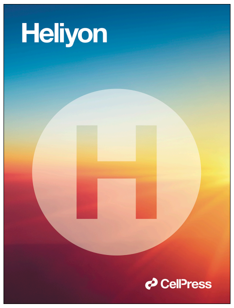

Randomized controlled trials of non-pharmacological interventions for healthy seniors: Effects on cognitive decline, brain plasticity and activities of daily Living—A 23-year scoping review

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Randomized Controlled Trials of Non-Pharmacological Interventions for Healthy Seniors: Effects on Cognitive Decline, Brain Plasticity and Activities of Daily Living—A 23-year Scoping Review

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ABSTRACT

Little is known about the simultaneous effects of non-pharmacological interventions (NPI) on healthy older adults' behavior and brain plasticity, as measured by psychometric instruments and magnetic resonance imaging (MRI). The purpose of this scoping review was to compile an extensive list of randomized controlled trials published from January 1, 2000, to August 31, 2023, of NPI for mitigating and countervailing age-related physical and cognitive decline and associated cerebral degeneration in healthy elderly populations with a mean age of 55 and over. After inventorying the NPI that met our criteria, we divided them into six classes: single-domain cognitive, multi-domain cognitive, physical aerobic, physical non-aerobic, combined cognitive and physical aerobic, and combined cognitive and physical non-aerobic. The ultimate purpose of these NPI was to enhance individual autonomy and well-being by bolstering functional capacity that might transfer to activities of daily living. The insights from this study can be a starting point for new research and inform social, public health, and economic policies. The PRISMA extension for scoping reviews (PRISMA-ScR) checklist served as the framework for this scoping review, which includes 70 studies. Results indicate that medium- and long-term interventions combining non-aerobic physical exercise and multi-domain cognitive interventions best stimulate neuroplasticity and protect against age-related decline and that outcomes may transfer to activities of daily living.

Keywords

Healthy older adults - Non-pharmacological interventions – Randomized Controlled Trials - Cognitive decline – Psychometrics – Cognitive - Aerobic – Non-aerobic – Physical - Artistic Interventions - Magnetic Resonance Imaging – Brain plasticity – Activities of Daily Living

1. INTRODUCTION

Age-related decline is inevitable. It affects cognition, specifically processing speed, memory, visuospatial skills, executive functions, fine and gross motor skills, and perceptual capacities [1, 2]. This decline stems from general cerebral atrophy, though some regions of the brain, such as the prefrontal cortex (PFC) and the hippocampus (Hc), deteriorate more markedly [3-5]. Crucially, working memory, a fundamental building block of general cognition that supports more complex functions like executive control, is highly dependent on connections between the PFC and the Hc [6].

Various non-pharmacological interventions (NPI) have been developed and implemented to prevent, mitigate, or counteract cognitive, sensorimotor, and cerebral decline in normal aging. They aim to support the maintenance of independence and well-being in healthy elderly persons (HE) through the transfer of learning to activities of daily living (ADL) [7].

In light of the surge in life expectancies worldwide, effective and efficient strategies to mitigate early stages of age-related behavioral and neurobiological decline are essential for preventing or slowing down further deterioration. Ideally, these interventions should be stimulating and easy to integrate into ADL. In an elderly population, lack of motivation often thwarts training regimen effectiveness and maintenance over the longer run [8, 9].

Most existing studies of training regimens in older adults have focused on the behavioral benefits of different longitudinal training regimens. However, these changes are accompanied by functional and structural changes to the brain [10-12].

Brain plasticity refers to potentially interactive functional and structural brain modifications in response to experiences in the external world or the internal environment. Brain plasticity and behavioral plasticity are intricately linked [10, 11, 13].

Robust evidence exists that such functional and structural organization of the human nervous system is a continuous and dynamic process that endures across the lifespan [14-17] and is inextricably tied to the concept of cognitive reserve [18, 19]. Cognitive reserve, the brain's ability to resist aging effects, develops throughout life. Older adults continue to exhibit plasticity in numerous learning activities, ranging from mastering new skills to complex cognitive tasks and their interplay [11].

Engaging in non-invasive NPI at an advanced age is gaining traction as an effective means for HE to increase cognitive and brain function and build on their existing cognitive reserve [20]. NPI foster self-empowerment while carrying little or no risk and very few if no side effects. They impact cognitive, sensorimotor, and cerebral functions in a holistic manner and thus elevate the quality of life of aging individuals.

Combined brain and behavior empirical research is relatively rare in the context of NPI and HE. Yet, integrating psychometric and brain imaging data to measure the effects of different kinds of NPI allows for gaining more profound insight into their distinct benefits and differences and sheds light on the neural foundations of NPI behavioral outcomes.

To our knowledge, nine reviews have investigated combined brain and behavior data to evaluate the effects of NPI on HE: [21-29]. Each reaches interesting conclusions, but all have a limited scope.

Ahlskog et al. (2011) [21] conducted a broad review of both animal and human studies to present evidence of the cognitive neuroprotective effects of aerobic exercise on normal and pathological aging and its brain substrates. They found that regular exercise lowered the risk of cognitive decline and dementia. The authors proposed two possible explanations: deceleration of neurodegeneration and reduction of vascular risk factors. **Duffner et al. (2023)** [22] conducted a systematic review and meta-analysis of 43 studies to investigate the relationship between social activity (SA), cognitive activity (CA), and brain structure. They excluded studies focusing on specific neuropsychological functions, such as memory training. Most of the included studies were cross-sectional, and only a limited number involved longitudinal NPI. The age of participants ranged from 20 to 85 years, though most studies focused on HE. A meta-analysis hinted at a moderate positive correlation between CA/SA and hippocampal volume and a negative correlation with white matter hyperintensities (WMH), both aging-related phenomena. **Haeger et al. (2019)** [23], in a systematic review, looked at 23 MRI studies of structural plasticity following physical activity in the context of cognitive decline and compared patients with mild cognitive impairment (MCI) and Alzheimer's disease against HE. They observed that aerobic exercise and fitness predominantly affected brain regions vulnerable to neurodegeneration. However, they acknowledged a need for more evidence on complex and multi-component interventions. **Hortobagyi et al. (2022)** [24], in a systematic review of 50 studies, assessed the impact of low- vs. high-intensity aerobic and resistance training on motor and cognitive abilities, brain function, structure, and neuroplasticity markers in healthy young and older adults and patients with multiple sclerosis, Parkinson’s disease, and stroke. They reported that exercise intensity correlated with neuroplasticity in healthy young adults but not in older adults or patient groups. **Intzandt et al. (2021)** [25], in a systematic review of 38 studies, compared the effects of cognitive and physical exercise training, respectively, on MRI outcomes in HE and concluded that “a combination of both cognitive and exercise training would likely be ideal to target specific pathways that are impacted in aging, but also to enhance global brain health”. This notwithstanding, they excluded interventions that combined cognitive and physical training from the review. **Oschwald et al. (2019)** [26] carried out a comprehensive review of the relationship between brain structure and cognitive ability in the context of healthy aging, focusing specifically on longitudinal correlated change. They observed positive associations between distinct brain regions and specific cognitive functions but warned against generalization due to methodological variability and weaknesses of the included studies. However, they did not evaluate or compare NPI; the 31 included articles involved prospective observational studies, and the age of study participants ranged from 19 to 103 years. **Pan et al. (2018)** [27] focused exclusively on tai chi chuan (TCC) interventions for HE in their systematic review. They critically appraised 11 studies (five RCTs) that used EEG and other brain imaging techniques to study the effects of TCC on HE. They concluded that TCC might positively alter brain function and structure, but that this field of research required expansion. **Ten Brinke et al. (2017)** [28] investigated the effects of computerized cognitive training (CCT) on neuroimaging results in healthy and pathological older adults in a systematic review of studies. Of the nine included studies, only two were high-quality RCTs. The authors found that multi-domain CCT could increase hippocampal functional connectivity. **Van Balkom et al. (2018)** [29] analyzed 20 RCTs in a systematic review examining the impact of cognitive training on brain network function using task-related Magnetic Resonance Imaging (fMRI) and resting state fMRI (RS-fMRI). They focused on HE and patients with MCI, Alzheimer's, Parkinson's, and multiple sclerosis, and excluded interventions that combined cognitive and physical activity. Multi-domain training reduced age- or disease-related network dysfunction by improving within-network connectivity, particularly in the default mode network (DMN). Single-domain training increased intra-network connectivity but decreased inter-network connections, suggesting enhanced neural resource efficiency. This was also supported by reduced task-related activations in HE and MCI individuals.

None of these reviews comprehensively explored and compared the impact of the different NPI documented in the literature on behavior (including cognitive and sensorimotor/physical functions) and brain functional and structural changes in HE.

