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Review

The impact of aerobic and resistance training intensity on markers of neuroplasticity in health and disease

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ABSTRACT

Objective: To determine the effects of low- vs. high-intensity aerobic and resistance training on motor and cognitive function, brain activation, brain structure, and neurochemical markers of neuroplasticity and the association thereof in healthy young and older adults and in patients with multiple sclerosis, Parkinson's disease, and stroke.
Design: Systematic review and robust variance estimation meta-analysis with meta-regression.
Data sources: Systematic search of MEDLINE, Web of Science, and CINAHL databases.
Results: Fifty studies with 60 intervention arms and 2283 in-analyses participants were included. Due to the low number of studies, the three patient groups were combined and analyzed as a single group. Overall, low- ($g=0.19$, $p = 0.024$) and high-intensity exercise ($g=0.40$, $p = 0.001$) improved neuroplasticity. Exercise intensity scaled with neuroplasticity only in healthy young adults but not in healthy older adults or patient groups. Exercise-induced improvements in neuroplasticity were associated with changes in motor but not cognitive outcomes.
Conclusion: Exercise intensity is an important variable to dose and individualize the exercise stimulus for healthy young individuals but not necessarily for healthy older adults and neurological patients. This conclusion warrants caution because studies are needed that directly compare the effects of low- vs. high-intensity exercise on neuroplasticity to determine if such changes are mechanistically and incrementally linked to improved cognition and motor function.

Abbreviations: AT, aerobic training; HOA, healthy old adults; HYA, healthy young adults; NEU, neurological patients including people with multiple sclerosis, Parkinson's disease, and stroke; PEDro, physiotherapy evidence database; PwMS, people with multiple sclerosis; PwPD, people with Parkinson's disease; PwST, people with stroke; N_s, number of studies; N_p, number of participants; N_i, number of interventions; NP, neuroplasticity; PRISMA-P, preferred reporting items for systematic review and meta-analysis protocols; PICOS, population, intervention, comparators, outcomes, study design; RT, resistance training.

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1. Introduction

Physical exercise is a subset of physical activity that is planned, structured, and repetitive and as such a potent physiological perturbation of human bodily homeostasis (Caspersen et al., 1985). A 30-minute-long, single exercise bout modifies nearly 10,000 molecules (Contrepois et al., 2020). Repetition of bouts of running, cycling, rowing, and swimming constitutes chronic aerobic training (AT). Overcoming external loads by forceful muscle contractions represents resistance training (RT). Both AT and RT favorably impact virtually all organ systems' cellular machinery, cardio-metabolic, neuronal, and motor and cognitive functions, health, and mortality (Fyfe et al., 2022; Gallardo-Gomez et al., 2022; Garatachea et al., 2015; Ruiz-Gonzalez et al., 2021). Of the many parameters that help dosing AT and RT (training frequency, volume, session and intervention duration, inter-bout and inter-session rest) perhaps the most critical is its 'intensity'. In physics terms, exercise intensity can be captured by the rate of performing mechanical work, which is the generation of positive mechanical power. Physiologically, high-intensity AT is characterized by 76–95 % of maximal heart rate, 80 % of maximal oxygen consumption, or 70–90 % of cardiac output. High-intensity RT is characterized as >70 % of the 1-repetition maximum load. AT and RT intensities can be subjectively rated by perceived exertion (>15/20) and mental and muscular fatigue (Ainsworth et al., 2000; Garber et al., 2011). Intensity is a key dosing variable because it potentiates (augments) the magnitude of behavioral, neuronal, and biochemical adaptations induced by exercise at lower intensities. High- vs. low-intensity AT produces greater improvements in peak oxygen consumption, systemic vascular function, and metabolic profile (blood lipids, insulin sensitivity) (Swoap et al., 1994). High- vs. low-intensity RT, including exercise to failure (Grgic et al., 2022), also produces greater increases in maximal voluntary force, and cardio-metabolic responses (Taaffe et al., 1996; Tsuzuku et al., 2001) with less of a dose-effect on muscle hypertrophy (Schoenfeld et al., 2017).

Both AT and RT are thought to improve brain health through neuroplasticity (NP), i.e., the brain's ability to create new and reorganize existing synaptic connections (Lin et al., 2018; Smith et al., 2010). While repeatedly suggested (Ainsworth et al., 2000; Garber et al., 2011), whether or not NP scales with exercise intensity has not been systematically examined. This is a highly relevant issue because exercise-induced NP presumably underlies improvements in motor (e.g., gait speed) and cognitive functions (e.g., working memory) and reductions in behavioral symptoms (e.g., tremor in Parkinson's disease) in healthy young adults (HYA), healthy older adults (HOA), and people living with neurological conditions such as multiple sclerosis (PwMS), Parkinson's disease (PwPD), and stroke (PwST) (Erickson et al., 2013; Petzinger et al., 2013; Silva-Batista et al., 2020; Tymofiyeva and Gaschler, 2020). The idea is that high- vs. low-intensity exercise would induce greater and longer-lasting NP effects which would in turn produce more robust improvements in cognitive and motor functions or slow the progression of existing neuro-cognitive impairments (Johansson et al., 2022; Tsukita et al., 2022). The implications are that the efficacy of a non-pharmaceutical, easily accessible, and inexpensive option could be increased for the prevention and/or treatment of motor and cognitive functions in healthy individuals and those affected by illness (Riemenschneider et al., 2018). It could perhaps even reduce drug doses or eliminate drug prescriptions (Naci et al., 2019).

The extant animal data reveal an unclear picture with respect to the effects of exercise intensity on NP. In healthy adult animals, a single bout of exercise caused reversible methylation of DNA (Rodrigues et al., 2015), posttranslational modification of histone residues (Elsner et al., 2017), gene expressions and increases in short-lived proteins like cytokines (Etnier et al., 2016; Vilela et al., 2020). Voluntary wheel running increased mRNA levels of nerve growth factors just 6 h following running but the volume and not the intensity of exercise correlated with brain-derived neurotrophic factor mRNA levels (Oliff et al., 1998). In other studies, relative workload (i.e., intensity) instead of running distance seemed to affect nerve growth factors (Lee et al., 2012). These short-term exercise protocols improved learning, memory, brain NP and neurogenesis, which were primarily related to increased hippocampal brain-derived neurotrophic factor levels (Vaynman and Gomez-Pinilla, 2005; Vaynman et al., 2004). Longer-term high-intensity exercise programs lastingly improved mitochondrial biogenesis, mitochondrial fusion and increased nerve growth factors levels (Afzalpour et al., 2015; Hu et al., 2021). Six weeks of high-intensity AT decreased kinesin family 5 mRNA and protein levels, linked to use-dependent presynaptic plasticity and dendritic spine morphogenesis in the hippocampus (Cai et al., 2007; Kerendi et al., 2019). Voluntary wheel-running increased the number of dendritic spines and excitatory postsynaptic currents in an intensity-dependent manner (Chatzi et al., 2019). Exercise generates reactive oxygen species that can cause molecular damage. Reactive oxygen species-generation is exercise intensity-dependent in a way that low- vs. high-intensity chronic (long-term) exercise produces less reactive oxygen species (Lee et al., 2021; Radak et al., 2013). In addition, spatial memory, hippocampal neurogenesis and brain-derived neurotrophic factor levels changed independently of exercise intensity in rats (Okamoto et al., 2021) and the levels of key brain NP markers increased in the hippocampus without improving cognitive function (Constans et al., 2021). While AT dominates animal experiments, RT also produces neuroprotective and neurogenerative effects but the intensity-dependence remains unexamined (Cassilhas et al., 2012, 2007; Remple et al., 2001; Serra et al., 2022; Tuon et al., 2014; Vilela et al., 2017). These data in healthy adult animals suggest that both AT and RT can induce NP probably through different molecular paths. All in all, the balance of evidence weakly favors the idea that NP responses to exercise scale with its intensity in healthy animals.

Animal models of neurological diseases also provide insights into the nature of exercise-induced NP (Lourenco et al., 2019). Responses to exercise in experimental autoimmune encephalomyelitis animal models of multiple sclerosis revealed conflicting data (Motl and Sandroff, 2015; Olson et al., 2006; Sandroff et al., 2020). One reason could be that the inflammatory response exacerbates neuropathology but this response also stimulates mechanisms of tissue repair through the release of growth factors and affects NP. Animal models of PD suggest that exercise improves motor and mitochondrial function, nerve growth and glial cell line-derived neurotrophic factors, levels of nigrostriatal neurotrophic factor, and reduced excitotoxic effects of glutamate and aberrant cortical spike-local field potential synchronization (Feng et al., 2021; Ferreira et al., 2021; Lau et al., 2011; Shi et al., 2021). Perhaps exercise training can even rescue dopamine neurons (Ferreira et al., 2020; Torikoshi et al., 2020). In animal models of stroke, forced exercise at moderate to high intensity increased levels of growth factors and synaptogenesis in multiple brain regions but moderate instead of high-intensity exercise seemed to facilitate dendritic branching (Ploughman et al., 2015). Altogether, none of the studies has directly examined the intensity-dependent effects of AT or RT on NP in animal models of MS, PD, or stroke, hindering the translation of basic science data to patient care (Svensson et al., 2015).

