological PA effects could be partially explained by mechanisms which are epigenetic.[40]

Exercise, type 2 diabetes and obesity

Exercise is very important for controlling both body weight and glucose homeostasis. However, exercise mechanisms for metabolic functions related with the CNS have not been clear.[41] In a study, 45 male mice were split into three groups including a high-fat diet (HFD) treatment and normal chow diet alongside HFD including wheel exercise training with voluntary running which lasted for twelve weeks.[41] The authors found that exercise training which was voluntary lasting 12 weeks, slightly lowered body adiposity and weight gain caused due to HFDs.[41] Leptin and insulin sensitivities became higher for the exercise training group against the HFD group. Moreover, pro-opiomelanocortin (POMC) expressing neurons which were HFD-impaired were restored for the exercise training group. Restoring the POMC neuron number could have occurred because of exercise's neuroprotective effects for POMC neurons, demonstrated through changed apoptosis and proliferation.[41] Insulin resistance plays big parts for cognitive impairments and obesity.[42] Similar with leptin, insulin resistance takes part in obesity due to complex mechanisms. Higher risks of insulin resistance, central obesity and dyslipidaemia have been found among children.[43] Type 2 diabetes (T2D) risks become increased due to obesity in youth and they are both considered as neurocognitive deficit risk factors. Risks of T2D and obesity could be reduced with exercise along with cognitive function improvements. Reduction of some diabetes risk factors as a result of exercise have been related to BDNF increases in obese adolescents.[32] One study for post-pubertal obese adolescents demonstrated that increases in BDNF were related to lower fasting glucose levels ($p=0.05$, standard error (SE)=3.37, beta (β)=-6.57) in the exercise group and increases in homeostasis model assessment [(HOMA)-B ($p=0.004$, SE=0.03, $\beta=0.093$) once control of confounders took place.[32] However, no significant associations were discovered between BDNF changes or diabetes risk factors.[32]

Exercise and Alzheimer's disease

A recent study has shown that hippocampal subareas which are especially vulnerable to volume loss in AD can be protected by resistance exercise when training for a year.[44] The authors of this study mentioned functional and neuro-structural changes over the trial period lasting eighteen months and the association with executive function and global cognitive measures. The neuroprotective effects from this had bigger cognitive advantages that were long-term. However, posterior cingulate plasticity throughout training deteriorated once training was stopped, not having any relation with cognitive advantages in the longer term.[44] This study showed that six months of resistance exercise with high intensity can protect hippocampal subfields vulnerable to AD for about twelve months from degenerating before treatments.[44] Additionally, multiple structural mechanisms can result in global cognitive advantage of resistance exercise in the longer term. In an intention-to-treat analysis, a previous RCT found an increase of 0.26 points (95% CI -0.89 to 0.54) for adults with memory impairment, while normal care group people declined by 1.04 points (95% CI 0.32 to 1.82) for the AD Assessment Scale-Cognitive Subscale (ADAS-Cog).[17] The absolute outcome measure difference between control and intervention groups were -1.3 points (95% CI -2.38 to -0.22).[17] Those in the intervention group at 18 months improved by 0.73 points (95% CI -1.27 to 0.03), whereas those in the normal care group improved only 0.04 points (95% CI -0.46 to 0.88).[17]

Exercise and multiple sclerosis

People with multiple sclerosis (MS) demonstrate predominantly low rates of PA. Although exercise may result in symptoms for a few MS patients temporarily worsening, it usually is believed to be safe and there is no relapse risk increase. PA therefore signifies health behaviour that is modifiable as a potential management for MS vascular comorbidity risks, and as a result, lowering the disease burdens.[45] Evidence has shown potential relationships between exercise, PA and risk factors connected with vascular comorbidities for MS patients. A connection was found between higher cardiorespiratory fitness and PA levels, or reduced sedentary behaviour, and improved function for a risk factor associated with vascular comorbid conditions in MS patients.[45] Exercise and PA training interventions could show efficient therapeutic strategies for managing vascular comorbidities for MS people and requires more investigation.[45]