To date, no systematic inventory of the comprehensive combined effects on behavior and brain plasticity of NPI in HE exists.

1.2 Rationale

Given today's explosive age expectancy increase, we decided to undertake a scoping review of neurobehavioral research on NPI in HE published as of January 1, 2000. We sought to carry out a comprehensive investigation of how NPI impact the adaptability of behavior, brain function, and brain structure in HE before the potential onset of pathological age-related decline. These interventions aimed to counteract cognitive and sensorimotor decline to prolong the independence and well-being of older individuals. We deliberately chose the start date of January 1, 2020, to ensure that the MRI data met the latest standards, thus bolstering the reliability and replicability of findings [30]. The synthesis of these neurobehavioral studies will shed a comprehensive light on the potential benefits of non-pharmacological interventions (NPI) and their neural foundations, contributing to expanding research in this area. This knowledge may serve to optimize NPI for future health prevention and promotion efforts and inform social, public health, and economic policies concerning senior care.

1.3 Scoping review question

What are the effects of NPI on brain plasticity as measured by functional and structural MRI, and how do they relate to the plasticity of cognitive and sensorimotor function in HE above a mean age of ~55 years?

Key questions

- What are the methods and contents of these NPI?
- Did the interventions induce behavioral benefits?
- Did the interventions induce brain plasticity, and if so, did these changes relate to behavioral results?
- Did the brain and behavioral changes persist over time in the case of delayed measurements?
- How do the different NPI overlap and differ regarding brain plasticity and associated behavioral changes, and what does this reveal about underlying brain mechanisms?
- Which intervention categories and characteristics (e.g., training characteristics and procedure, duration, intensity) resulted in the most substantial behavioral benefits?

1.4 Objectives

- To put forth guidelines for best practices to countervail cerebral, cognitive, and sensorimotor decline in HE and to improve ADL through NPI.
- To make recommendations for future research to further investigate the topic of NPI in the context of cognitive aging and to determine the most effective interventions to combat natural cognitive loss associated with aging.

Analyzing and comparing the various approaches may shed light on general and specific brain mechanisms underlying NPI and how they might countervail age-related cognitive and sensorimotor decline, brain structural shrinkage/expansion, and changes in brain activity.

A scoping review seemed appropriate as our aim was not to answer a specific clinical question but rather to take stock of regimens that have been investigated and discuss their impact on brain plasticity and behavior.

From the findings of this review, our ultimate aim is to suggest guidelines for optimizing future interventional studies and to highlight the regimens that yield the most substantial benefits, especially concerning ADL. We also sought to address unresolved issues (nature, duration, intensity of regimens) with the aim of contributing to the development of widely implementable and motivating healthy aging strategies accessible to all**.**

To facilitate future research and to render the review accessible to as broad a readership as possible, we defined key concepts in **Appendix 1**, such as transfer of learning, adaptive training, and experience-driven brain plasticity. Moreover, in **Appendix 2,** we briefly explain MRI techniques and derivative measures for evaluating the structural brain plasticity of gray matter (GM) and white matter (WM) and for assessing functional plasticity. The latter includes task-related functional MRI (fMRI), resting-state functional MRI (RS-fMRI), and arterial spin labeling (ASL).

2. METHODS

2.1 Protocol and registration

We did not register a protocol prior to undertaking this scoping review. No universally agreed-upon platform or repository exists specifically for scoping review protocols, unlike systematic reviews and meta-analyses, which have platforms like PROSPERO. PROSPERO does not accept scoping reviews.

This scoping review is based on the methodological framework proposed by Arksey and O'Malley [31]. However, we applied the more recent PRISMA extension for scoping reviews checklist (PRISMA-ScR), described by Tricco et al. [32].

2.2 Eligibility criteria

2.2.1 Inclusion criteria

- Non-pharmacological, non-invasive, experimental intervention/training studies (longitudinal)
- HE without major physical or mental health issues
- RCT: use of randomization to compose distinct experimental and control groups from a pool of HE
- Mean age of participants ≥ 55 years[1] (without a ceiling age)
- Investigation of structural and/or functional brain plasticity using MRI
- At least one behavioral outcome
- Peer-reviewed published articles in English
- Published in the period spanning January 1, 2020, to August 31, 2023

2.2.2 Exclusion criteria

- Major physical or mental health issues of the participants (severe cardiovascular, neurological, or psychiatric conditions; diabetes)
- Interventions shorter than two weeks
- Institutionalization of participants (residents of nursing homes)
- Studies that examined exclusively neurochemical markers of brain health through Magnetic Resonance Spectroscopic Imaging[2] (MRSI)

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[1] According to the World Health Organization, old age begins at 55 (NIH Publication no. 11-7737).

[2] MRSI, although related to MRI, primarily provides information about chemical composition and metabolites in tissues that have no direct relationship to behavior.

2.3.

2.3.1 Information sources

We searched the literature using Web of Science, PubMed/Medline, and Google Scholar. Together, these databases provide a quasi-comprehensive inventory of English-language peer-reviewed articles regarding studies of NPI for healthy older adults in the domain of cognitive neuroscience.

2.3.2 Identifying relevant studies using data items

The use of Medical Subject Headings (MeSH) terms for scoping reviews in emerging interdisciplinary fields, like the study of the combined brain and behavior effects of NPI in HE, is not recommended because of their limitations in capturing the breadth and nuances of such topics. We opted, instead, for alternative search strategies combining keyword category variations that would provide a more comprehensive and relevant outcome database [33]. We employed an iterative process and identified eight main conceptual categories of keywords [34], each declined into a set of closely related concepts, which constituted the data items/variables (see **Table 1)**.

We obtained a series of studies by systematically combining data items from a subset of the eight keyword categories using the "AND" and “OR” operators. We alternated systematically between items from category 4 or 5 and category 6 or 7, as those categories are akin to one another. This exhaustive combinatory approach yielded a relatively limited set of studies, which did not warrant using a traditional decision tree or flowchart. We refer to **Table 2** for an illustration of how these searches were run.

INSERT TABLE 1 HEREABOUTS

Table 1: Keyword classification and Data Items

INSERT TABLE 2 HEREABOUTS

Table 2: Search Examples

The idea for this scoping review of RCT studies of NPI in the context of healthy aging came from DM. Five independent evaluators (authors CEJ, DMM, CAHM, DM, and YVDL) followed the data charting process described in section 2.3.3. The search lasted from January 2021 to August 2023. Our efforts to synthesize the identified studies and meanwhile run search updates to keep our data up-to-date explain the long search timeline.

Two junior researchers, DMM and CAHM, performed the initial search, based on comprehensive combinations of Data Items from the eight categories shown in Table 1, which CEJ and DM conceived together. Then, CEJ and DM validated and finalized the initial search process with the help of YVDL. CEJ wrote the first draft of the final manuscript. Authors DVDV, MK, and EA, all three experts in their fields (DVDV in advanced MRI analyses; MK in cognitive aging; and EA in experience-driven brain plasticity and neurology), performed a critical review. DM performed a final review of the manuscript. YVDL, a Ph.D. in physics and MRI expert, verified all supplementary tables. CEJ drafted the final manuscript.

2.3.3 Data charting process/data extraction

Our combined keyword research described in section 2.3.2 yielded 321 studies. Of these, after removing duplicates, a selection of 90 studies met all our eligibility criteria at first sight. However, we excluded 26 post hoc for the following reasons: 1) not a genuine RCT; 2) only one study group consisted of HE (e.g., comparison/control group consisted of younger adults); and 3) MRI was applied only post-intervention (no baseline data). This left us with 63 articles.

Six studies that were not genuine RCTs were nonetheless retained. In these, either the experimental and control groups of HE were well-matched beforehand, or the control group was well-matched post hoc to the randomized experimental group (at least for sex, age, and education level). The six studies were: [35-40]. **See section 6 and Supplementary Tables 1-6** for details on these studies' randomization and matching procedures.

In the end, 70 studies were included in the review.

2.4 Collating, summarizing, and reporting results

Table 3 lists the abbreviations used in the body of the text and Supplementary Tables 1-6. In the text, each abbreviation is placed within parentheses the first time the term it refers to is used. These supplementary tables almost exclusively employ abbreviations on account of the limited space available.

INSERT TABLE 3 HEREABOUTS

Table 3: Abbreviations

As all the reviewed studies involved HE, all the recommendations and guidelines for future research apply exclusively to this target population.

2.4.1 Descriptive results of the studies

We broke the 70 included studies down into six classes by intervention type: 1. single-domain cognitive intervention; 2. multi-domain cognitive intervention; 3. physical aerobic intervention; 4. physical non-aerobic intervention; 5. combined cognitive and physical aerobic intervention; and 6. combined cognitive and physical non-aerobic intervention. See section 6 and Supplementary Tables 1-6 for a detailed comprehensive and schematic description of each study. The results are presented according to these types.