The fundamental question, whether exercise intensity makes a difference in inducing NP and whether such changes are associated with changes in motor and cognitive function, also remains unanswered in healthy adults and PwMS, PwPD, and PwST. On the one hand, evidence suggests that as short as 4-s bouts (Allen et al., 2021) and as little as 7000 daily steps at an intensity twice the resting metabolic rate (~7 ml/min/kg oxygen uptake, i.e., low volume- and intensity-dosed exercise) already provides health benefits, reduce mortality, and induces NP (Lee et al., 2019; Saint-Maurice et al., 2020). In addition, yoga and Tai Chi, i.e., low-intensity activities with a mindfulness component, have consistently shown improved motor and cognitive function across the lifespan (Cole et al., 2022; Hoy et al., 2021; Liu et al., 2021; Ren et al., 2021). These observations are consistent with the most recent recommendation of exercise prescription according to the principles of

exercise specificity and disease level (Brahms et al., 2021). Indeed, low-intensity walking increased: gray matter volume in cortical and sub-cortical brain areas; microstructural integrity in several white matter tracts; cortical and hippocampal gray matter volume, and reduced white matter lesions in a correlated manner with improvements in aerobic fitness (Best et al., 2015; Burzynska et al., 2017; Chen et al., 2020; Mendez Colmenares et al., 2021; Oberlin et al., 2016). Low-intensity RT and cognitive training were also efficacious to improve cognitive function and markers of NP (Chow et al., 2021; Intzandt et al., 2021). In fact, there is meta-analytical evidence suggesting that exercise, including RT, even below World Health Organization guidelines could provide health and mortality benefits (Bull et al., 2020; Dempsey et al., 2022; Fyfe et al., 2022; Gallardo-Gomez et al., 2022).

On the other hand, the prescription of exercise for healthy adults across the lifespan and rehabilitative exercise for patients has undergone a major paradigm shift to intensities often used by athletes (Boyne et al., 2019; Cancela et al., 2020; Conradsson et al., 2015; Constans et al., 2021; Crozier et al., 2018; Dempsey et al., 2022; Diechmann et al., 2021; Frazzitta et al., 2014; Gamborg et al., 2022; Hejazi, 2017; Hsu et al., 2021; Hu et al., 2021; Hugues et al., 2021; Johansson et al., 2020; Kolmos et al., 2016; Landers et al., 2019; Langeskov-Christensen et al., 2021; Luo et al., 2019; Martland et al., 2020; Morberg et al., 2014; Okamoto et al., 2021; Orban et al., 2019; Renteria et al., 2020; Rosenfeldt et al., 2021; Steen Krawcyk et al., 2019; Tang et al., 2016; Taylor et al., 2022; Tollar et al., 2021; Tollár et al., 2018, 2020; Zimmer et al., 2018). For example, PwMS, PwPD, and PwST exercised at 80 % of the age-predicted maximum heart rate (Tollar et al., 2021; Tollár et al., 2018, 2020). This shift has occurred with the premise that exercise intensity moderates the effects of exercise on markers of NP, which in turn would improve cognitive and motor function to a greater extent. The general mechanistic cascade would involve an intensity-scaled improvements in: (a) levels of nerve growth factors (brain-derived neurotrophic factor, insulin-like growth factor, vascular endothelial growth factor); (b) neuroinflammation markers (C-reactive protein, cytokines); (c) cerebral blood flow, brain glucose, and oxygen transport, and brain arterial vessel stiffness, which would then improve (d) brain activation, network function, and structural properties, underlying improvements in (e) motor (gait, balance) and cognitive function (attention, executive function, processing speed, memory) following AT and RT. This expectation was not always met (Hortobágyi et al., 2021; Quigley et al., 2020; Taylor et al., 2022) and there is mounting evidence suggesting that, after all, exercise may not be as potent as previously proposed in affecting neurogenesis in humans (Gogniat et al., 2021; Hvid et al., 2021; Nano and Bhaduri, 2022). Because focal neuronal damage affects the function of undamaged areas (Allegra et al., 2021; Gratton et al., 2012), it is likely that neurological patients would be less responsive to intensity dosing of exercise. Taken together the extant animal and human data, the aim of the present systematic review with meta-analysis was to determine, for the first time, the effects of AT and RT intensity on markers of NP in healthy adults and selected patient groups. We examined the effects of AT and RT at low and high intensities on three domains of NP (brain activation [functional connectivity], brain structure, neurochemicals) in HYA, HOA, and in individuals with a diagnosis of MS, PD, and stroke. The global hypothesis was that AT and RT-induced changes in markers of NP would scale with exercise intensity but this relationship would be weaker in PwMS, PwPD, and PwST.

2. Methods

2.1. Literature search and selection criteria

Supplement 1 shows flowcharts and the Boolean Search syntaxes. In consultation with two of the authors (EF, HJ), expert librarians designed and performed computerized systematic literature searches in MEDLINE (Ovid), Web of Science Core Collection (Clarivate Analytics), and CINAHL (EBSCO) for the period between 1946 and 23 June 2021 following PRISMA-P review guidelines. The syntax aimed to determine the effects of the intensity of AT and RT exercise interventions on selected measures of NP in HYA, HOA, PwPD, PwMS, and PwST. The syntax consisted of three main terms: population, AT, RT, and markers of NP using Boolean operators AND, OR.

Inclusion and exclusion criteria were defined according to the population, intervention, comparators, outcomes, and study design, i.e., PICOS. In terms of 'P' (population), we included HYA (age $\leq$30 y, authors: PSRS, MV), HOA (age $\geq$50, TLA, NCBSS, GMB), PwPD (EF, HJ), PwMS (FD, AM), and PwST (CK, MK) of either sex. With regards to 'I' (intervention), we included AT (aerobic activities, physical therapy, running, jogging, cycling, cardiopulmonary conditioning) and RT (resistance and power training, i.e., high-velocity resistance training). Exercise studies or specific arms of a study were included that delivered only one form of physical exercise stimulus repeatedly (i.e., long-term intervention studies $\geq$4 weeks). Studies in patients were included with any age, medication, disease stage, or disease sub-type. For 'C' (comparator), we considered both active (i.e., contrast with different intervention programs) and passive control groups. In terms of 'O' (outcomes), the NP term included measures related to (a) brain activation, (b) brain structure, and (c) neurochemical markers of NP. With regards to 'S' (study design), only randomized controlled trials were included. Studies were excluded when it was clear from the article title or abstract that the trial was not relevant or if it did not meet inclusion criteria, the journal was not peer-reviewed (e.g., gray literature), failed to use at least one marker of NP, failed to report the pre-post means or change scores and their standard deviations numerically or graphically, was a case report, used a cross-over design, its duration was shorter than three weeks and used fewer than nine sessions, and failed to report or administer minimum requirements concerning exercise intensity. Searches were delimited to studies available in full text, journal articles, English language, and in humans. Blinded to each other, two authors per population screened the searches based on title and abstract. After this initial screening, the two review authors unblinded their decisions and disagreements were resolved through discussions or a third author. Reference lists of all included studies and relevant review articles were screened for the inclusion of additional potential studies. Duplicates between searches were removed. We determined the age criterion by averaging the age of subjects across intervention and control groups in a given study and if this averaged value corresponded to the age limit (young: 30; old: 50), the study was included. The PubMed syntax was adapted to the search in Web of Science and CINAHL databases. The review protocol was registered in PROSPERO (CRD42021257357).

2.2. Data extraction

Each study was coded for: first author, publication year, population, age, sex and number of participants, health status, type of exercise intervention, the total number of training sessions, exercise intensity, behavioral outcomes (cognition, motor), NP outcomes (brain activation, brain structure, neurochemicals), and the association between behavioral and NP outcomes. In several cases, we requested data or pertinent data from corresponding authors and if not received, the study was excluded. In case of data reported only in charts and plots, a semi-automated software (http://getdata-graph-digitizer.com/) was used to extract data from x-y plots. Low vs. high intensity was determined for AT based on the percentage of maximal oxygen uptake (with 63 % as the threshold between the two intensities), percentage of maximal heart rate (77 %), heart-rate reserve (60 %), metabolic equivalent (6.0), rate of perceived exertion (Borg scale: 15/20; 5/10), second ventilatory threshold, and anaerobic threshold (below: low intensity) (Ainsworth et al., 2000; Garber et al., 2011). Intensity for RT was categorized as low intensity vs. high when the load was, on average, below 69 % of the 1-repetition maximum and high when, on average, the load was above 69 % of the 1-repetition maximum (Garber et al., 2011). We also considered the number of repetitions and number of sets and rest

intervals to determine intensity. Power training intensity was classified as low when participants were instructed to move loads lower than 60 % of the 1-repetition maximum as fast as possible and high intensity when the load to be moved was greater than 60 % of the 1-repetition maximum at high movement velocity (Garber et al., 2011). When AT and RT intensity progressively increased during an intervention, we averaged the intensity values to arrive at an overall intervention intensity. Two authors per population group blindly categorized the intensity of the studies. Disagreements were resolved in discussions with the two lead authors. If a study had two groups performing a different number of sessions of AT or RT or if there were both low- and high-intensity groups performing AT or RT, these interventions arms were coded as a separate study.

We also extracted motor and cognitive outcomes. Motor outcomes comprised walking speed over various distances, maximal oxygen uptake (fitness), cycling power, maximal leg, arm, and grip strength, maximal voluntary isometric force, and muscle power. Measures of cognition were extracted including neuropsychological tests assessing executive function, processing speed, and forms of memory.

Measures of NP were categorized as brain activation (e.g., change in blood-oxygen-level-dependent signal, etc.), brain structure (e.g., white matter integrity, cortical gray matter volume, etc.), and neurochemical outcomes (brain-derived neurotrophic factor, insulin-like growth factor-1, etc.).

2.3. Assessment of methodological quality and statistical analyses

The methodological quality of the included studies was assessed using the Physiotherapy Evidence Database (PEDro) scale. This assessment was performed by two raters who were blinded to each other's ratings. The PEDro Scale is used to rate internal study validity and the presence of replicable statistical information on a scale from 0 (high risk of bias) to 10 (low risk of bias). The quality assessment was interpreted using the following 10-point scale: $\leq$3 points were considered poor quality, 4–5 points as moderate quality, and 6–10 points as high quality (de Morton, 2009).