Types of exercise

Exercise improves cognitive and physical performances along with life quality in older people.[46] Many factors, for example, frequency, duration and intensity of the exercise and whether they are done alone or in groups, can determine if an exercise is successful.[37] Clinical and experimental studies showed that PA prompts functional and structural changes within the brain, with huge psychological and biological advantages.[40] In the elderly, other than cognition a higher level of PA was related to lower white matter hyper-intensity(WMH) burdens on motor function.[47] Higher WMH burden resulted in reduced motor function ($p=0.006$) while total daily activity had been associated positively alongside motor function ($p=0.002$).[47] Total daily activities changed associations between motor function ($p=0.007$) and WMH. However, the WMH burden had no associations with motor function for people with higher activities (90th percentile).[47] Lifelong exercise can preserve white matter microstructure associated with coordination and motor control for older people.[48] There was 83% reductions for deep WMH volumes were observed for the intervention group in comparison with controls ($0.05\pm0.05\%$ versus $0.29\pm0.29\%$, $p<0.05$).[48] Additionally, inverse relationships were found between deep WMH volume ($p<0.001$, $r=-0.78$) and aerobic fitness (VO_2max).[48] In the intervention group, larger FA values were found in the double-sided superior longitudinal fasciculus (SLF), the right superior corona radiata (SCR), right inferior front occipital fasciculus (IFO), left inferior longitudinal fasciculus (ILF), left cingulum hippocampus

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and lower mean diffusivity (MD) values with left posterior thalamic radiations (PTRs).[48]

Frequent PA can effectively improve both obesity and other related problems.[49] Aerobic fitness was associated with large amounts of unique variance for hippocampal volume (adjusted R=0.27), executive function (adjusted R=0.34) and processing speed (adjusted R=0.44).[49] In overweight children, doing exercise five days a week for fifteen weeks improved executive functions.[50] Improvements were observed in body composition and fasting insulin ($p<0.05$), power output and VO_2 at peak power output ($p<0.05$) and ventilatory threshold.[51] Significant improvements were observed after training in cognitive functioning, including verbal and short-term memory, processing speed ($p<0.05$) and attention and cerebral oxygen extraction ($p<0.05$).[51] PA of high-intensity (both endurance and aerobic training) for four months improved oxygen extraction and cognition for people who are obese.[51] During regular PA, there are lower risks of developing dementia, less cognitive decline and improved cognition.[52] A study showed that training lasting two weeks for stress-free mild exercise (ME) while not having intense exercise (IE) improved adult hippocampal neurogenesis, which can potentially improve memory. The study found that only IE caused general adaptive syndrome (GAS), including adrenal hypertrophy, hypercorticosteronemia and thymic atrophy.[52] ME resulted in improved memories, although with learning unaffected, compared to sedentary control, while IE was without any changes in either capacity, possibly as a result of GAS.[52]

Aerobic exercise

Aerobic exercise improves how oxygen can be utilised in the body. Aerobic exercise includes running, swimming, cycling and jogging.[40] Most types of aerobic exercise occur at average intensity levels for longer periods of time. Aerobic exercise encourages re-synthesis of adenosine triphosphate (ATP) through duration (usually long), adjusting intensity (between low and high intensity), aerobic mechanisms and availability of oxygen.[40] Aerobic fitness usually predicts cognitive performance throughout time in children.[53] Those who are aerobically trained or are highly fit have larger parietal and prefrontal activations for inhibitory functioning and spatial selection.[54] Aerobically trained or highly fit people had greater task-related activities for the parietal and prefrontal cortices regions helped cause spatial selection and inhibitory functioning, in comparison with non-aerobic or low-fit controls.[54] An exploratory study in 165 non-demented older adults looked at if people with higher aerobic fitness levels had better spatial memory performances and greater hippocampus volumes than people who had reduced fitness levels.[55] Increased fitness levels were found to be involved with bigger left/right hippocampi and larger hippocampi and larger fitness levels had been correlated with improved spatial memory performances.[55]

Advantages of aerobic exercise

The advantages of aerobic exercise are that it can improve strength of muscle throughout the whole body, lungs and heart, reduce blood pressure and improve muscle blood flow and blood circulation. It also increases red blood cell counts for more transportation of oxygen. It can reduce risks of stroke, diabetes and cardiovascular disease (CVD), improve life expectancies and symptoms in people who have coronary artery disease. It can stimulate bone growth and reduce osteoporosis risks during high intensities, improve sleep hygiene, enhance stamina through improving the body's ability of storing energy molecules, which include carbohydrates and fats, inside the muscles. The intensity could depend on the cardiorespiratory effort in respect with maximum oxygen consumption (VO_2max) or maximum heart rate (HRmax) determining increases in oxygen consumption during rest conditions.[40] However, evidence from scientific reports suggests that exercise performed in anaerobic or aerobic modality have different effects on wellbeing and cognitive functioning.[40] Aerobic training increases hippocampal volume for older people (without or with mild cognitive impairments) along with increasing plasma BDNF levels in both healthy controls and AD patients.[56,57] An animal study showed that a treadmill exercise for five months ameliorated impairments of memories with age and spatial learning corresponding to synaptic plasticity increases.[56] Additionally, synaptic plasticity enhancement caused by exercise resulted in large soluble amyloid β-protein (Aβ) level reductions rather than the deposition of Aβ plaques, while total, right and left hippocampal volumes were significantly improved ($p\leq0.03$).[57] Higher left hippocampal volumes were associated independently with lower learning performances and verbal memories while indexed through losses after interferences ($r=0.42$, $p=0.03$).[57]