2.4.2 Quality assessment

We focused exclusively on RCTs to ensure a basic level of quality.

In section 6, the 70 included RCT studies are each summarized, and their overall quality assessed Supplementary Tables 1-6 allow for verifying study robustness by presenting participant numbers and experimental plans. Studies with a passive control group are less methodologically rigorous than those with multiple experimental groups and or an active control group. An active comparison group enables researchers to control for variables like participant expectations and commitment and the effects of attention or intervention, thereby bolstering study validity and conclusions.

Table 4 shows the spatial organization of Supplementary Tables 1-6: categories and characteristics.

INSERT TABLE 4 HEREABOUTS

Table 4: Organization of Supplementary Tables 1-6

According to the recent PRISMA-ScR Checklist described by Tricco et al. (2018) [32], summary measures, additional analyses, and risk of bias across studies are considered "not applicable" for scoping reviews.

Finally, sections 4 (Conclusion) and 5 (Guidelines for future research and interventions) summarize the extensive data and outline opportunities for expanding and improving studies to identify optimal strategies to counteract cognitive, sensorimotor and cerebral decline in HE through NPIs.

3. DISCUSSION

In this discussion section, all studies are first discussed according to the six types of intervention. Subsequently, the topics covered include the efficacy of NPIs on neurobehavioral plasticity (3.7), the influence of intervention duration and intensity (3.8), delayed measures (3.9), the relationship between post-intervention behavioral changes and activities of daily living (ADL) (3.10), post-intervention brain plasticity in the structural and functional domains (3.11), and sex differences (3.12).

Regarding the first two intervention types, it should be noted that most single-domain cognitive interventions (3.1) were relatively short-term. In contrast, multi-domain cognitive interventions (3.2) tended to have longer durations, rendering direct comparisons difficult.

3.1 Single-domain cognitive interventions

For the majority of the short-term single-domain studies, effects were limited to near transfer: Performance of the trained tasks improved, but this improvement did not spread to other cognitive domains [41-49].

In contrast to the studies by Biel et al. (2020) [41] and Mozolic et al. (2010) [42], which examined monotonous, one-month and two-month low-intensity interventions without notable gray matter (GM) changes, Engvig et al. (2010, 2012) [45, 46] and de Lange et al. (2018) [50] adopted a more stimulating approach. Using the associative "Method of Loci" (see Table 2) wordlist training, Engvig's two-month study and de Lange's 4x10 weeks (intermittent training and rest) study involved short-term yet intensive interventions that yielded increased cortical thickness (CT) in Engvig's work and positive white matter (WM) diffusivity changes in de Lange's study. Remarkably, these brain structural changes correlated with improved verbal learning, demonstrating near-transfer effects. The more intensive and mentally engaging nature of the Method of Loci likely accounts for these pronounced effects on brain plasticity.

Three studies [7, 44, 51] found that engaging in intensive gaming interventions strongly affected GM and WM, verbal memory, working memory, and executive function(s) (EF). Apparently, gaming reinforced motivation and learning and generated direct associations with brain changes. In the West et al. study (2017) [51], a comparison was made between two six-month interventions: a long-term video gaming intervention and computerized music lessons. Both NPI showed specific gray matter increases, in the Hc and dlPFC respectively.

Strenziok et al. (2014) [7] revealed that a six-week intensive adaptive gaming intervention exerted far-transfer effects on abstract thinking and daily living problems, mediated by decreased functional connectivity (FC; see **Appendix 2**) between the dorsal attention network and the ITL. In contrast, Brehmer et al. (2011) [52] observed that the results of an intensive five-week adaptive computerized working memory intervention, without gaming, produced less far-reaching effects and mainly incited gradually improving working memory (near transfer). Erickson et al. (2007) [47] found that a two- to three-week intensive computerized intervention involving color and/or letter detection induced functional brain changes correlated with improved performance on the fMRI dual task. The latter results were likely due to the dual-task training that drives cognitive flexibility.

In the same vein, Heinzel et al. (2016, 2017) [35, 36] evaluated a challenging double adaptive computerized working memory intervention over only one month. Results showed EF, processing speed, and fluid intelligence improvements associated with brain activity changes (fMRI) in the dlPFC.

Importantly, these findings demonstrate the positive and rapid impact of individualized adaptive learning relevant for ADL.

Only five weeks of moderate- and low-intensity computerized functional Field of View (FOV, see Table 3) interventions produced a near-transfer effect of improved FOV performance [48, 49], particularly in Ross et al. (2019) [48], when the task was adaptive. The interventions contributed to the efficiency of the brain's visual attention system. FOV performance is predictive of everyday functioning (e.g., driving).

In sum, among relatively short-term single-domain interventions, *adaptive, challenging, motivating, and intensive* regimens brought about the strongest behavioral and brain changes that may transfer to ADL.

3.2 Multi-domain cognitive interventions

Six medium- and long-duration multi-domain cognitive interventions, compared with single-domain ones of shorter duration on average, showed a broader effect on behavioral plasticity and yielded cognitive improvements supporting ADL. In the first, learning a new language over four months at moderate intensity changed FC of the DMN (see **Appendix 2**), which was associated with a transfer to general cognition [53]. In the second, six months of providing intensive assistance to primary-school children improved attentional capacities and increased BOLD activity in the PFC during a flanker test in low-education older women [37], indicating a far-transfer effect. This study shed new light on the cerebral and cognitive benefits of gratifying post-retirement lifestyle behaviors in social settings. In the third, moderately intensive abstract-reasoning interventions lasting three months elicited progressive WM integrity in the uncinate fasciculus and increased FC and cerebral blood flow (CBF) in the DMN and the central executive network (CEN; see **Appendix 2**) [54]. The fourth intervention by Hardcastle et al. (2022) [55] entailed computerized multi-domain adaptive cognitive training targeting attention, processing speed, and working memory. Participants improved on almost all tasks, notably the Double Decision task involving EF. The results were underpinned by increased FC in the frontoparietal control network (similar to the CEN). The results of these four studies support the notion that learning-induced metabolic, functional, and structural brain changes are intertwined [10, 13]. In the fifth study, three months of an intensive robot-assisted cognitive intervention was compared against a traditional multi-domain cognitive intervention of equal duration. Both brought about decreased CT thinning in the frontotemporal association cortices [56]. However, only CT changes in the left (L) temporo-parietal junction in the robot-assisted group correlated with EF performance. Finally, in the sixth study, moderately intensive computerized multi-domain cognitive training over three months gradually increased GM density in the post-central gyrus [57], which correlated positively with a global cognition score. FC decrease in the DMN preceded structural and cognitive brain changes after three weeks and correlated with global cognition post-training.

In their systematic review evaluating the effects of single- and multi-domain cognitive training in HE, using functional brain imaging, Van Balkom et al. (2020) [29] uncovered that multi-domain approaches countered age-related dysfunctional connectivity patterns through compensatory mechanisms. Li et al. (2014) [58] observed the same phenomenon. Similarly, Cao et al. (2016) [59] and Luo et al. (2016) [60] reported that multi-domain training for HE enhanced functional connectivity of the posterior cingulate cortex within the DMN and increased within-network connectivity in the frontoparietal network and the salience network (SN). These changes were associated with improved information processing efficiency and reduced age-related brain asynchrony and activity decline.

3.3 Physical aerobic interventions

Studies demonstrated that a minimum of six months of physical aerobic training was required to induce structural brain changes and that the duration of intervention outweighed intensity in terms of effect. Studies of six- to twelve-month aerobic training at various intensities showed gray matter gains in prefrontal, temporal, and hippocampal regions [61-63], prone to gradual volume loss after midlife [3, 4]. In contrast, when participants engaged in three hours of training per week for only three months, no GM volume increase occurred [64, 65].

Various studies showed that functional changes appeared earlier (see subsection 3.11.1): three months of low-intensity spinning thrice weekly [66] strengthened verbal fluency co-occurring with decreased fMRI BOLD activity in the right inferior frontal gyrus (R IFG), evidencing greater processing efficiency. It may seem surprising to find that pure aerobic exercise impacts language function. Yet, numerous studies have demonstrated the influence of aerobic exercise on inferior frontal areas involved in language activities or other cognitive aptitudes [61, 63, 67], which might be explained by improved cardiovascular fitness [68]. After a three-month comparison of aerobic exercise and relaxation/stretching [40], increased cardiorespiratory fitness (CRF) was linked to Hc perfusion and spatial memory improvements. However, the aerobic group showed no unique brain or behavioral benefits [40], questioning the efficacy of short-term aerobic training.