2.4. Statistical analyses

For the analyses, we used robumeta (version 2.0), metafor (version 3.0–2), and clubSandwich (version 0.5.5) packages in R, version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). A random-effects meta-regression method called robust variance estimation for multilevel data structures was used in all analyses. RVE allows for the inclusion of multiple dependent outcomes from the same study. RVE assesses the variance of meta-regression coefficient estimates with the use of the observed residuals and does not require the weights or distributional assumptions (Hedges et al., 2010; Tipton, 2015). To account for the correlated effects within the studies, 'study' was used as the clustering variable. The observations were weighted with the use of the inversion of the sampling variance. First, we computed the overall summary effect for all included studies and visualized the effects using a caterpillar plot (i.e., effect size estimates ordered by magnitude). We performed sensitivity analyses by assessing the effects of influential cases on the results. The influential cases were diagnosed using a combination of several methods (externally standardized residuals, difference in fits values, Cook's distances, covariance ratios, leave-one-out estimates of the amount of heterogeneity, leave-one-out values of the test statistics for heterogeneity, hat values, and weights) as implemented in the 'influence' function within the metafor package (Viechtbauer and Cheung, 2010). We also examined potential publication bias using a funnel plot and Egger's regression test (Sterne and Egger, 2005). Second, we performed a series of subgroup meta-analyses for different populations (HYA, HOA, and neurological patients (NEU) which combined, due to low yield, PwMS, PwPD, PwST), domains of NP markers (brain activation, brain structure, neurochemicals), and interventions (AT, RT at low and high intensities) to determine main and interaction effects. For all analyses, we computed Hedge's *g* effect size, standard error of effect size, 95 % confidence intervals, the statistical significance of the effect (set at $p < 0.05$), percentage of heterogeneity (I^2), and the absolute value of true heterogeneity (Tau^2). The values of I^2 >25 %, >50 %, and >75 % indicate, respectively, low, moderate, and high heterogeneity (Higgins et al., 2003; Melsen et al., 2014). The direction of effect sizes was standardized so that positive effect sizes would reflect improvements in a given outcome. Third, to explore potential effect moderators, we fitted a series of initial meta-regression models, using age, sex, population, exercise type, exercise intensity, intervention duration, the total number of sessions, domains of NP markers, whether the study used an active or passive control group, and their interactions as covariates. The statistical significance of the moderators was tested using *t*-tests for continuous and binary moderators and Hotelling-Zhang tests for categorical moderators with three or more levels. Those moderators that showed significance in at least one of the initial models were then combined into one full model. Starting with this model, the moderators and their interactions that were not significant ($p > 0.05$) were then eliminated from the full model one by one; only those with significant moderating effects were included in the final model. Finally, to assess the association between NP and behavioral outcomes within individual studies, we used cognitive and motor outcomes in a series of random-effects meta-regressions, treating the NP effect sizes as the outcome and the behavioral effect sizes as the continuous moderators (Falck et al., 2019). Because the current review was anchored on NP, we did not perform meta-analyses on motor and cognitive outcomes. This has previously been reported in the literature. Such analyses would have biased effect size estimates, as we would have failed to include potentially hundreds of studies summarized by targeted reviews on the effects of exercise on cognitive and motor outcomes (Chow et al., 2021; Dascal et al., 2019; Falck et al., 2019; Gallardo-Gomez et al., 2022; Landrigan et al., 2020; Li et al., 2018; Lopez et al., 2018; McSween et al., 2019; Quigley et al., 2020; Sanders et al., 2019; Song and Yu, 2019; Yeh et al., 2021).

3. Results

3.1. Characteristics of the included studies

Supplement 1 shows the flowcharts of study selection for HYA, HOA, PwMS, PwPD, and PwST and the search syntaxes. We identified 19,051 studies. After the removal of duplicates, we screened 16,071 unique records. Fifty studies with 60 intervention arms were included in the meta-analyses (Antunes et al., 2015; Best et al., 2015; Bolandzadeh et al., 2015; Briken et al., 2016; Burzynska et al., 2017; Cassilhas et al., 2007; Cheng et al., 2018; Coelho-Junior et al., 2020; Erickson et al., 2011; Feys et al., 2019; Fisher et al., 2008; Flodin et al., 2017; Fragala et al., 2014; Frazzitta et al., 2014; Hejazi, 2017; Hsu et al., 2021; Jonasson et al., 2016; Kang et al., 2020; Landers et al., 2019; Langeskov-Christensen et al., 2021; Liu-Ambrose et al., 2012; Luft et al., 2008; Maass et al., 2016, 2015; Martins et al., 2010; Marx et al., 2001; Matura et al., 2017; Mokhtarzade et al., 2018; Moore et al., 2015; Mortimer et al., 2012; Muscari et al., 2010; Nagamatsu et al., 2016; Niemann et al., 2014; Nindl et al., 2010; Ploughman et al., 2019; Renteria et al., 2020; Sacheli et al., 2019; Sandroff et al., 2017; Savsek et al., 2021; Seifert et al., 2010; Sexton et al., 2020; So et al., 2013; Svatkova et al., 2015; Tsai et al., 2017, 2015; Umutlu et al., 2020; Voss et al., 2013b, 2010; Zhu et al., 2021; Zimmer et al., 2018). Table 1 summarizes the study characteristics and Supplement 2 details these characteristics. Supplement 3 shows the study quality evaluation PEDro scores. The median scores ranged between 5 and 6.5 for the five groups (HYA, HOA, PwMS, PwPD, PwST), with an overall median score of 5.0, signifying average study quality with respect to internal validity, statistical replicability, and bias. The criteria most often unmet were blinding and concealment.

Overall, 2421 participants were enrolled in the 50 studies with a mean age of 53 y (range: 18–77, ~60 % female). Forty-three intervention arms used AT and 17 used RT. Thirty-seven intervention arms used high intensity and 23 used low exercise intensity. High-intensity AT was performed most often (28) and low-intensity RT (6) least often. Intervention duration ranged from 3 to 52 weeks. The number of sessions ranged from 9 to 156. The number of sessions per week ranged from 1.5 to 5.0. More studies used a passive (29) vs. active control group (21). AT comprised supervised walking, running, cycling, rowing, swimming, aerobics, and boot camp. RT comprised supervised exercises with elastic bands and weight-lifting equipment (e.g., machines, barbells) at slow, moderate, or fast movement velocity. This latter denotes power training. In one study, participants exercised at home.

There were 74 markers of brain activation, 94 markers of brain structure, and 76 markers of neurochemicals. Brain activation outcome included imaging of changes in basal blood flow and functional magnetic resonance imaging using the blood-oxygen-level-dependent technique during motor paradigms. Electroencephalography was applied to identify changes in cortical electric activity (frequency, duration and peak) over specific scalp areas. Metabolic brain activity was measured by positron emission tomography and motor cortical silent period (a measure of motor cortical inhibition induced by transcranial magnetic stimulation). Network function was measured by global efficiency and betweeness centrality (graph theory, network analyses), and functional connectivity. Brain structure outcomes included changes in measures of cortical gray and numbers of white matter hyperintensities, white matter lesion by MRI magnetic resonance imaging, diffusion tensor imaging outcomes, magnetic resonance spectroscopy, and brain area viscoelasticity measured by magnetic resonance elastography. Neurochemical outcomes included levels of brain-derived neurotrophic factor in blood or serum, brain-derived neurotrophic factor-tropomyosin receptor kinase B signaling, insulin-like growth factor-I, insulin-like growth factor-binding proteins, vascular endothelial growth factor, homocysteine, C-reactive protein, brain metabolites (N-acetylaspartate/total choline ratio, phosphocreatine/inorganic phosphate, ATP/inorganic phosphate, glycerophosphocholine/phosphocreatine, phosphocholine/phosphocreatine), growth hormone, tumor necrosis factor-α, and interferon-γ.

Table 1
Summary of study metrics included in the analyses.

Variable	HYA	HOA	PwMS	PwPD	PwST	All
Participants	312	1558	282	110	159	2421
Males	145	599	75	64	102	985
Females	167	959	207	31	57	1421
Experimental	163	856	152	64	80	1315
Control	149	702	130	46	79	1106
Age, y	22.6	69.0	42.8	65.7	62.9	52.6
Min	18	66	30	63	56	18
Max	36	77	50	68	69	77
AT	8	18	7	6	4	43
RT	3	14	0	0	0	17
LI	4	15	2	1	1	23
HI	7	17	5	5	3	37
LIAT	2	9	2	1	1	15
HIAT	6	9	5	5	3	28
LIRT	1	5	0	0	0	6
HIRT	2	9	0	0	0	11
Duration, week	14.1	31.8	11.4	7.3	16.3	16.2
Min	4	6	3	4	10	3
Max	26	52	24	12	24	52
Sessions	49.3	87.5	28.4	23.2	48.8	47.4
Min	12	12	9	12	30	9
Max	120	156	48	36	72	156
Session/week	3.3	2.8	2.6	2.9	3	2.92
Min	2	1.5	2	2.5	3	1.5
Max	5	3	3	3	3	5
Passive control*	8	11	7	2	1	29
Active control	0	15	0	3	3	21

HYA, HOA, healthy young and older adults.
PwMS, people living with multiple sclerosis.
PwPD, people living with Parkinson's disease.
PwST, people living with stroke.
All values are frequencies other than age (years) and intervention durations (weeks).
Not all studies reported sex data.
AT, aerobic training.
RT, resistance training.
HI, high intensity.
LI, low intensity.
Study number and intervention number differ because there were studies that included both high- and low-intensity intervention arms.
* there are fewer control than intervention groups because some studies had multiple intervention arms but one control group.

Motor outcomes included measures of upper and lower extremity muscle strength and power, maximal or peak oxygen uptake, metrics of cardiac function, various motor tests, reaction time, walking and balance performance, and gait properties (Supplement 2). Cognitive outcomes included measures of global cognition, elements of executive function, various forms of memory, and processing speed predominantly in HOA. Clinical outcomes in patient groups included disease-specific metrics, depression, and fatigue.

As reported by individual studies, in HYA and HOA combined, AT and RT exercise interventions improved ($p < 0.05$): 72 % of 125 NP outcomes; the performance in 85 % of 55 motor test outcomes, but only 27 % of the 133 cognitive test outcomes. In NEU, AT and RT exercise interventions improved: 21 % of 125 NP outcomes; the performance in 93 % of 54 motor test outcomes, but only 25 % of 116 cognitive and clinical test outcomes (Supplement 2).