At midlife, aerobic exercise improves myelin dysregulation, astrocyte hypertrophy and vascular dysfunctions connected to sedentary lifestyles.[58] Exercise increases densities of glial fibrillary acidic protein (GFAP) positive astrocytes along with cellular and regional GFAP expressions and also altered astrocytic morphology.[58] A meta-analysis demonstrated aerobic exercise may largely increase right hippocampal volumes ($p<0.05$), and similar effects had been observed for total, left or right anterior hippocampal volumes (all $p<0.05$) compared with interventions without exercise. Some studies mentioned that aerobic exercise compared with no-exercise interventions may slow anterior cingulate cortex (ACC) volume losses, enhance ACC and cingulate gyrus signal activations, increase hippocampus functional connections and reduce medial temporal lobe atrophies.[21]

Anaerobic exercise

Anaerobic exercise is usually short, of high intensity with unavailability of oxygen, looking at shifting the production of ATP, reduction of the muscles' ATP or reserves of phosphocreatine (PCr), to anaerobic energy mechanisms, alactacid or lactacid.[40] These usually are activities of high-intensity.[59] Anaerobic exercises include sprinting, weightlifting, fast and intensive rope skipping, isometrics, interval training and any quick bursts of intensive activity.[40] During the process of anaerobic exercise, oxygen is not used for gaining energy. Anaerobic exercise is used for building strength, muscle mass and power however, not enough evidence is present for suggesting that anaerobic exercise improves both brain function and cognition.

Exercise intensity and cognition

Previous studies have shown that exercise intensity is usually an important component adding to associations between cognition and PA.[60,61] A Dutch cross-sectional study showed that regular intensities of PA every week and activity variations are significantly and positively involved with cognitive performance to process memory, mental flexibility and speed along with overall cognitive function performances.[60] Cognitive decline rates were not variable with men having low or high activity durations at baseline.[61] However, reductions for activity durations around >60 min/day throughout 10 years caused declines of 1.7 points ($p < 0.0001$).[61] These declines were 2.6 times stronger compared to declines in males maintaining their activity durations ($p = 0.06$).[61] Males with lowest intensity quartiles at baseline were between 1.8 ($p=0.07$) and 3.5 ($p=0.004$) times bigger cognitive declines over 10 years compared to people with the other quartiles.[61] PA intensity reduction of around half a standard deviation took place alongside a decline which was 3.6 times stronger compared

to maintaining intensity levels (p=0.003).[61] Many studies have demonstrated PA's positive impacts on cognitive function.[18] However, as these studies have mostly used surveys or questionnaires, reporting biases might have influenced the results. A cohort study found a large association between intensities of cognitive functioning and PA.[18] The cohort had been stratified into tertiles founded upon the intensities of PA.[18] In comparison with people in the lowest tertile of PA intensities, people in the highest tertile had scored 21%, 9%, 6%, and 9% higher for the Rey Figure Test 30-min recall test, digit symbol, Rey Complex Figure Test (RCFT) copy and digit span, respectively.[18] They also found that people in the highest PA tertile shad been better on cognitive tasks such as verbal fluency test, RCFT copy and digit symbol (all p<0.05).[18] The authors concluded that intensities rather than quantities of PA could be more important in associations between cognitive function and PA.[18]

The intensity of exercise can be related to both brain structure and BDNF level changes, and behavioural outcomes. Larger PA amounts for children are related to bigger hippocampal and prefrontal volumes.[55] BDNF level was found to depend on exercise intensity and the magnitude of increase was dependent on intensity.[62] Although cognitive function scores were better after all exercise conditions, BDNF changes were found to have no correlation with VO_2max throughout a graded exercise test (GXT), but they correlated with lactate changes (p<0.05; r=0.57).[62] Increases of BDNF expressions were detected in people receiving exercise of low intensity but not people exercising with high intensity.[63] Studies have observed that exercise of moderate intensities is most effective for promoting BDNF for older people.[64]