Other research also suggests that transfer effects of aerobic workouts on HE might have been interpreted with excessive optimism. The Generation 100 study [69] compared two times weekly high-intensity interval or continuous moderate-intensity aerobic training against following national guidelines for older adults (five times daily 30 minutes of moderate activity per week). Only Fractal Dimension (FD), a measure of brain complexity, correlated positively with CRF but not with exercise type [70]. Other studies within the Generation 100 framework also all failed to link cognition and brain health to 5-year aerobic exercise, including white matter (WMH, microstructure) and gray matter (CT, brain volume), when compared against control groups following national guidelines [70-73]. One of them, Pani et al. (2021) [72], observed that adherence to daily moderate activity guidelines yielded the lowest hippocampal and thalamic atrophy rates compared with bi-weekly aerobic training. This suggests that following daily moderate activity recommendations more effectively preserves brain health in older adults than specific aerobic exercise regimens.

3.4 Physical non-aerobic interventions

Non-aerobic training is highly suited for fragile elderly individuals, yet this type of intervention has been the focus of very little evaluation research. On the plus side, one study demonstrated that 12 months of resistance training twice a week positively impacted brain function and cognition in older women [74], whereas training only once a week produced no significant results. In another study, six weeks of intensive slack-line training[3] [75] increased striatal network efficiency associated with improved balance.

On the negative side, in a follow-up study, strength training [76] was found not to protect against GM atrophy three years after intervention completion. Initial chair stand performance[4] at baseline predicted of GM volume than the subsequent high- or moderate-intensity strength training. However, these results gathered three years post-training were likely affected by a wash-out bias.

In contrast, the results of a meta-analysis by Ludyga et al. (2020) [77] support the notion that non-aerobic exercise can be a promising intervention strategy over the lifespan, potentially outperforming purely aerobic interventions. These authors concluded that the effect of exercise on cognition was small but uniform across cognitive domains. Coordination exercises yielded the highest benefits. Nevertheless, coordinative exercise inherently contains a cognitive component (cf. music practice, juggling, handicraft; see Supplementary Table 6).

Voelcker-Rehage et al. (2011) [67], comparing aerobic training to non-aerobic coordination training, found improved executive function (flanker test) in both groups, suggesting that coordination training may also impact higher-order cognitive functions.

In their systematic review and meta-analysis, Hortobagyi et al. (2015) [78] also concluded that exercise intensity played only a minor role among elderly persons. They further demonstrated that when participants were free to choose their training, whether it was resistance, coordination, or multimodal training with an aerobic component, all had an equally beneficial effect on gait speed.

3.5 Combined cognitive and physical aerobic interventions

Compared to multimodal fitness training, adaptive dancing [79-81] over six to 18 months exerted a more substantial effect on the volume of the left precentral gyrus after six months, and on the (para)hippocampal brain volume after 18 months. Dancing did not have a stronger effect on cognitive behavior, however. Both interventions improved verbal memory but without a link to neuroplasticity. The results produced by dancing were attributed to the combination of physical, cognitive, and social

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[3] Slackline training involves balance-centric exercises performed on a taut line

[4] A person's to rise from a seated position to a standing position without the use of their arms for assistance

engagement and music listening, which require accurate temporo-spatial organization of complex movement patterns under motivating conditions. Burzynska et al. (2017) [82] observed increased fractional anisotropy (FA; see **Appendix 2**) in the fornix after six months of an adaptive dance intervention compared with brisk walking. The fornix is involved in episodic memory function [83]. Adaptive dancing thus afforded added value over aerobic exercise, as it also solicits cognitive and emotional domains, aside from body coordination. However, the cognitive benefits of adaptive dancing were not found to be associated with the fornix WM increase.

In their meta-analysis on the effects of dance interventions on HE, Hewston et al. (2021) [84] concluded that dancing likely improved global cognitive function but not complex attention or memory and learning. They added, however, that dancing did not affect cognitive function more than walking did. In other words, simply walking regularly according to national exercise guidelines remained an equivalent alternative.

A three-month challenging intervention, which combined simultaneous computerized working memory and aerobic training, as reported by Takeuchi et al. (2020) [65], resulted in increased brain activity in regions associated with attentional reorientation and correlated with better 2-back accuracy (during fMRI) and improved EF (out-of-scanner), illustrating far-reaching benefits relevant to activities of daily living (ADL).

Two studies compared a cognitive intervention group to an aerobic intervention group. The first study by Chapman et al. (2017) [20] conducted a comparison between a three-month program of moderately intensive Strategic Memory Advanced Reasoning Training (SMART) and an equivalent duration of aerobic training. Post-intervention, the most notable result for the SMART group was improved innovation performance associated positively with FC in the CEN and negatively with FC in the DMN. Innovation performance may support ADL. The lack of cognitive benefits from aerobic training can be explained by the targeted reasoning training and the evaluation's exclusive focus on innovation performance (higher-order cognition). The second study by Gu et al. (2021) [85] compared moderate intensive multi-domain cognitive training for 12 weeks against aerobic training by way of a delayed measurement 12 months post-intervention. Both cognitive training and aerobic exercise modified FC of the entorhinal cortex (EC), known to play a central role in age-related cognitive decline, associated with improved general cognitive functioning (measured with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; see Table 3). However, these improvements occurred via distinct neural pathways, indicating different underlying neural mechanisms. That these benefits persisted 12 months post-training is remarkable (see section 3.9).

3.6 Combined cognitive and non-aerobic physical interventions

Combined cognitive and non-aerobic physical interventions were the ones with the strongest cognitive and cerebral plasticity benefits.

Moderately intensive multi-domain cognitive training over three months combined with handcrafting and stretching [59, 60, 86, 87] resulted in increased FC in the CEN that correlated with improved RBANS performance (general cognitive functioning). Moreover, positive WM plasticity (see Appendix 2) co-occurred with improved scores on the Chinese version of the Mini Mental State Examination (CMMSE). Additionally, improved lateralization effects (activations more similar to younger adults) in two frontoparietal networks were observed post-training. In other words, this combination of multi-modal cognitive and non-aerobic sensorimotor training mitigated aging-related dysfunction of higher-order cognitive networks. Frontoparietal networks help coordinate behavior swiftly, correctly, flexibly, and in a goal-driven manner [88]. ADL relies on these networks. That these positive WM and FC plasticity effects persisted 12 months after completion of this combined multi-domain and sensorimotor intervention is also remarkable.

Four months of musical practice in large groups of musically inexperienced HE [38] improved different memory functions, including working memory, and this improvement was associated with reduced FC in the L putamen and R STG. Working memory is a basic building block of cognition and deteriorates considerably in normal aging. An explanation for these salient results may lie in the intensity of the training: weekly one-hour interventions plus daily homework. Another possible explanation is ensemble playing, which requires continuous memory updating [89]. That this would transfer to ADL seems obvious.

James et al. (2020) [8] conducted a series of analyses to investigate the effects of one year of music education on initially music-naïve elderly individuals, comparing two groups: piano practice and active music listening. The outcomes demonstrated improvements in tasks crucial for ADL, such as working memory, verbal long-term memory, speech in noise perception, and fine hand motor dexterity associated with structural brain plasticity (GM and WM). WM integrity of the fornix correlated positively with increased verbal long-term memory scores across both experimental groups [90], which made for richer results than those obtained with adaptive dancing [82]. Overall, piano practice produced more substantial benefits than musical listening. In various analyses, the benefits in the piano group took the form of WM and GM stabilization [90-93]. In contrast, the listening group showed significant WM and GM decrease over as little as six months. These findings suggest that music education's impact on older adults may extend to ADL, with piano playing being more effective than active musical listening (see section 6 for more details).

The research referenced in [58-60, 87, 94] has already acknowledged that multimodal interventions integrating complex cognitive and non-aerobic sensorimotor aspects are strong drivers of cognitive development. Music-making [38, 90, 92] is another such intervention that additionally triggers a cascade of neurochemical effects linked to motivation, pleasure, and reward [95, 96], which may reinforce learning.

In a study comparing highly intensive, challenging real-life adaptive digital interventions lasting five weeks against low challenging non-adaptive ones of similar duration [39], the former produced widely distributed increased brain activations that correlated with verbal fluency. Certain BOLD increases persisted one-year post-intervention.

Studies comparing three months of intensive TCC against Baduanjin (BDJ) [97, 98], two distinct body-mind practices, showed that both interventions may counteract age-related memory decline by improving DMN network connectivity. FC increase between bilateral Hc and mPFC correlated positively with a memory quotient in all individuals. However, the FC increase was significant only for the TCC group, suggesting that this practice has a greater impact on functional brain plasticity than BDJ (see section 6 for more details).