The updated search in July 2022 identified no new eligible studies for inclusion in HYA, 9 studies in HOA (Cassilhas et al., 2022; Castells-Sanchez et al., 2022; DuBose et al., 2022; Frost et al., 2021; Pani et al., 2022a, 2022b, 2021; Park, 2022; Tarumi et al., 2022), 2 studies in PwMS (Bahmani et al., 2022; Riemenschneider et al., 2022), 1 study in PwPD (Johansson et al., 2022), and 2 studies in PwST (Hsiao et al., 2022; Kufner et al., 2021).

3.2. Overall summary effects

Table 2 shows that 2283 participants were included in the meta-analyses. We used the post-intervention sample sizes in the analyses, which were often lower than the sample sizes at enrollment. Of the 95 pre-defined sub-group analyses (Supplement 4), Table 2 shows selected results. The number of studies in patients with neurological conditions was too low for a meta-synthesis, thus the three patient groups were combined into a 'neurological group' of 16 studies (NEU, Table 2, Supplement 2).

Across all variables ($N_s = 50$ studies; $N_p = 2283$ participants in analyses, $N_i = 60$ interventions; $k = 244$ outcomes), AT and RT combined ('exercise') improved NP with an effect size of $g = 0.32$ (CI: 0.21–0.43, $p < 0.001$, Fig. 1). The sensitivity analysis revealed that the removal of the identified influential cases did not substantially alter the results (Supplement 5). The visual inspection of the funnel plot (Supplement 6) complemented Egger's regression test for funnel plot asymmetry ($p = 0.086$) and indicated that publication bias was unlikely to have influenced the results significantly.

3.3. Sub-group meta-analyses

Across interventions, intensities, and the three domains of NP markers, exercise improved NP in HYA (g=0.67; CI: 0.15–1.19), NEU ($g = 0.36$; CI: 0.17–0.54), and HOA ($g = 0.22$; CI: 0.10–0.35; each $p \leq 0.017$). Low-intensity exercise did not improve NP in any of the three groups ($p \geq 0.073$). High-intensity exercise improved NP in HYA (g=0.93, CI: 0.26–1.59, $p = 0.013$), HOA ($g = 0.27$, CI: 0.11–0.44, $p = 0.003$), and in NEU ($g = 0.33$, CI: 0.08–0.58, $p = 0.016$). Across all factors, the improvement of NP markers was similar for AT (g=0.31; CI:

Table 2
Summary of sub-group meta-analyses.

Factors	g	SE	LL	UL	p	I^2	Tau^2	N_i	k	N_s	N_p
All factors combined	0.32	0.05	0.21	0.43	**0.001**	58.9	0.17	60	244	50	2283
Population											
Healthy young adults	0.67	0.23	0.15	1.19	**0.017**	69.5	0.45	11	30	8	312
Healthy old adults	0.22	0.06	0.09	0.35	**0.001**	47.8	0.09	32	137	26	1479
Neurological patients*	0.36	0.09	0.17	0.54	**0.001**	62.1	0.26	17	77	16	492
Intervention											
AT	0.31	0.06	0.18	0.44	**0.001**	62.9	0.17	43	201	41	1826
RT	0.35	0.11	0.11	0.58	**0.006**	46.3	0.16	17	43	11	457
LI	0.19	0.08	0.03	0.35	**0.024**	34.1	0.06	23	95	22	886
HI	0.40	0.07	0.25	0.54	**0.001**	65.6	0.23	37	149	33	1397
LIAT	0.18	0.09	-0.01	0.37	0.066	38.1	0.06	17	79	17	729
HIAT	0.39	0.08	0.21	0.56	**0.001**	69.2	0.24	26	122	26	1097
LIRT	0.24	0.16	-0.18	0.65	0.202	29.5	0.07	6	16	6	157
HIRT	0.42	0.16	0.07	0.77	**0.023**	54.8	0.23	11	27	7	300
Neuroplasticity marker											
Brain activation	0.38	0.09	0.16	0.59	**0.003**	63.9	0.27	13	74	11	418
Brain structure	0.13	0.07	-0.01	0.28	0.066	33.3	0.04	19	94	17	1047
Neurochemicals	0.46	0.10	0.26	0.65	**0.001**	62.9	0.24	32	76	26	1046

g: effect size.
SE: standard error of effect size.
LL: confidence interval lower limit.
UL: confidence interval upper limit.
p: probability.
I^2: percent of heterogeneity.
Tau^2: absolute value of true heterogeneity.
N_i: number of interventions.
k: number of outcomes.
N_s: number of studies.
N_p: number of participants.
*Neurological patients: multiple sclerosis, Parkinson's disease, stroke.
HIAT, LIAT high- / low-intensity aerobic training.
HIRT, LIRT high- / low-intensity resistance training.

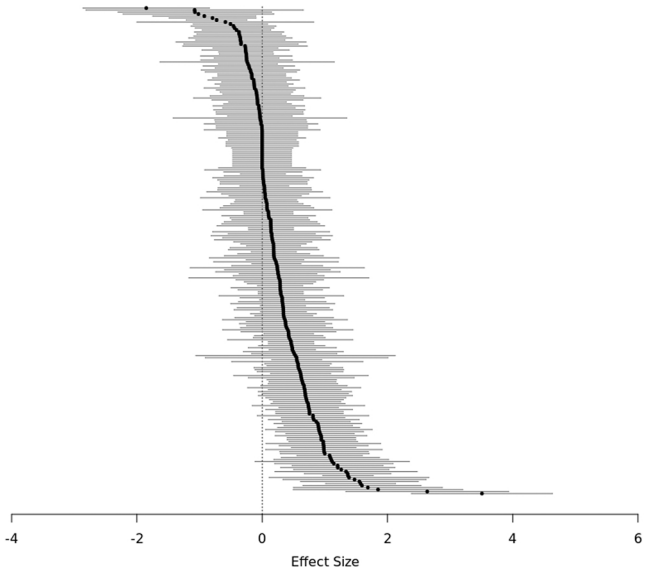

Fig. 1. Caterpillar plot of effects sizes for the included studies and outcomes.

0.18–0.44) and RT (g=0.35; CI: 0.11–0.58) interventions (each $p \leq 0.006$). Across all factors, high intensity ($g = 0.40$: CI: 0.25–0.54) vs. low intensity ($g = 0.19$; CI: 0.03–0.35; all p values ≤ 0.024) exercise improved markers of NP more strongly. Of the 4 combinations of AT and RT at low and high intensities, only high-intensity AT ($g = 0.39$; CI: 0.21–0.56, $p < 0.001$) and RT ($g = 0.42$, CI: 0.07–0.77, $p = 0.023$) did each improve markers of NP. Exercise improved NP when tested with neurochemical markers (g=0.46; CI: 0.26–0.65, $p < 0.001$; 76 outcomes) and brain activation markers ($g = 0.38$, CI: 0.16–0.59, $p = 0.003$; 74 outcomes). Exercise did not significantly improve NP when tested via brain structure markers ($g = 0.13$; CI: −0.01 to 0.28; $p = 0.066$; 94 outcomes). Fig. 2 shows the intensity effects on NP in HYA, HOA, and NEU. (Other forest plots are available upon request from the primary author but Supplement 4 shows all effect sizes).

In general, heterogeneity was high. To reduce heterogeneity, we coded studies for intensity more stringently than the coding used in the main analysis by including only those studies that administered the exercise program for its entire duration at high or low intensity ($N_s = 36$ studies; $N_p = 1402$ participants; $N_i = 40$ interventions; $k = 149$ outcomes). However, the modeling of these data produced fundamentally similar results as those detailed above.

3.4. Moderator analyses

Among all potential moderators, exercise intensity, domains of NP, number of sessions per week, type of intervention, population, and age showed significance in at least one of the initial models (Supplement 7) and thus entered the full model. However, after sequentially eliminating non-significant moderators from the full model, the final model only comprised the 'Intensity*Population' interaction element and the domain of NP as a confounder (Supplement 8). The final model demonstrated that the moderating effect of exercise intensity was different in HYA compared to HOA and NEU. In HYA, high intensity significantly improved the effect size of exercise compared to lower intensity ($\Delta g = 0.80$, $p = 0.039$). In contrast, high vs. low intensity did not increase effect sizes in HOA ($\Delta g = 0.09$, $p = 0.420$) and in NEU ($\Delta g = -0.10$, $p = 0.557$).

3.5. Association NP markers with cognitive and motor function

Effect sizes reflecting changes in motor outcomes were associated with effect sizes reflecting changes in NP outcomes as a whole (beta:

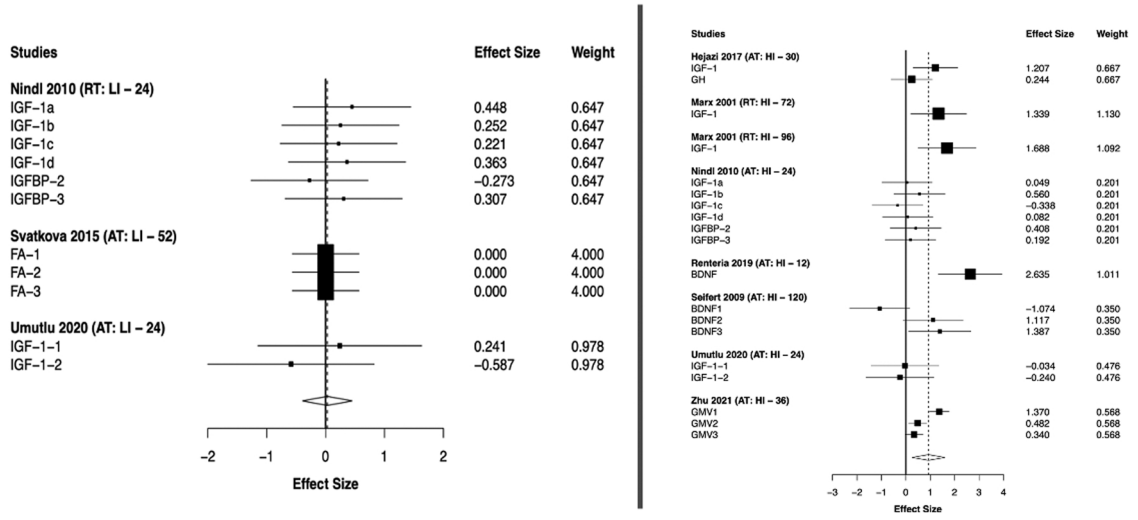

Fig. 2. Exercise intensity effects on measures of NP based on sub-group analyses. Top: healthy young adults (left, low intensity: g = 0.03, CI: −0.390 to 0.448, p = 0.707; right: high intensity: g = 0.93, CI: 0.264–1.591, p = 0.013). Middle: healthy older adults (left, low intensity: g = 0.17, CI: −0.044 to 0.376, p = 0.112; right, high intensity: 0.27, CI: 0.110–0.435, p = 0.003); Bottom: neurological patients (left, low intensity: g = 0.40, CI: −0.064 to 0.869, p = 0.073; right, high intensity: g = 0.33, CI: 0.075–0.580, p = 0.016). Abbreviations in insets: AT: aerobic training; RT: Resistance training. LI: low intensity; HI: high intensity. Within each study, NP markers are listed.