Exercise duration and cognition

Along with exercise intensity, exercise duration also important. There was no increase in task switching performances after one round of moderately intense exercise.[65] Acute PA bouts were not influential in children's error rates or global switch cost scores.[65] Differences related to age in global switch costed scores, except error scores, had been collected.[65] An animal study looked at peptide amyloid-β production and synapsinIa expression, which have important roles in synaptic plasticity and neurotransmission.[66] In midlife mice, running training for four months activated the neuroprotective, anti-amyloidogenic, synaptogenic and pro-survival pathways, however this was not observed in running training for two months.[66] Voluntary access for running wheel sin both long and short term periods increased cell adult dentate gyrus (DG) proliferation in rats however neurogenesis increases needed long-term exercise exposure.[67] In the dentate gyrus, cell proliferation increased in wheel running for 14 days whereas wheel running lasting 56 days facilitated potentiation for the longer term.[67] These studies have demonstrated that a longer amounts of exercise cause beneficial brain changes. Furthermore, developmental stages for people exercising are also related to exercise advantages. In adult rats, 4-weeks of exercise improved recognition memory but no such improvement was observed 2-weeks after the training stopped although the improvement of recognition memory was retained in adolescent rats.[68] A recent study reported that ovalbumin (OVA)-sensitization caused deficits in cognition in the PA task, alongside higher tumour necrosis factor (TNF)-α within the hippocampus.[70] Exercise however improved those changes, causing the IL-10 levels to be higher in the hippocampus, highlighting that moderate treadmill exercise improves memory impairment within OVA-sensitized rats because anti-inflammatory properties are present.[70] One cross sectional study looked at fatness and fitness associations with academic achievement, cognitive processes and behaviour in an exercise trial. They showed that reading achievement, mathematics and executive function had an association with fitness and obesity at baseline.[71]

An earlier systematic review looked at PA effectiveness on older people's cognitive function without any known impairment of cognition.[72] Along 11 conducted studies, 8 mentioned that aerobic exercise interventions caused higher cardiorespiratory fitness for the intervention group around 14% and that was consistent with cognitive capacity improvements.[72] The largest cognitive function effects had been present in delayed memory functions, auditory attention and motor function (effect sizes of 0.50, 0.52 and 1.17 respectively).[72] However, results for memory functions that were delayed need to be carefully examined as they were obtained from a single study.[72] Additionally, improved cognitive functions were not the same for every study and most comparisons did not contain any significant results. Also, data is not sufficient enough for suggesting that cognitive function improvements being attributed with exercise are the result of cardiovascular fitness improvements.

Discussion

Evidence suggests that obesity results in both cognitive dysfunctions and aging. Key pathophysiological mechanisms in obesity, including neuroendocrine hormone dysfunction and impaired brain circuit regulation seem to be involved. Exercise and dieting are the main pillars of obesity treatment.[3] The brain has an enduring plasticity capacity and even moderate behavioural changes can change the brain function and size. Evidence is present that obesity, diet and PA may affect various disease and organ endpoints, including brain health, with distinct pathways. Higher functional connectivity resulted in greater executive function improvements.[25] RCTs, prospective longitudinal and cross-sectional studies showed that PA had an association with increasing grey matter volumes within the hippocampus and prefrontal cortex, which can sometimes improve cognitive function, including memory and executive function.[15] Several studies have shown that exercise improves brain function for obese and overweight people while others have suggested exercise improves both motor and cognitive declines related to obesity. Exercise has demonstrated positive brain effects, including improved brain cognition and volume. Exercise in the long term protects neurons against oxidative stress at early aging stages and comprises antioxidant properties.[26] Neuroprotective effects encouraged significant cognitive benefits in the longer term.[44] In contrast, posterior cingulate plasticity during training deteriorated after training ceased, unrelated to long term cognitive benefits.[44] Previous meta-analyses' and systematic reviews found that obesity and behavioural interventions were associated, which promoted neurocognitive health. An animal study confirmed that IL1-mediated neuro-inflammation has a central role in mechanisms for obesity and diabetes cognitive deficits.[9] Reductions for some diabetes risk factors due to exercise and the result of BDNF increases in obese adolescents, demonstrate exercise training could be useful for both BDNF increases and metabolic health.[32]