In two studies by Li et al. (2014) and Zheng et al. (2015) [58, 94], a six-week highly intensive intervention combining TCC training, Method of Loci word list learning, and EF training was compared against a passive control condition. The intervention enhanced functional connectivity between the mPFC (part of DMN) and the medial temporal lobe, which correlated positively with EF performance. Normal aging reduces DMN connectivity and is a biomarker of age-related cognitive decline, distinct from Alzheimer's changes [99]. Additionally, increased local resting-state activity in the left superior and right middle temporal gyrus predicted verbal category fluency and associative learning. Finally, the intervention group scored higher on paired associative learning, experiencing social support, and physical vitality post-training, all of which may impact ADL.

Four months of virtual navigation training while walking on a treadmill reduced CT thinning, whereas treadmill walking alone showed the opposite [100, 101]. After a four-month delay, however, the group difference faded. Spatial navigation performance in the experimental group improved post-training and was maintained after the four-month delay, whereas the control group showed a progressive decline in this regard.

Naito et al. (2021) [102] demonstrated that complex bimanual exercises trained the interhemispheric inhibitory system and thus improved deteriorated hand/finger dexterity, which training the dominant hand only did not do.

West et al. (2017) showed that six months of intensive Super Mario video gaming, compared with computerized piano training [51], increased GM in bilateral hippocampi correlated with improved short-term memory, and also increased GM in the L cerebellum. The piano training group showed increased GM in the right dlPFC and cerebellum, but with no link to behavioral changes. In a passive control group, GM decrease did occur in those areas.

An eight-week meditation intervention improved self-referential emotional control by enhancing the pons' regulation of the posterior cingulate cortex (PCgC)/precuneus [103]. This improved regulation was associated with less extreme ratings of positive and negative pictures, identifying meditation as a potential alternative treatment for elderly individuals with affective disorders [103].

3.7 Efficacy of different NPI on neurobehavioral plasticity

Combined cognitive and physical non-aerobic interventions appear to induce the strongest and most long-lasting combined cognitive and cerebral benefits, compared with all other types of NPI. The series of studies by X. and W. Cao, Deng, Luo and colleagues [59, 60, 86, 87] on non-computerized multi-domain cognitive interventions combined with non-aerobic physical activities lasting only three months produced some of the most striking results showing changes in structural and functional connectivity associated to a general measure of cognition. The adaptive capacity model (ACM) [104] could explain those results, as it postulates that lifestyle changes combining the benefits of moderate physical exercise with novel cognitive challenges may have a greater neuroplasticity impact and, therefore, provide stronger neuroprotection against age-related decline. This notion will be developed further in section 4.

Our findings align with a 2022 systematic review by Rieker et al. (2022) [105], which underscored the effectiveness of combined cognitive and physical interventions in enhancing health and cognitive performance, with no neuroimaging involved. This dual approach outperforms singular interventions, especially in improving executive functions and balance. Notably, simultaneous cognitive and physical exercises, like interactive exergames and square stepping, lead to the most significant improvements in executive functions, speed, and global cognition. In the context of combined training, aerobic training was particularly beneficial for attention and fitness, while non-aerobic training had larger effects on global cognition and balance.

Where aerobic interventions are concerned, the five-year study by Pani et al. (2021) [72], part of the Generation 100 studies [69, 106] , stands out and provides food for thought. What proved to protect best against GM brain atrophy was not high-intensity aerobic interval training twice weekly or sustained aerobic exercise twice weekly for 50 minutes but a minimum of one-half hour of moderate physical activity daily as per the Norwegian physical activity guidelines for seniors. This regimen protected best against hippocampal and thalamic atrophy, known to occur in normal aging, particularly in Alzheimer patients. Hippocampal function impacts memory function, while the thalamus influences attention and inhibition of irrelevant sensory input [107]. The high-intensity aerobic training in the Generation 100 study might have been perceived as stressful by the older adults, which could have hindered neuroplastic adaptation [108]. Alternatively, the higher frequency of daily moderate exercise recommended by the Norwegian physical activity guidelines may outweigh the benefits of more strenuous twice-weekly aerobic routines in HE.

Notwithstanding, in other studies on HE, aerobic training was found to primarily impact brain plasticity in frontal areas, while also affecting parietal regions and the hippocampus [61-63, 66, 67, 109], reflected in improved EF [109], general cognition [63] verbal fluency [66], and spatial navigation [62].

Natural training procedures based not on laboratory experiments but on real-life activities, such as musical practice [38, 90-93, 110], dancing [79-82], juggling [111], learning a new language [53], participating in social service programs [37], and body-mind approaches like TCC and BDJ [58, 94, 97, 98], seem best suited to induce generalized learning in HE because they are complex, variable and highly motivating if they correspond to the individual's preferences [9, 112]. Real-life training seems the better bet for ensuring the lasting benefits of interventions. This is due to its potential for frequent and prolonged practice, its feasibility and accessibility (as it can be conducted at home), and the support it garners from self-motivation and enjoyment. To maintain persistence in HE, it's crucial to integrate these activities into daily living activities (ADL) over the long term, and to tailor the intervention to individual preferences.

Those real-life approaches are generally adaptive. They can grow increasingly complex as a function of progress made by the individual. Adaptive interventions, whether cognitive and/or physical and whether computerized or not, produced the widest range of results [7, 35, 36, 47, 48, 66, 74, 79, 81, 82, 90-93, 110]. In the context of the diverse states of health among older adults, these findings highlight the impact of personalized adaptive learning.

For HE, learning *novel* skills, particularly if they comprise a digital dimension, like robot assistance, responding on a smart pad, or navigating a virtual environment, appears to be particularly stimulating [56, 100, 101].

This observation is plausible in that learning a new skill engages neural plasticity more strongly [19]. The benefits of intense new-skill acquisition for memory function in older individuals have been documented [113].

Three months of cognitive interventions involving intelligence technology (IT, e.g., computerized or robot-assisted training) suffice to provoke GM changes [56, 57] associated with cognitive changes (EF, general cognition). In contrast, aerobic training requires at least six months of exercise to provoke GM plasticity [61, 62].

In her narrative review, Netz [68] argues that "physical training" (aerobic and strength) impacts cognition through cardiovascular fitness improvement, whereas "motor training" (balance, coordination, and flexibility) affects cognition directly. This hypothesis is plausible but needs to be supported by studies combining ASL, cardiovascular fitness, and diverse cognitive measures.

In their systematic review and meta-analysis, Ludyga et al. (2020) [77] also argued that more substantial benefits of exercise for cognitive function were found after coordinative exercise compared to other types of physical exercise.

Supported by the assumptions of these two recent reviews and based on our analysis of the 70 articles we reviewed, we conclude that multi-domain cognitive interventions combined with non-aerobic physical training [39, 58-60, 86, 87, 94, 97, 98], even if only for three months or six weeks, seem most effective at inducing wide-ranging, sustainable brain and behavioral changes in HE relevant to ADL.

Aerobic training is also effective, as it induces frontal brain changes in particular. Still, it has a more limited effect on cognitive behavior and takes longer—at least six months of exercise—to bring about GM plasticity [61, 62].

Nonetheless, daily moderate nonaerobic physical activity showed stronger brain plasticity effects than twice-weekly strenuous aerobic exercise, as shown in the Generation 100 study [70-73].

Figure 1 depicts the relative impact of the six NPIs on ADL. Each NPI type is represented by a circle, with the circle's size indicating the general influence of the NPI on brain and behavioral changes. The degree of overlap between each circle and the ADL domain illustrates the extent of significant transfer effects from the intervention to ADL enhancement.

INSERT FIGURE 1 HEREABOUTS

3.8 Influence of duration and intensity of interventions

Intensive and moderately intensive interventions that combined cognitive and non-aerobic physical exercises seemed to afford the strongest benefits for behavioral and brain plasticity in HE, and a majority of the NPI in this class transferred to ADL.

In single-domain interventions of relatively short duration, the nature of the training seems to be a determining factor for far transfer to occur. Those that were adaptive, challenging, motivating and intensive provoked the strongest behavioral and brain changes (see **section 3.1**).

Compared with single-domain cognitive interventions, moderately intensive and highly intensive multi-domain cognitive interventions of intermediate and long duration (three and six months) exerted a broader effect on behavioral plasticity. What’s more, all of these without exception provoked a far transfer to ADL.

For many aerobic interventions, the effect of duration trumped that of intensity (see **section 3.3**). This was not the case in the Pani et al. study (2021) [72], where moderate physical exercise on a daily basis over five years (i.e., very intensive in the sense of more sessions per time unit) induced more benefits (i.e., less brain atrophy) than did twice-weekly strenuous aerobic training over the same period.