0.15, p = 0.008, N_s = 46 studies) and with changes in neurochemical (0.15 ± 0.07, p = 0.027, N_s = 26 studies) and brain structure (0.24 ± 0.12, p = 0.036, N_s = 13 studies) domains of NP. Effect sizes of changes in cognitive outcomes were not associated with effect sizes of changes NP as a whole nor with any of its individual domains (Table 3). Fig. 3 shows the association between the effects sizes of changes in cognitive and motor outcomes and in the neurochemical domain of NP.

We extracted the relationship between changes in clinical, cognitive, and motor outcomes and changes in measures of NP as reported by individual studies. The far-right last column in Supplement 2 shows that in HYA and HOA combined, 50 % of the 34 studies reported only 7 of the associations being significant between changes in markers of NP and changes in motor or cognitive function. In NEU, 50 % of the 16 studies reported only 2 of the associations being significant between changes in markers of NP and changes in motor or cognitive function. The median of these r values between changes in NP markers and clinical, cognitive, and motor outcomes studies was 0.38 (range: −0.47 to 0.93).

4. Discussion

We examined the effects of AT and RT intensity on domains of NP (brain activation, brain structure, neurochemicals) in HYA, HOA, PwMS, PwPD, and PwST. In 50, medium-quality studies, 60 randomized intervention arms, and 2283 in-analysis participants, the data partially supported the hypothesis that NP would scale with exercise intensity and this effect would decrease with age and disease. Specifically, the moderator analysis suggested that AT and RT-induced effect sizes increased with intensity only in HYA but not in HOA or NEU. The effect sizes of exercise-induced changes in NP outcomes as a whole and individually with the effect sizes of changes in neurochemical and brain structure outcomes were associated with the effects sizes of changes in motor but not cognitive outcomes. To our knowledge, this is the first comprehensive meta-synthesis examining causal relationships between AT and RT intensity, brain plasticity, cognition, and motor function in different populations.

4.1. High-intensity AT and RT similarly improve markers of NP

Animal and human data tend to suggest that intensity is a key determinant of cardiovascular, neuromuscular, NP, cognitive, and motor responses to AT and RT. Performing AT at increasing intensities incrementally potentiates the evoked cardio-metabolic responses produced by lower intensity exercise. High-intensity RT also augments contractile and neuromuscular functions produced by lower intensity RT. The summary effect sizes pooled across populations, exercise types, and NP outcomes confirm this idea: the overall effect size of high-intensity (g = 0.40, CI: 0.246–0.545, p = 0.001) vs. low-intensity exercise (g = 0.19, CI: 0.028–0.351, p = 0.024) was ~2-fold greater (Table 2, Fig. 2, Supplement 4). We note that the data also suggest that low-intensity exercise can still have a weak but significant overall impact on NP. On the whole, our results are in line with recent fitness and rehabilitation trends to train at high exercise intensities in diverse forms and as short duration as 4 s (Table 2) (Allen et al., 2021; Boullosa et al., 2022; Carpes et al., 2022; Gibala et al., 2006; Kovacevic et al., 2020; Marriott et al., 2021; McLeod et al., 2022; Satiroglu et al., 2021; Tollar et al., 2021; Tollár et al., 2018, 2020; Yeh et al., 2021; Zhang et al., 2017).

Both AT (g = 0.31, 0.18–0.44, p = 0.001) and RT (g = 0.35, 0.11–0.58, p = 0.006) improved NP outcomes significantly and similarly (Table 2, Supplement 4). Specifically, only high- but not low-intensity AT (g = 0.39; CI: 0.21–0.56, p < 0.001) and RT (g = 0.42, CI: 0.07–0.77, p = 0.023) improved markers of NP. These summary effect sizes represent pooled effects across populations and NP outcomes. The mechanisms of intensity-scaled improvements in NP are not entirely clear but certainly involve multiple and complementary paths. AT increases brain circulation in fronto-parietal and hippocampal areas known to control executive function, processing speed, and memory. Presumably, the brain takes up the muscle-generated lactate, which increases neuronal excitability, vascular endothelial growth factor release, cortical angiogenesis, ketone uptake, and the clearance of amyloid-beta and other cell-harming waste products in an intensity-dependent manner (Erickson et al., 2013, 2011; Ide and Secher, 2000; Li et al., 2019; Radak et al., 2006, 2013; Vilela et al., 2020). Cross-sectionally, cardiorespiratory fitness is associated with regional brain volume, gray and white matter integrity especially in the entorhinal cortex and hippocampus in humans and animals, implying AT-induced neurogenesis (Burzynska et al., 2015; Tsai et al., 2018). It is assumed that high- more so than low-intensity AT-generated lactate

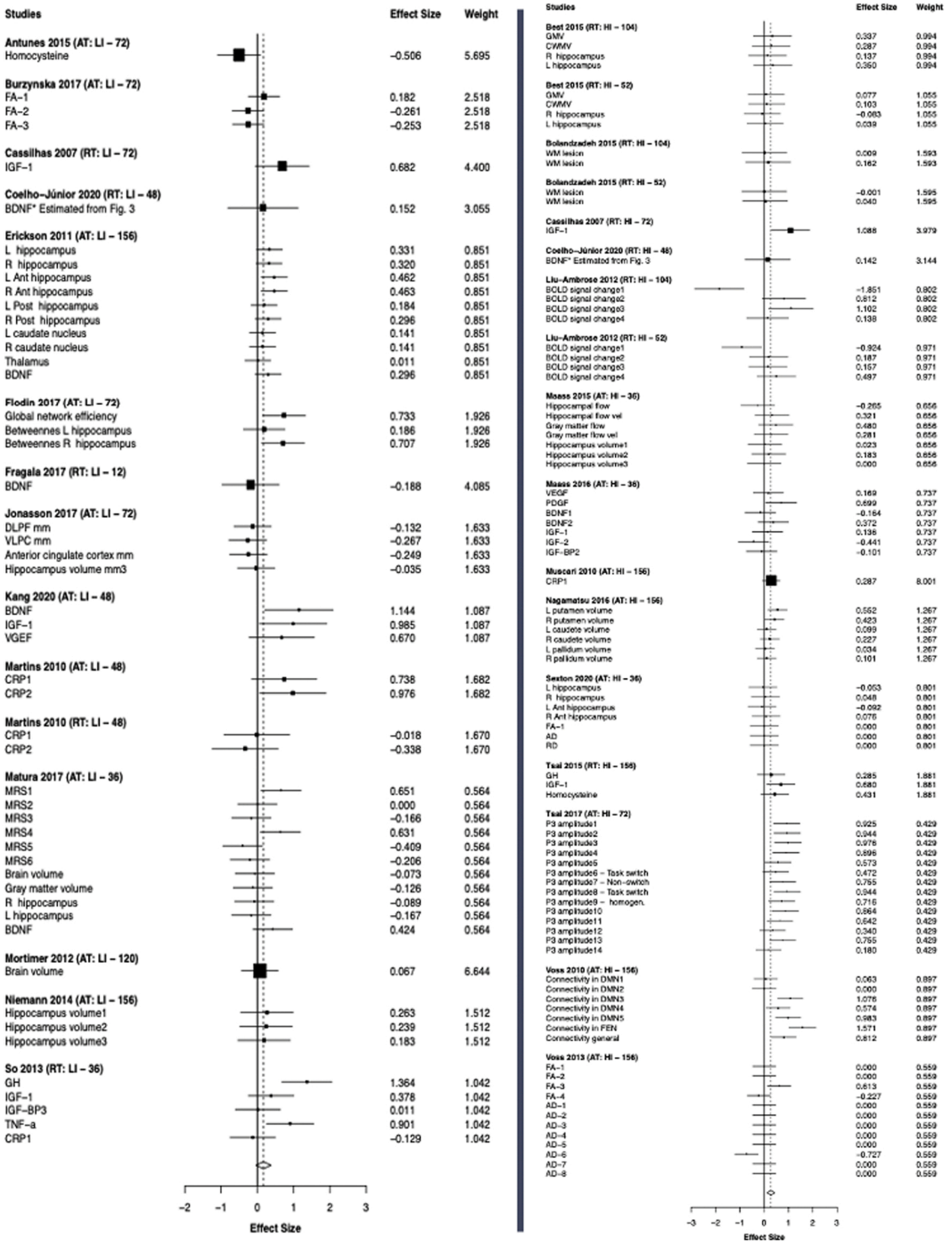

Fig. 2. (*continued*).