Analysis of effect sizes backs up exercise roles as strategies for increasing BDNF activities for humans, however, it demonstrates that magnitudes of these effects might be less in females compared with males.[31] Capillary increases caused by exercise in female rat cortex could provide a structural base for exercise-induced improvements for spatial learning capacities for middle-aged female rats.[28] Exercise effects on hippocampal plasticity have been dependent on subsequent TrkB signalling and BDNF processing, with important neuronal function implications.[35] Life-long exercise can be involved

with reduced WMH as mentioned by a cohort study and could conserve white matter (WM) fibre microstructural integrity involved with coordination and motor control for older adults.[48] Several observational studies have shown that PA reduces cognitive decline risks. PA even in old age, throughout medium-low intensities, could postpone cognitive decline.[61] An RCT of adults containing variable impairments of memory showed that PA programmes lasting six months provided slight cognition improvements over follow-up periods of eighteen months.[17] However, while some clinical exercise trial interventions had shown positive exercise effects on cognitive performances,[17] other trials have shown minimal or no effect.[19] Regular PA may be effective in improving achievement, cognitive, and neurological outcomes for obese or overweight youth.[38] Quasi-experimental studies which tested PA tests in youth who were obese or overweight have shown potential.[38] PA could be a preventive measure against cognitive function impairment along with being a treatment.[20] One exploratory study showed the hippocampal volume partially encouraging relationships between increased spatial memory and higher fitness levels.[55]

PA has many advantages for healthy ageing. It also could help in the maintenance of good cognitive functions for older people. Observational studies have supported a neuroprotective relationship which is dose-dependent between cognitive performance and PA in older people. Hippocampal BDNF levels and TrkB receptor activation increased after PA.[34] As two cohorts showed, short exercise bouts demonstrated feasible behavioural strategies for improving cognition and synaptic plasticity in aging rats which needs to be further considered in future studies.[33] PA which was higher reduced WMH burden effects on motor function for older people who were healthy.[47] Cohort studies have shown therapeutic potentials for resistance exercise although more research is required to establish if they are enough for delaying dementia and additionally how long lasting the outcomes are.[44] However, future work is required for establishing how long these outcomes last and they can sufficiently delay dementia.[44] A cross sectional study reported that muscle quality is affected by obesity and neurological factors.[8] However, it was a cross-sectional study based upon a small sample size. Another cross sectional study showed that fitness did result in better behaviour cognition and achievement while inferior scores were present in obesity.[71] Fitness can be an advantageous factor for maintaining hippocampal volume, executive function and processing speed, which are vulnerable to obesity or age-related declines.[49] Obesity does not prevent fitness advantages for brain volume and cognition in older people.[49] It has been suggested aerobic exercise has benefits for the right hippocampus and possible advantageous effects for the cingulate cortex, the other and overall hippocampus parts and the medial temporal DMN areas. A previous RCT provided evidence for functional plasticity caused by exercise in brain systems of larger scales for aging brains, using techniques of functional connectivity, and offer new insights into aerobic fitness roles for gaining brain dysfunction related to age.[25] Furthermore, aerobic exercise could increase activation or cingulate cortex functional connectivity, hippocampus and para-hippocampal gyrus DMN regions. When looking at limitations and quantities for included studies, however, there is no definite conclusion. More RCTs containing longer intervention periods alongside rigorous designs would therefore be needed later on.[21] Aerobic exercise could have positive right hippocampus effects and improve other hippocampus parts alongside the medial temporal areas and the cingulate cortex of the DMN.[21] Aerobic exercise furthermore could increase functional activation or connectivity in the para-hippocampal gyrus, cingulate cortex and hippocampus DMN regions.[21]