In the context of non-aerobic interventions, the intensity of training, for instance for resistance training [74], determined the outcome success. In the same vein, the Intensity of piano practice at home correlated with increased fiber density (WM microstructure) in the body of the fornix [90]. Only five weeks of highly intensive, challenging, real-life, adaptive digital interventions in the McDonough et al. (2015) study, yielded widely distributed increased brain activations that partially persisted after a one-year delay.

3.9 Delayed measures

Delayed measures after pausing or stopping intervention studies were relatively rare. When used, however, they often showed brain plasticity stabilizing or returning to baseline. After three or four months of cognitive training, physical training, or a combination of these, CT, mean diffusivity (MD; a diffusion tensor imaging (DTI) measure; see **Appendix 2)**, GM and FC benefits faded after a delay as long as the duration of the training [100, 101, 111]. De Lange et al. (2018) [50] observed intermittent dynamic diffusivity benefits when training for 10 weeks alternated with resting for 10 weeks, underlining that short-term training tends to result in transient WM brain plasticity. Behavioral benefits were moderately preserved after the delay [50, 100, 101], demonstrating that, unlike WM microstructure (WMM) and CT, they do not require continuous training to persist.

One of the most effective interventions described in this scoping review was an intensive three-month multi-domain intervention combining non-computerized cognitive, handicraft, and other non-aerobic physical activities [59, 60, 86, 87]. The researchers who conducted the evaluation demonstrated associated higher-order cognitive and cerebral plasticity benefits (WM and functional plasticity) one full year after training completion. These results included restored lateralization effects on frontoparietal networks, essential for effective goal-driven coordination [88]. Their results suggest that functional network plasticity appears relatively early during learning and is persistent. Their subsequent use in ADL may have contributed to their maintenance.

These results stand in contrast with the findings of Wenger and Lovden (2012) [100, 101], who studied combined moderately intensive physical, non-aerobic, and cognitive training over three months. They observed positive post-training brain plasticity effects (CT, WM) that waned four months after training completion. An explanation for this discrepancy is that X. and W. Cao, Deng, and Luo [59, 60, 86, 87] provided their participants with a diverse range of cognitive exercises, whereas Lovden and Wenger exclusively focused on spatial navigation training. Notably, the improvement in spatial navigation skills persisted partially after the four-month delay [100, 101], underscoring that certain cognitive benefits can endure without continuous training.

In the study by McDonough et al. (2015) ([39] investigating the impact of challenging digital real-life adaptive interventions, fMRI showed that approximately two-thirds of the participants maintained BOLD increases one year after training completion.

Gu et al. (2021) [85] compared 12 weeks of moderately intensive multi-domain cognitive training against aerobic training in terms of their effects on FC of the entorhinal cortex (EC-FC) 12 months after completion. Both interventions showed long-term effects on neural plasticity, correlated with improved RBANS scores (see Table 3). These data support the idea that both cognitive training and aerobic exercise can have a lasting effect on EC-FC in aging people, though via separate brain pathways. These long-term effects one year after only 12 weeks of moderately intensive multi-domain training versus aerobic training are remarkable. Like the 12-month delayed results obtained by Cao and colleagues [59, 60, 86, 87], those by Gu et al. (2021) also suggest that functional network plasticity appears relatively early during learning and is persistent. Again, their subsequent use in ADL may have contributed to their maintenance.

But delayed measures have limits: after a delay of three years, initial one-year strength training failed to guard against GM atrophy. Baseline chair stand metrics were better GM volume predictors than subsequent training intensity [76]. Notably, a washout period bias likely compromises these results.

3.10 Relationship between post-intervention behavioral changes and ADL

The end purpose of NPI for countervailing age-related degeneration of cognitive, sensorimotor and cerebral functions in the elderly is transfer to ADL for better mental and physical health and greater autonomy and well-being. The numerous interventions covered in this scoping review induced a wide range of benefits linked to ADL.

ADL-related benefits observed in the reviewed intervention studies encompass a wide range of improvements, including enhanced cardiovascular function [40, 61, 62, 66, 109, 114], hand-eye and bi-manual motor coordination [90, 93, 102, 111], [visual attention (e.g., driving) [48, 49], overall cognitive abilities such as global cognition [53, 58, 59, 87], complex reasoning, problem-solving, innovation performance, executive function, associative learning, and verbal fluency [7, 20, 37, 39, 54, 58, 66, 94]. Additionally, these interventions have positively affected various memory functions, including short-term and working memory, spatial memory, logical memory, and verbal (long-term) memory [38, 62, 90, 91, 97, 98]. They also contribute to improvements in speech perception in noisy environments [92, 115] and foster a more positive mindset [103].

Results of multi-domain cognitive interventions involving collaboration and interaction of different mental processes, particularly when combined with physical activity, seem most valuable in the real world and induced the greatest ADL benefits in HE. Such combinations of cognitive and physical stimulation can often be found in real-life or "lifestyle" interventions involving activities like dancing, music making, digital photography, juggling, and TCC [39, 90-93, 97, 111, 115], which may explain their facilitated transfer to ADL, such as (working) memory, speech in noise perception, verbal long-term memory, verbal fluency, and bimanual dexterity.

3.11 Post-intervention brain plasticity

3.11.1 Order of appearance of brain changes following NPI

Different plasticity manifestations represent distinct but connected mechanisms of progressive brain changes.

Cerebral metabolism (cerebral blood flow or CBF, brain-derived neurotrophic factor or BDNF, choline concentrations), FC and perfusion changes appear sooner following training onset [40, 42, 64, 79, 116] than structural brain changes do, which makes them a more sensitive indicator of early learning-induced plasticity compared with volumetric GM measures that require longer training times to express. In Matura et al. (2017) [64], three months of low-intensity aerobic cycling stabilized choline concentrations but provoked no change in gray matter, cognitive performance, or VO_2max. In Mozolic et al. (2010) [42], though no GM changes occurred after a two-month monotonous attention intervention, marginal CBF increase was disclosed post-training in the R IFC. In Muller et al. (2017) [79] BDNF plasma levels increased at six months after baseline (T1) following an adaptive dancing intervention, but returned to baseline at 18 months after baseline (T2), whereas increased GM at T1 remained stable at T2. In Greeley et al. (2021) [116], twice-weekly spinning on a stationary recumbent bicycle for only two and a half weeks provoked spatially distributed FC increases between networks.

In Lampit et al. (2015) [57], a computerized multi-domain intervention led to a decrease in DMN FC from baseline after only three weeks of training, but this functional change returned to baseline after three months. Still, these early DMN FC changes at three weeks correlated with a global cognition improvement after three months. Finally, GM changes increased gradually over time between three weeks and three months after training onset.

Also, cerebral metabolism changes often co-occurred with structural or functional brain changes. For instance, Erickson et al. (2011) [62] found a volume increase in the bilateral anterior Hc to be associated with increased BDNF serum levels as measured by blood-sampling, and with spatial memory enhancement in HE after 12 months of aerobic training. In Chapman et al. (2017) [20], increased CBF as measured by ASL accompanied FC decrease in the DMN and was positively correlated with innovation performance after SMART training. Evaluating a gist reasoning intervention, Chapman et al. (2015) [54] observed that improved strategic reasoning and EF performance correlated positively with simultaneously increased FC and CBF in DMN and CEN post-training.

Numerous experiments using DTI in combination with cognitive training, regardless of cognitive domain, revealed changes in DTI diffusivity measures that ran counter to those identified in normal aging (see Appendix 2 and [117]) [46, 50, 54, 59, 101]. The diffusivity changes followed the onset of the interventions closely over time [50] and persisted up to one year post-training [59]. Many DTI changes occurred soon after training onset, after 6 to 10 weeks [7, 46, 50].

The total duration of aerobic training interventions appears to impact GM brain structure more strongly than the frequency (number of training sessions per week). In studies where HE trained aerobically for six or twelve months, varying in frequency from three times 30 minutes to three hours per week, results revealed GM increase in prefrontal, temporal, and hippocampal areas [61, 62], which are prone to lose volume gradually after midlife [3, 4]. In contrast, even with three hours of training per week, no GM volume increase was noted following the completion of three-month interventions [64, 65]. Similarly, [63] found that six months of 30-60 minutes of weekly training did not result in whole-brain CT differences between the EG and CG.

These time-related observations speak to the importance of taking measurements at multiple time points across the duration of interventions and after their completion, to better understand underlying step-wise mechanisms.

3.11.2 Most frequently involved brain areas in brain plasticity following NPI

3.11.2.1 Gray matter plasticity

The onset of GM brain deterioration occurs earlier in life than WM atrophy [26]. The PFC and the Hc are the areas of the brain most prone to age-related GM deterioration [3-5]. Working memory, a fundamental component of general cognition that supports more complicated tasks such as executive control, relies heavily on connections between the PFC and the Hc [6].