stimulates the proliferation of neurons and glia cells and brain-derived neurotrophic factor production (Diechmann et al., 2021; Ruiz-Gonzalez et al., 2021). However, recent evidence seems to question the neurogenesis mechanism at least in humans (Gogniat et al., 2021; Hvid et al., 2021; Nano and Bhaduri, 2022). Further, in an intensity-dependent manner, AT affects mitochondrial biogenesis and improves antioxidant capacity, the affinity of mitochondria for oxygen, protein levels involved in ATP generation, and mitophagy in muscle and brain (Burtscher et al., 2021). Such favorable changes in antioxidants are counteracted by AT intensity-scaled increases in reactive oxygen species-generation, which is detrimental to NP and cognitive functioning (Radak et al., 2006). The included studies did not specifically address which direction would exercise intensity tilt the balance between the favorable antioxidant effects of AT and unfavorable reactive oxygen species-generation with respect to NP (Flockhart et al., 2021; Radak et al., 2013). While the prevailing view is that RT acts primarily through insulin-like growth factor-1 mechanisms and promotes NP in an exercise intensity-dependent manner (Amiri et al., 2021; de Alcantara Borba et al., 2020; Jiang et al., 2020), there is also strong recent evidence suggesting that levels of circulatory brain-derived neurotrophic

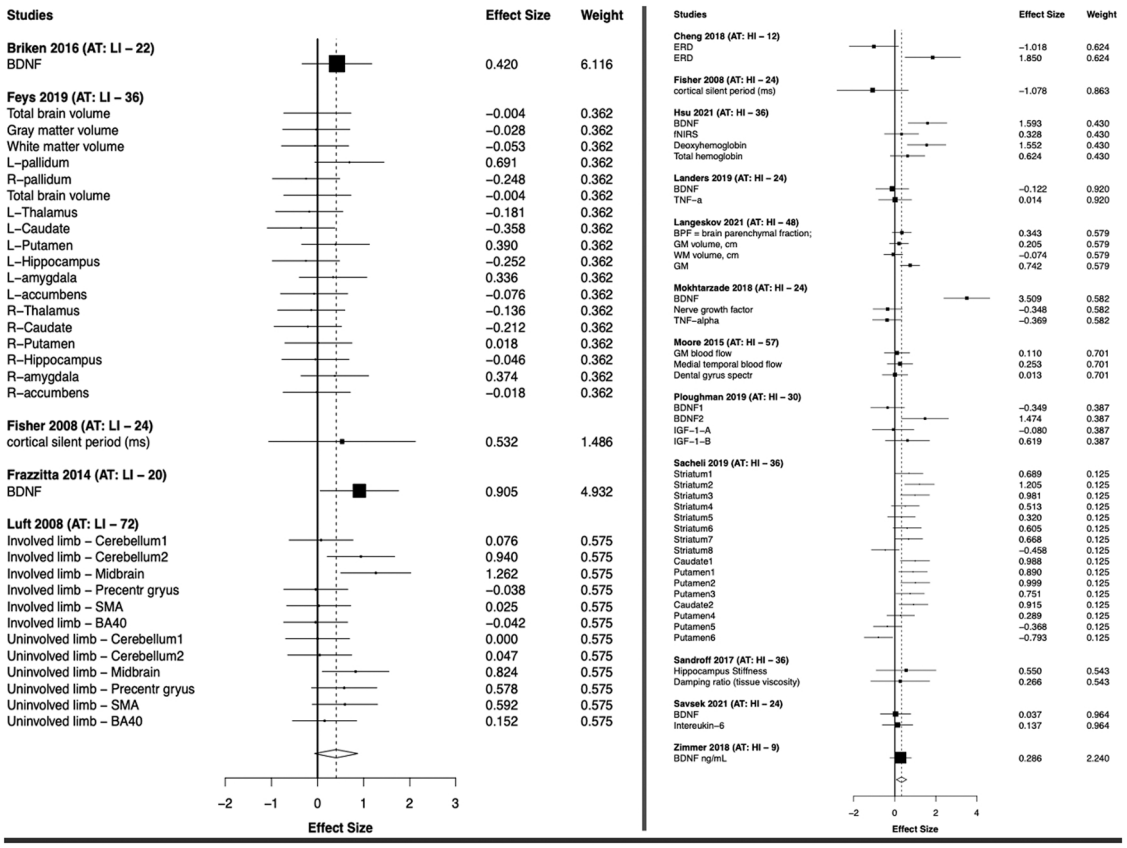

Fig. 2. (*continued*).

Table 3
Associations between markers of NP and motor and cognitive outcomes.

Analysis	N_s	Beta	±SE	p
Brain activation vs. Cognition	7	0.52	0.54	0.335
Brain structure vs. Cognition	10	0.31	0.27	0.245
Neurochemical vs. Cognition	14	-0.03	0.21	0.902
Neuroplasticity vs. Cognition	27	0.13	0.18	0.354
Brain activation vs. Motor	11	-0.21	0.28	0.459
Brain structure vs. Motor	13	0.24	0.12	**0.036**
Neurochemical vs. Motor	26	0.15	0.07	**0.027**
Neuroplasticity vs. Motor	46	0.15	0.06	**0.008**

N_s, number of studies

factor change independent of exercise type, intensity, duration, age, and health history (Babaei and Azari, 2021; Diechmann et al., 2021; Ruiz-Gonzalez et al., 2021). However, the results, including those with RT in particular, are highly inconsistent: some studies across the intensity spectrum reported no changes, increases, or even reductions in insulin-like growth factor levels (Chow et al., 2021; Coelho-Junior et al., 2020; Moreno-Cabanas et al., 2022; Olesen et al., 2021) (Table 2). The results are similarly inconsistent with respect to exercise-type and intensity-dependent modulation of vascular endothelial growth factor-mediated NP (Maass et al., 2016; Voss et al., 2013a). Methodological issues such as time of sampling during the day and when sampling is done after the last exercise bout, if sampling is done from plasma or serum and other such factors can underlie these inconsistent data. Taken together, our data lend preferential support for the efficacy of high-intensity AT ($g = 0.39$, $p = 0.001$) and RT ($g = 0.42$, $p = 0.023$, Table 2) to improve NP and expands the evidence-based options for exercise prescription for individuals of different ages and health status.

4.2. High-intensity exercise interacts in its effects on NP with age and disease status

We further explored these intensity and exercise type effects on NP across populations and NP markers. Across the 2 intensity levels and 3 domains of NP, exercise overall improved NP in HYA ($g = 0.67$, CI: 0.149–1.187, $p = 0.017$). However, the effect sizes denoting these favorable overall effects decreased substantially albeit remained significant in NEU ($g = 0.36$, CI: 0.172–0.544, $p = 0.001$) and further decreased in HOA ($g = 0.22$, CI: 0.097–0.348, $p = 0.001$, Table 2, Supplement 2). The final model of the moderator analysis confirmed the sub-analyses and further specified these results through the 'Intensity*Population' interaction. Accordingly, high- vs. low-intensity exercise significantly improved the effect size by 0.80 unit in HYA ($p = 0.039$). In contrast, exercising at high vs. low intensity did not increase the effect sizes in HOA (Δg: 0.09, $p = 0.420$) and NEU (Δg: −0.10, $p = 0.557$) (Supplement 8). Neither sex, domains of NP, total number of sessions, number of sessions per week, or type of intervention showed significance, thus, they did not enter the model as moderators of the intensity effects on NP.

Considering the premise that HYA 'are already at the lifetime peak of their cognitive health and performance' (Chow et al., 2021) and that previous reviews failed to include any chronic AT or RT studies examining NP (Erickson et al., 2019), it was unexpected that our search has identified 8 studies. The present data thus add to and expand the current knowledge. In young animals, AT improved visuospatial ability and these changes correlated with enhanced synaptic activity in hippocampal cells. AT also rescued the capacity for synaptic plasticity in young animals whose synaptic plasticity was experimentally compromised (Cabral et al., 2019; Christie et al., 2005; van Praag, 2008). Our data show that sedentary HYA still seem to have the residual capacity for improved NP and respond if the exercise stimulus is strong enough.

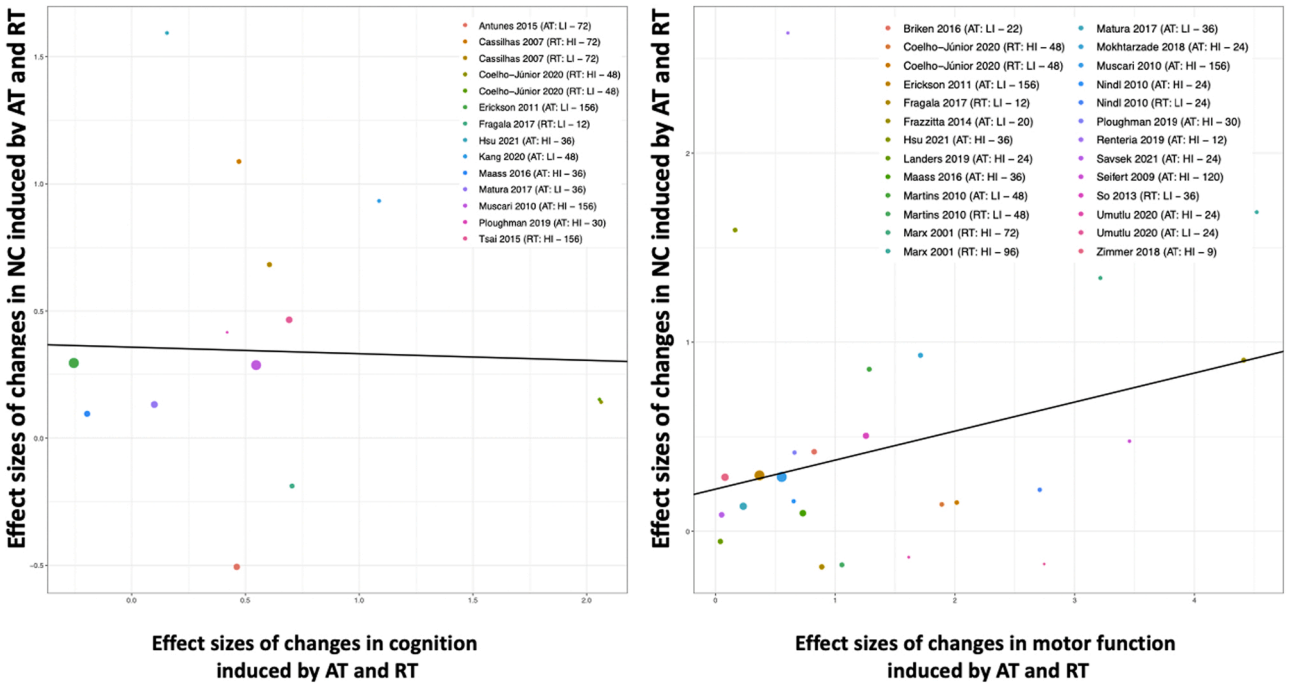

Fig. 3. Associations between the effect sizes of changes in cognition (left) and motor function (right), respectively, and the effect sizes of changes in measures of neurochemical (NC) domain of NP after aerobic and resistance training (AT, RT). Each symbol represents one study. Multiple outcomes within one study were aggregated into one effect size value. The left panel comprises 14 studies conducted at low (n = 7) and high (n = 7) intensities using AT (n = 8 studies) and RT (n = 6 studies). The right panel comprises 26 studies conducted at low (n = 11) and high (n = 15) intensity using AT (n = 18 studies) and RT (n = 8 studies). Symbol sizes scale with the contribution to the model. There was an association between effect sizes in motor (but not cognition) outcomes and measures of NC. Healthy young and older adults entered the model. Neurological patients did not enter the model.