Aerobic activity can improve cardiovascular fitness, which is also important for improved cognitive function. Positive relationships were found between spatial memory and aerobic fitness which was facilitated by hippocampus volume.[55] Decreased levels of phospho-tau and glycogen synthase kinase 3-beta (GSK3β) activation were observed in the hippocampus of exercised animals.[36] Evidence suggests that aerobic exercise improving cardiorespiratory fitness also improves cognitive function in older people who are healthy, along with observed effects for delayed memory functions, cognitive speed, motor function and visual and auditory attention.[60] An increase in cardiovascular fitness improves aging human brain plasticity in people and could reduce both cognitive and biological senescence.[54] Bigger aerobic fitness levels resulted in increased hippocampal volumes for older people, showing improved memory function.[55] Aerobic training hugely increased hippocampal volume for older females.[57] Metabolic symptoms caused by HFD can be improved by exercise, partially as a result of protected HFD neurons that are POMC-expressing and increased leptin signalling in the hypothalamus which controls energy homeostasis in the whole body.[41] As brain tumour survivors who are children with reduced fitness compared to healthy children, and differences are not present in substrate utilization throughout sub maximal exercise, child brain tumour survivors should be encouraged to do PA.[43] Evidence of lower bilateral posterior parietal cortex activities caused by exercise and larger bilateral prefrontal cortex activity was observed.[71] These results provide standardized and reliable measures of behaviour, achievement and cognitive processes related with detailed measures of obesity and fitness.[71] Key astrocyte changes encouraged by exercise support that they take part in regulating neural plasticity and activity.[58] Treadmill exercise for the long term has improvements on synaptic plasticity and cognition even the brain developing Aβ depositions.[56] Exercise can result in improvements of physical function however it should also be an addition to specific training that is task-based.[69] Studies have demonstrated that younger animals are aided more from exercise and starting to exercise when younger is important for protection against neurodegeneration for older people. In rodent models, exercise result in improvements for major brain parameters, especially for the hippocampus.[36]

Exercise could be a treatment for impairments in cognitive function.[20] Therapy using exercise is a promising non-pharmacological therapy for those who have MS. Exercise therapy was a potent and safe nonpharmacological treatment for MS, with improvements on both the brain and functional capacity.[69] It is indicated from the results that intensities rather than PA quantities could be more important in associations between cognitive function and PA.[18] Humans BDNF levels are raised significantly as a result of exercise and increased magnitudes are dependent on exercise intensity.[62] One high-intensity interval training programme lasting four months for obese patients improved both cerebral oxygen extraction and cognitive functioning.[51] As BDNF cross blood-brain barriers in both directions, planning exercise prescriptions which are intensity-dependent could help in improving or maintaining neurological health.[62] A study in overweight/obese older adults has shown that morning rounds of moderate-intensity exercise improves working memory and serum BDNF along with executive function[14] and exercise may protect neurons from oxidative DNA damage.[11] Moderate exercise intensities seem to be optimal.[18] Throughout a cohort study, the intensity of PA rather than quantity seems to have had more prominence concerning PA relationships with cognitive function.[18] Reducing intensity or duration of PA caused stronger cognitive decline compared with maintaining intensity or duration.[61] Exercise programs which are individualized, structured, longer duration, multicomponent and higher intensity could potentially maintain cognitive performances for older people.

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Future implications

Evidence usually demonstrates that obesity results in brain changes that are either structural or functional however causal links between the two needs more research. Recent evidence demonstrates that exercise activates potent neuroplastic phenomena, partially facilitated through mechanisms which are epigenetic[40] and may protect neurons from oxidative DNA damage.[11] Exercise changes gene expression along with its protein products through epigenomic expressions.[39] Increasing literature suggests aerobic exercise can achieve similar benefits.[40] These findings can reflect on beneficial exercise effects and encourage its standing as a modifiable factor for preventing, enhancing mood and for improving cognitive abilities.[40] Regular PA benefits both cognition and motor behaviours. Exercise effectiveness could be regulated through exercise duration and intensity.[15,55] A cohort study confirmed significant associations between intensities of cognitive functioning and PA, however not brain volume.[18] Exercise of moderate intensities for a long time is favourable however training parameters in optimal outcomes need more research. Most current research has focussed on aerobic exercise however anaerobic exercise efficacies are not well understood. Therefore, anaerobic exercise efficacies for improving obesity, brain function, cognition and related dysfunctions need to be investigated compared with aerobic exercise.

Conclusion

To conclude, exercise can improve the brain through various mechanisms for people of different weights. Most studies have shown that exercise improves brain function for overweight and obese people. Studies have looked up obesity effects on factors causing deteriorating cognitive and motor functions. Exercise additionally can counteract pathological and normal aging. There is consistent evidence that regular PA or exercise has an association with a reduced cognitive decline, cognitive function and reduced dementia or AD risks. However, exercise effectiveness depends on training parameters, like duration, intensity and developmental stages. Exercise interventions early in life have huge benefits for brain function. Future studies including longer follow-up periods should investigate these associations in both animals and humans, to establish PA optimum intensity and receive maximum benefits for cognitive health.

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Conflicts of interest

The authors declared that they have no conflicts of interests.

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