Most short-time single-domain cognitive interventions did not result in plasticity of GM volume or density. (see **section 3.1**). Still, in one study [45], HE showed an increase in CT in the **R insula** after two months of word list learning (Method of Loci). In that study, an additional increase in CT in the **R fusiform cortex and R lateral orbitofrontal cortex (OFC)** was directly related to improved verbal memory (near transfer, see Appendix 1). In another study [44], increased CT in the **R inferior frontal gyrus IFG** correlated with response inhibition after a two-month adaptive inhibition game intervention [44]. The highly stimulating nature of these two specific short-time interventions may explain this (see **section 3.1**).

A three-month multi-domain computerized cognitive intervention induced GM density and CT increase in **the R post-central gyrus** associated with improvement of global cognition [57] and three months of robot-assisted multi-domain cognitive training [56] resulted in less CT thinning in **bilateral anterior cingulate cortex (ACC)**. Additional CT changes in **L temporo-parietal junction and L inferior temporal gyrus (ITG)** correlated with EF scores. These two studies [56, 57], therefore, have revealed far transfer (see Appendix 1). Only four weeks of multi-domain adaptive combined auditory-cognitive training increased regional GM volume in **R dlPFC, ITG, L superior frontal gyrus, L OFC, and R cerebellum (CB)** (lobule 7 Crus 1); for sole auditory training, GM increased in the **L temporal pole** [118].

Aerobic interventions increased GM in **ACC, supplementary motor area (SMA), R IFG and superior temporal lobe** [61] and in **bilateral anterior Hc** [62]. This last improvement correlated with improved spatial memory function.

Concerning aerobic interventions, six to 12-month training increased GM in **ACC, SMA, R IFG, and the superior temporal lobe** [61], **and in the bilateral anterior Hc** [62]. This last GM increase correlated with improved spatial memory function. In contrast, within the sub-studies of Generation 100, only Fractal Dimension (FD, see section 6) in the temporal lobe showed a positive correlation with cardiorespiratory fitness (CRF), and this correlation was not associated with any particular training group [70].

Regarding combined cognitive and physical aerobic interventions, after six months, adaptive dancing increased GM in the **L precentral gyrus** [79], and California Verbal Learning Test (CVLT) scores improved but were unrelated to brain changes. After 18 months, GM in the **R Hc** augmented [80]. After six months only, widely distributed GM increase occurred in frontal and temporal areas (**ACC, medial cingulate cortex, L insula, L STG, SMA, L pre- and post-central gyrus**) [81]. In both of the Rehfeld studies, no coinciding cognitive results were observed.

Combined cognitive and physical non-aerobic interventions produced various effects. Three months of juggling training resulted in transient GM increase in **hMT/V5, L frontal and cingulate cortices, R precentral gyrus, and bilateral Hc and nuclei accumbens** [111]. Four months of computerized navigational training combined with walking [101] stabilized **bilateral Hc volume** and improved navigation performance. It also provoked less CT decrease in the **R middle frontal gyrus (MFG)** [100]. Six months of playing Super Mario increased **bilateral Hc** GM volume, which correlated with improved short-term memory, and **L Cb** volume [51]. Learning to play the piano over six months increased CT and GM volume in **bilateral Heschl's gyrus, bilateral superior temporal sulcus, L planum temporale, and bilateral inferior Cb (Lobules VIII & IX)** [91, 92].

GM areas most impacted by NPI comprising cognitive training are the **Hc, the ACC, pre- and post-central gyrus, prefrontal areas, and inferior and posterior Cb** (considered the “cognitive part” of the Cb [119]).

Pure aerobic interventions most strongly affected frontal areas (**ACC, prefrontal areas, SMA) and the Hc.**

3.11.2.2 White matter plasticity

In a study by de Lange et al. (2018), short single-domain cognitive interventions using word list learning (Method of Loci), alternating training and rest were found to induce a general **increase in fractional anisotropy (FA) and a decrease in radial diffusivity (RD) and axial diffusivity (AD).** There was also a **mean diffusivity (MD) decrease in the inferior longitudinal fasciculus (ILF) and hippocampal cingulum bundle (HcCB)** [50] **(**see Appendix 2 for an interpretation of WM measures**).** The WM brain changes closely followed the training periods, whereas verbal learning increased steadily, also across the intermittent rest periods. Also using the Method of Loci, Engvig et al. (2012) [46] found an **FA increase in the left anterior thalamic radiation** paired with **stabilized RD**. The FA increase correlated with improved memory scores. Six-week computerized cognitive gaming interventions using three different games by Strenziok et al. (2014) [7] exhibited **increased AD in the L lingual gyrus and the R thalamus**, evidencing a group main effect. **Thalamic AD increase** correlated with working memory performance. Tract Based Spatial Statistics (TBSS) results for one game indicated that the **AD increase in the temporo-occipital junction** correlated with the time needed to complete the Everyday Problems Test.

Chapman et al. (2015) [54] found that non-computerized gist reasoning training over three months induced a **gradual FA increase in the L unicate fasciculus** that co-occurred with improved strategic reasoning and EF performance. Colcombe et al. (2006) [61] observed that 12 months of aerobic walking **increased WM in the anterior corpus callosum**, but they did not report behavioral results. In contrast, in the context of the Generation 100 study, in the sub-study by Arild et al. (2022) [73], twice weekly aerobic training did not offer advantages in slowing the progression of white matter hyperintensities (WMH), a sign of brain aging [120], compared to adhering to national physical activity guidelines, i.e. 30 minutes of moderate exercise five days per week. Burzynska et al. (2017) [82] reported that six months of adaptive aerobic dancing provoked an **FA increase in the fornix** unrelated to behavior. Finally, in Junemann et al. (2022) [90], **microstructure in the body of the fornix** stayed more stable after six months of piano practice, directly associated with training intensity and verbal memory. The fornix connects the two hippocampi and plays a role in episodic memory functions [83]. It is a biomarker of aging.

WM changes following different NPI preponderantly occurred in **white matter tracts within frontal areas, the thalamus, and the fornix** (medial part of the brain).

3.11.2.3 Functional plasticity

fMRI

Following short-term single-domain cognitive NPI, BOLD changes most often appeared in the **PFC, specifically the dorsolateral PFC (dlPFC) and the ventrolateral PFC (vlPFC), as well as the ACC** [35, 36, 47-49, 52]. These brain areas are part of the working memory network and are also implicated in higher-order cognitive functions (e.g,. EF). Thus, frontal regions were most affected. An intensive social intervention over six months also reported increased BOLD responses in the **L dlPFC, L vlPFC, and ACC** during a flanker task [37], a clear example of far transfer.

In the context of learning-induced functional plasticity, BOLD decreases may indicate increased efficiency in performing a well-trained task, whereas BOLD increases may indicate increased resources to perform a task earlier in the learning process.

After long-term aerobic training, BOLD activation increased in the **middle and medial frontal gyrus and ACC** —attentional control areas— during an untrained flanker task (only measured pre- and post-intervention) [109].

In another long-term study involving the aerobic training [67], decreased BOLD activation was shown in widely distributed areas (**L superior frontal gyrus (SFG), L MFG and bilateral medial frontal gyrus, L ACC, L para-Hc gyrus and R STG and R MTG**) during an fMRI flanker task. However, the test was also performed at midterm, potentially causing a learning effect. The authors argued that the task-related BOLD activation decrease following aerobic training might have reflected increased neural efficiency driven primarily by an increase in VO_2 max. This seems a plausible explanation given the widely distributed regions that were affected.

After a one-year non-aerobic resistance intervention [74], HE demonstrated increased BOLD activation in the **L AI (Left anterior Insula)** during a flanker test, which co-occurred with interference reduction, an indicator of improved inhibition. Again, the task was not trained. AI activation may indicate task difficulty and uncertainty [121].

After a three-month intervention combining spinning on an ergocycle with computerized working memory training, Takeuchi et al. (2020) [65] observed increased BOLD activation in **R TPJ and R STG**, two attentional reorientation areas. Post-training BOLD increase correlated with improved two-back working memory performance during fMRI, and improved EF performance outside the MRI scanner. In a study where music-naïve HE received four months of musical practice in large groups, Guo et al. (2021) [38] observed decreased BOLD activation in **R SMA, L precuneus, and bilateral PCgG** during the fMRI one-back task (indicating decreased FC with the DMN), however, without improvement in working memory performance.

Investigating the impact of challenging digital adaptive interventions, McDonough et al. (2015) [39] observed **widely distributed increased BOLD activation** in fMRI both post-training and one year after training completion when participants performed a difficult task condition correlated with verbal fluency.

Finally, Naito et al. (2021) [102] found that short-term complex bi-manual dexterity training for HE provoked reduced BOLD activation in **ipsilateral motor-cortical activity** correlated with improved dexterity, which likely reflected increased efficiency in fine hand/finger movements.