Within the limits of our data from 8 studies, high-intensity exercise had strong effects on NP (g = 0.93, CI: 0.264–1.591, p = 0.013, Supplements 2, 8). In 5 studies, neurochemical and in 3 studies brain structural markers of NP improved significantly and incrementally more so with high compared with low intensity. Our chronic data extend the acute AT and RT exercise studies in sedentary HYA, suggesting that the initial gains in markers of NP and cognitive function likely would not increase beyond what is achieved after a few initial sessions. However, the cumulative effects from chronic training may play a role in sustaining the initial effects after training is stopped (Chow et al., 2021; Mellow et al., 2020; Nicolini et al., 2021; Wanner et al., 2020).

According to the 'Intensity*Population' interaction, unlike in HYA (Δg=0.80, p = 0.039), the difference between high- and low-intensity exercise effects was negligeable and non-significant in HOA (Δg=0.09, p = 0.420). The non-significant increase in effect size from low- to high-intensity training does not nullify the result that high-intensity exercise is effective to improve markers of NP in HOA. The interaction suggests that exercise intensity has less of an effect on NP in HOA compared with HYA. These data extend and requalify summary reports of previous narrative reviews that compared intensity effects on NP only between individual studies qualitatively (Cabral et al., 2019; Chen et al., 2020; Erickson et al., 2019; Heisz et al., 2017; Hugues et al., 2021; Nicolini et al., 2021; Quigley et al., 2020).

The picture emerging from the current data is that high- vs. low-intensity AT and RT is needed to produce beneficial effects on markers on NP. But from the current data we detected only a global effect on NP and cannot specify which NP marker would be preferentially affected by exercise, i.e., brain activation, brain structure, or neurochemical markers. For NP to be a mediator of improved cognitive or motor function, our data suggest that high-intensity exercise should be used. This observation contrasts with several reviews specifically recommending the use of moderate- or even low-intensity exercise to improve cognitive function through NP. For example, one review explicitly states with respect to PwST: 'Low-intensity aerobic training seems to be more effective than high-intensity training to promote cognitive health' (Constans et al., 2016). Indeed, these reviews refer correctly to data suggesting that Tai Chi and yoga, low-intensity activities, also improved HOA's cognition (Cabral et al., 2019; Chow et al., 2021; Northey et al., 2018; Quigley et al., 2020). Our data suggest that such changes might occur through mechanisms not or partially including NP.

According to the 'Intensity*Population' interaction, unlike in HYA, the difference between high- and low-intensity exercise effects was negligeable and non-significant in NEU (Δg=−0.10, p = 0.557). Again, the non-significant increase in effect size from low- to high-intensity training does not negate the finding that high-intensity exercise is effective to improve markers of NP in NEU. We in fact hypothesized exercise would be least efficacious in the NEU compared with HYA and HOA. The basis for this expectation was that: (1) even focal damage affects the function of remote brain areas, grossly impairing NP; (2) the levels of neurotrophic factors decline and the structure and function of neurons become impaired, and (3) neurodegeneration impairs NP which in turn tends to affect cognition and motor function. However, the overall exercise effects were higher in NEU (g = 0.36; CI: 0.172–0.544, p = 0.001) than in HOA (g = 0.22, CI: 0.097–0.348, p = 0.001), driven by the high-intensity AT effects in both groups (Supplement 2). The number of studies or the percent of heterogeneity did not drive the somewhat higher effect size for high-intensity training effects in NEU (N_s = 12, I^2 = 71 %) than HOA (N_s =14, I^2 = 49 %). While there have been reviews examining the effects of fitness, acute and chronic bouts of exercise on markers of NP in PwMS, PwPD, and PwST, none did meta-analytically examine interactions among exercise type, exercise intensity, NP domains, and populations (Ada et al., 2006; Calautti and Baron, 2003; Cruickshank et al., 2015; Diechmann et al., 2021; Dorsch et al., 2018; Ferreira et al., 2021; Gamborg et al., 2022; Hvid et al., 2021; Jorgensen et al., 2017; Lin et al., 2021; Ploughman et al., 2015; Ramazzina et al., 2017; Roeder et al., 2015; Ruiz-Gonzalez et al., 2021; Salter et al., 2016; Sandroff et al., 2020; Tablerion et al., 2020; Tillman et al., 2015; Wonsetler and Bowden, 2017). Our results in NEU agree with the

general conclusions of these reviews that high-intensity AT is a feasible rehabilitation option for each of the three patient groups with the caveat that potential intensity-related side effects rarely assessed or reported (see limitation 4 in Section 4.4). Further comparisons with these reviews are difficult. For example, a systematic review of the effects of AT on brain-derived neurotrophic factor reported an effect size of $z = 4.3$ in PwMS and $z = 2.61$ in PwPD (Ruiz-Gonzalez et al., 2021). However, this review included single and multi-modal interventions and patient groups with multiple levels of disability from a given study and used inverse variance vs. random variance estimate analyses. Inverse variance analysis does not account for study weight when multiple outcomes are used from one study and could potentially inflate effect size estimates. Even after combining diverse types of studies, there were still insufficient data for intensity sub-analyses (Ruiz-Gonzalez et al., 2021).

Our results revealed inconsistent patterns in the changes of NP in NEU (Supplement 2). In PwMS, a handful of studies reported small changes in a wide array of NP outcomes with one study reporting no changes in any of the 24 brain volume and neurochemical outcomes (Savsek et al., 2021). In PwPD, 1 of 6 neurochemical measures (Landers et al., 2019) and only 3 of 16 magnetic resonance imaging brain activation measures were significant but the positron emission tomography and dopamine release / binding potential data revealed significance (Sacheli et al., 2019). In PwST, changes only in a limited number of NP measures were significant in the 4 studies identified (Supplement 2). In PwST, limited data are available concerning exercise intensity effects on NP but animal models of stroke seem to suggest that moderate-intensity exercise might be most effective for dendritic branching in these patients (Ploughman et al., 2015). Other rodent data however suggest that high- instead of moderate-intensity exercise might be needed to induce NP in the hippocampus and cortex during the first 2 weeks after a stroke (Constans et al., 2021; Luo et al., 2019; Pin-Barre et al., 2017).

While the data are promising with respect to the effects of (high-intensity) AT on NP in NEU, we noticed that none of the studies included in the current review used RT in NEU (Cherup et al., 2019; Chow et al., 2021; Dorsch et al., 2018; Gamborg et al., 2022; Hortobágyi et al., 2021; Jorgensen et al., 2017; Kjolhede et al., 2018; Manca et al., 2019; Ruiz-Gonzalez et al., 2021; Salter et al., 2016; Wist et al., 2016; Wonsetler and Bowden, 2017). Altogether, the data from NEU population in the present study seem to align with recent trends toward the use of high-intensity motor rehabilitation, nonetheless it remains unclear if NP mediates the reported changes in cognitive and motor function (Boyne et al., 2019; Cancela et al., 2020; Conradsson et al., 2015; Constans et al., 2021; Crozier et al., 2018; Dempsey et al., 2022; Diechmann et al., 2021; Frazzitta et al., 2014; Gamborg et al., 2022; Hejazi, 2017; Hsu et al., 2021; Hu et al., 2021; Hugues et al., 2021; Johansson et al., 2020; Kolmos et al., 2016; Landers et al., 2019; Langeskov-Christensen et al., 2021; Luo et al., 2019; Martland et al., 2020; Morberg et al., 2014; Okamoto et al., 2021; Orban et al., 2019; Renteria et al., 2020; Rosenfeldt et al., 2021; Steen Krawcyk et al., 2019; Tang et al., 2016; Taylor et al., 2022; Tollar et al., 2021; Tollár et al., 2018, 2020; Zimmer et al., 2018).

4.3. Association between NP, cognition, and motor function

Our review found no association between effect sizes of changes in cognition and effect sizes of changes in NP in 31 studies. We identified a weak association between effect sizes of changes in motor function and effect sizes of changes in NP in 46 studies in HYA and HOA without NEU entering these analyses (Fig. 3). We also extracted the associations between changes in NP and cognitive and motor function reported by individual studies (Supplement 2, far-right column). This analysis overall confirmed our own association analyses: altogether 9 of the potentially hundreds of associations were only significant with a median value of $r = 0.38$ (range: −0.47 to 0.93). across the 50 studies.

As evidenced by the data from the current and many past reviews (Babaei and Azari, 2021; Chen et al., 2020; Gallardo-Gomez et al., 2022; Gamborg et al., 2022; Gogniat et al., 2021; Huang et al., 2022; Intzandt et al., 2021; Mellow et al., 2020; Quigley et al., 2020; Ruiz-Gonzalez et al., 2021; Sandroff et al., 2020; Tymofiyeva and Gaschler, 2020; Yeh et al., 2021), physical exercise can favorably modify markers of NP and measures of cognitive function at the group level. However, it has been difficult to establish a mechanistic or causative link between exercise-induced NP and cognition at the participant level. One likely reason is that a given NP marker can control a host of behavioral functions. Hence its specificity is low even for a domain of cognitive function such as executive function not to mention a specific cognitive marker such as reaction time, a measure of central information processing speed. While cardiorespiratory fitness at baseline is associated with neuronal activation, structural, and neurochemical markers of NP, exercise intervention-induced changes in these markers, as do cognitive outcomes, vary greatly between responders and non-responders (Herold et al., 2019), making it difficult to establish a causal link between exercise-mediated improvements in NP and cognition. Establishing such a causal link is further complicated by a lack of studies examining if any correlated reversal would occur in exercise training-induced gains in NP and cognition following detraining. While AT is unequivocally associated with systemic and brain circulatory health in aging, the current data seem to side with the conclusions of previous studies, including reviews, that also failed to support an association between exercise-induced improvements in NP and cognition in HOA (Etnier et al., 2006, 2016; Forte et al., 2013; Quigley et al., 2020; Sanders et al., 2019; Smiley-Oyen et al., 2008; Voelcker-Rehage et al., 2011; Young et al., 2015). Our data also agree with selected but not all reviews reporting parallel exercise training-induced improvements in inflammation, brain activation, brain structural, and neurochemical markers and selected measures of cognition but no association between the changes in the two sets of outcomes in PwMS, PwPD, and PwST (Crozier et al., 2018; Freidle et al., 2022; Hugues et al., 2021; Ruiz-Gonzalez et al., 2021; Soke et al., 2021).

The right panel of Fig. 3 shows the association between exercise training-induced changes in effect size of NC markers of NP and changes in effect size of measures of cognitive and motor function. Table 3 further specifies that the association between overall NP and motor function was driven by adaptations in brain structures ($N_s = 13$, $p = 0.036$) and neurochemicals ($N_s = 26$, $p = 0.027$) but not measures of brain activation $N_s = 11$, $p = 0.459$). These data strengthen and expand the current view that both AT and RT can favorably modify morphometric gray and white matter properties, white matter lesion burden, and brain tissue viscoelasticity. The current data also lend support for the capacity of AT and RT to favorably modify levels of neurochemicals (serum or plasma brain-derived neurotrophic factor, BDNF brain-derived neurotrophic factor-tropomyosin receptor kinase B signaling, insulin-like growth factor-1, insulin-like growth factor-binding proteins, vascular endothelial growth factor, homocysteine, C-reactive protein, brain metabolites, growth hormone, tumor necrosis factor alpha-α, interferon-γ). Such changes may in turn help improve motor function in HYA, HOA, and NEU (Babaei and Azari, 2021; Chen et al., 2020; Crozier et al., 2018; Domingos et al., 2021; Erickson et al., 2019; Falck et al., 2019; Ferreira et al., 2021; Gogniat et al., 2021; Hugues et al., 2021; Hvid et al., 2021; Intzandt et al., 2021; Mellow et al., 2020; Ruiz-Gonzalez et al., 2021). When taken together, these data are consistent with the view that AT and RT-induced changes in neurochemical markers are precursors that act as facilitators of structural changes in the brain. In this scheme, our data are not fully compatible with the idea that these steps in the mechanistic cascade modify brain activation. Our data specifically support this path in relation to motor but less so concerning cognitive function (Fig. 3, Table 3). However, we draw attention to the emerging controversy concerning the role of neurogenesis being a putative function-improving mechanism of neural control, including exercise-induced improvements in (cognitive) and motor function in humans (Gogniat et al., 2021; Hvid et al., 2021; Nano and Bhaduri, 2022). There is indeed meta-analytical

evidence against exercise moderating functional improvements via brain volumetric changes (i.e., neurogeneration) in populations at risk for neurodegeneration (Hvid et al., 2021). Fig. 4 summarizes the main results in a conceptual model.

4.4. Limitations and future directions

First, we categorized exercise intensity dichotomously according to established cut-off values. However, as always with cut-offs, these are somewhat arbitrary. If intensity values are just below or above the cut-off, there is hardly any difference between two adjacent categories yet one study is classified as high and the other one as low intensity. Second, some studies did not target either intensity zone and had instead an intensity range across study duration. We computed the mean value and classified it as either high or low intensity. In a secondary analysis, we used a strict classification scheme and included only those studies that were below or above the threshold throughout the entire intervention period. The findings were similar which is why we decided not to include this additional analysis. Third, we did not examine NP responses to acute bouts of exercise. This limitation is important and should guide future studies. The magnitude of change in markers of NP after chronic intensive exercise, i.e., at least 9 or more sessions up to a year, seems to be often similar to the magnitude of changes in these markers after just a few or even a single bout of exercise (Boyne et al., 2019; Mellow et al., 2020; Wanner et al., 2020). Such a response pattern resembles NP observed after manual and balance skill learning: a lack of effects of session number on NP (Bakker et al., 2022; Berghuis et al., 2017). That is, our review could not shed light on the cumulative effects produced by repeated exercise bouts on NP markers. Fourth, high-intensity exercise evokes a stress response. However, very few studies have examined stress markers in conjunction with high-intensity exercise even though such exercise can selectively disrupt sensorimotor resting-state connectivity, an emerging marker of NP (Schmitt et al., 2019) as well as cognitive functions (Costello et al., 2021). Changes in markers of stress are consistent with signs of central fatigue and overtraining. However, the included studies did not quantify or report these side effects. Fifth, heterogeneity was high, which is unavoidable in comprehensive analyses. We addressed this limitation by performing sub-group analyses and meta-regressions to explore sources of heterogeneity and also by pooling the three neurological patient groups into NEU. High heterogeneity can also imply that our analyses had some degree of external validity by reflecting real-life scenarios. Sixth, we were unable to determine if the lasting effects of exercise differed according to intensity: very few studies performed follow-ups, a key area for future research. Seventh, directional coding of NP markers can be complicated. While we had multiple rounds of checking to ensure the accuracy of directional coding, in several studies it was still unclear and unknown if certain changes, for example, in brain activation in given brain areas was a favorable or maladaptive change. Specifically, a team of authors reached consensus to exclude interleukin as outcomes because several studies and reviews suggested conflicting views concerning the direction that would constitute a positive change. Eighth, many studies used cognitive measures (e.g., Mini-Mental State Examination) that are insensitive to change, dampening effect sizes and guiding future studies toward using change-sensitive measures (i.e., Montreal Cognitive Assessment). Ninth, this review identified the effects of exercise intensity on domains of NP instead of individual NP markers. Still, our results seem to agree with most recent ideas that life-style factors, among them exercise (intensity), have a key role in modifying specific neuronal paths toward risk reduction for dementia including the amyloid/tau, microglia, and the tumor necrosis factor-α paths (Bellenguez et al., 2022). Tenth, HOA were considered based on eligibility criteria in each study. However, it was not possible to determine whether included participants presented with unreported chronic health conditions, such as diabetes, hypertension, and hypercholesterolemia. We also limited inclusion to HYA, HOA, and NEU and omitted to include studies focusing on individuals with mild cognitive impairment, as well as Alzheimer's disease, which comprise a large population of those living with dementia. Eleventh, we did not know participants' physical activity levels at baseline. Increases in physical activity levels could have varied tremendously from individual to individual, which might explain lower effects of exercise in some studies. Finally, we did not include peripheral markers of NP, i.e., motor unit remodeling, an avenue that future research should target (Alix-Fages et al., 2022; Power et al., 2022) and it remains unclear if neuroimaging and neurochemical markers are reflective of NP.

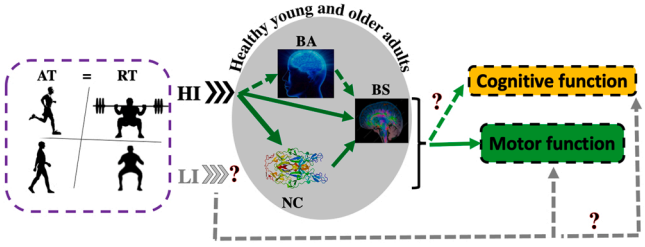

Fig. 4. Schematic summary of the results produced by the current review. We examined the effects of chronic high- (HI) and low-intensity (LI) aerobic (AT) and resistance (RT) exercise training on brain activation (BA), brain structure (BS), and neurochemical (NC) markers of neuroplasticity (NP, gray oval) in healthy young and older adults and patients with multiple sclerosis, Parkinson's disease, and stroke. Random-effects meta-regression, i.e., robust variance estimation for multilevel data structures analyses, revealed that HI AT and RT exercise each modified markers of NC and BS (thick-lined arrows). Exercise training did not significantly modify markers of BA (dashed line). Changes in NP overall (gray oval) and in NC and BS markers in particular (vertical bracket) were associated with improvements in motor function in healthy young and older participants only. Such an association was absent in a group that combined three patient populations. The equal sign between AT and RT denotes that the data revealed no difference in the effects of the two intervention types on markers of neuroplasticity. HI exercise had medium to strong effects on markers of NP ($g=0.40$, $N_p = 1397$ participants, confidence interval: 0.246–0.545, $p = 0.001$, $I^2 = 65.6$, $T^2 = 0.23$). LI exercise had low but significant effects on markers of NP ($g=0.19$, $N_p = 886$ participants, confidence interval: 0.028–0.351, $p = 0.024$, $I^2 = 34.2$, $T^2 = 0.06$). Question marks denote weak or no effects or associations between interconnected variables. The text provides further details on the Intensity*Population interaction and moderation analyses. Inset images of BA, BS, and NC are from public domain.

5. Conclusions

To our knowledge, this is the first comprehensive meta-synthesis examining causal relationships between AT and RT intensity, NP, cognition, and motor function in different populations. Exercise intensity is an important variable to dose and individualize the exercise stimulus for healthy young individuals but not necessarily for healthy older adults and neurological patients. This conclusion warrants caution because studies are needed that directly compare the effects of low- vs. high-intensity exercise on NP to determine if such changes are mechanistically and incrementally linked to improved cognition and motor function.

Declaration of Competing Interest

None of the authors declare any conflict of interest.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101698.

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