RS-fMRI

NPI had a strong impact on FC within and between networks. FC change was evoked quickly, as early as two and a half weeks into an intervention and maintained for up to 12 months after training completion [60, 87, 116]. The network that has been implicated most frequently following NPI was the DMN, followed by the CEN. All types of NPI yielded changes in these networks, but most frequently the combined cognitive and physical non-aerobic interventions.

Two short-term interventions were found to induce FC changes. In Ross et al. (2019) computerized adaptive Useful Field of View training provoked increased FC in **AI-ACC, AI-visual cortex, AI-SMA and dlPFC-SMA** [48]. In Strenziok et al. (2014) three distinct gaming interventions [7] demonstrated that the **dorsal attention network** was implicated in complex cognitive training, and two of the three games could show that this network mediated far transfer effects [7] (see section 6).

Four months of second-language learning proposed by Bubbico et al. (2019) [53] provoked increased **FC of the DMN with the R IFG, R SFG, and L SPL**, associated with improved Mini-Mental State Examination (MMSE) scores. Three months of gist reasoning training **increased FC and CBF in the DMN and the CEN** in Chapman et al. (2015). Both the DMN and the CEN (major nodes dlPFC and PPC respectively) likely support executive processes as observed in the Bubbico and Chapman studies, involved in second-language learning and fluid intelligence [53, 122].

Five times weekly multi-domain adaptive cognitive training over 12 weeks in a study by Hardcastle et al. (2022) led to enhanced FC in a frontoparietal control network, akin to the CEN [55]. This increase was correlated with better performance on the Double Decision task, which assesses divided attention and processing speed.

After only two and a half weeks of spinning on a recumbent bicycle, participants in the Greeley et al. study (2021) [116] showed increased FC between brain regions that link the **limbic system and the cerebellum.** Twelve months of aerobic training [123] **increased FC within the DMN and in a frontal executive network (FEN).** The increase correlated with improved EF.

After six weeks of slackline training [75], only participants who improved their balance showed increased **striatal network** efficiency (decreased FC between the striatum and widely distributed frontal and parietal brain areas).

In a study by Chapman et al. (2015) [54], three months of gist reasoning training **increased FC in DMN and CEN** in correlation with improved reasoning and EF. In a similar study on SMART training by Chapman et al. (2017) [20], innovation performance positively correlated with **FC in the CEN,** and negatively with **FC in the DMN.**

Gu et al. (2021) [85] showed that **FC between the entorhinal cortex (EC-FC) and other brain areas** changed in opposite ways for aerobic and multi-domain cognitive training 12 months after training completion. EC-FC with R Hc decreased in the case of cognitive training (increased efficiency) but EC-FC increased with the left angular gyrus in the case of aerobic training. Both FC changes were linked to positive cognitive outcomes. The entorhinal cortex, situated within the medial temporal cortex, is very sensitive to aging and serves as a hub for time-related and memory processing.

In studies that combined multi-domain cognitive training with handcrafting and stretching and measured their effects after a 12-month delay, W. Cao et al. (2016) [87] showed **increased FC within the DMN, the salience network (SN), and the CEN** (see Appendix 2) and a correlation between the FC increase in the CEN and RBANS scores. Based on the same experimental plan, Luo et al. (2016) [60] found that **R and** L frontoparietal networks showed better-conserved lateralization effects.

Guo et al. (2021) [38] observed that four months of musical practice induced **decreased FC between R PCgG (DMN seed) and L MTG and between L putamen (seed) and R STG**. They also showed that improved memory performance (DSF-DSB and logical memory) correlated with reduced FC between the L putamen and R STG.

Evaluating an intervention combining multi-domain cognitive training with TCC over six weeks, Li et al. (2014) [58] demonstrated **strengthened FC between the DMN and the medial temporal lobe**, which correlated with Trail Making Test (TMT) scores. In another sub-study of the intervention, Zheng et al. (2015) [94] observed **increased regional homogeneity (ReHo)** maps (see Supplementary Table 6) in **L STG and L posterior Cb and decreased ReHo maps in L MTG**. ReHo of local spontaneous resting-state activity **in L STG and R MTG** predicted cognitive performance improvements for verbal fluency and associative learning. In short, this NPI **enhanced the intrinsic functional brain architecture in the temporal cortex and Cb.**

In a study of a two-month meditation training intervention, Shao et al. (2016) [103] found that **increased FC between the PCgC/precuneus (DMN) and the pons** predicted positive changes in affective processing.

Studies comparing three months of TCC and BDJ [97, 98] showed **increased FC between the DMN and R temporal gyrus** for TCC and **decreased FC between the DMN and the R orbital prefrontal gyrus and the putamen** for BDJ. Both groups improved their memory scores. **Increased FC between bilateral Hc and mPFC** correlated positively with the memory quotient only in TCC, suggesting that this activity has a more substantial effect on functional brain plasticity than BDJ.

3.12 Sex

The studies included in this scoping review did not provide sufficient evidence to draw valid conclusions about how sex may affect intervention outcomes.

4. CONCLUSION

Kolb and Gibb (2014) [10] wrote: "Virtually every experience has the capacity to alter the brain and behavior, at least briefly" (p. 256). However, what we are looking for is sustainable change derived from engaging in NPI in different settings, including at home and in eldercare facilities, and for these interventions to be attractive and pleasant enough to be maintained over the long term.

These non-pharmacological interventions (NPIs) for (relatively) healthy older adults should meet three critical criteria: 1) They must be backed by robust scientific evidence demonstrating their effectiveness in mitigating age-related cognitive decline. 2) They should align with the unique requirements, choices, and physical and mental states of the intended recipients. 3) They should be available to all older adults, irrespective of their financial circumstances.

As described above, learning-induced brain plasticity arises from a complex interplay between cerebral metabolism and functional and structural brain changes [10, 13]. Given that the brain remains malleable as we age, life-course experiences of various kinds continue to shape its function and structure in a dynamic way ("compensatory scaffolding") [26, 124], adding to existing cognitive reserve [11].

The combination of non-aerobic physical exercise and complex cognitive training seems to provoke substantially stronger brain plasticity and associated cognitive plasticity than do either single-domain physical exercise or single- or multi-domain cognitive regimens [39, 58-60, 87, 94, 97, 98, 100, 101]. Other authors have already drawn similar conclusions. Wollesen and Voelcker-Rehage (2014) [125] reported that dual tasks involving motor-cognitive training usually resulted in larger cognitive gains than single-task training did.

Notably, in all these studies combining moderate physical exercise and complex cognitive training, the sensorimotor component did not involve strenuous aerobic training but rather motor coordination and body-mind exercises, which also have a cognitive dimension to them [68]. The same holds true for musical training [8, 38, 90-93]. In 2020, Sutcliffe et al. [126] also asserted that music-making, which involves the integration of various cognitive and sensorimotor processes, including complex motor learning and multisensory integration, can serve as a potent driver for both cognitive and cerebral growth. These interventions also counteracted certain components of age-related decline that impact ADL.

The field of evolutionary medicine, which examines the impact of lifestyle on health and well-being, may provide us with a theoretical framework for making sense of our main conclusions. According to the theory put forth by Eaton and Eaton [127], the combination of moderately intensive physical activity and simultaneous cognitive load is consistent with the phylogenesis of the human species. The associated adaptive capacity model (ACM) [104] postulates that lifestyle modifications combining the benefits of moderate physical exercise and novel cognitive challenges stimulate neuroplasticity most strongly and, consequently, provide neuroprotection against aging. Moderate-intensity physical exercise—and not strenuous aerobic exercise—is what provides the strongest cognitive benefits in humans when combined with multi-domain cognitive training [128]. This neuroprotection, potentially resulting in increased cognitive reserve or resilience, may also enhance psychological well-being (mental health) [129]. More research is needed to confirm this hypothesis [104].

5. GUIDELINES FOR FUTURE RESEARCH AND INTERVENTIONS

5.1 Single- versus multi-domain cognitive interventions

RCTs comparing the effects of single- and multi-domain cognitive interventions of equal duration and of the same nature, with the single-domain training also included in the multi-domain intervention, could clarify the impact of single- vs. multi-domain training. Long-term studies of single-domain interventions are sorely lacking at present.

5.2 Nature of interventions

The NPI that reinforced learning were challenging and motivating, and involved associative approaches (like the Method of Loci[5]) [45, 46, 50], dual tasking [47], adaptive training that took account of various dimensions such as cognitive load and interstimulus interval (ISI) [35, 36, 44], and training that made use of novel technologies (e.g., computer interface, gaming) [7, 44]. These strategies seemed more effective and, therefore, should be favored. Comparing these approaches using similar tasks would allow disentangling the specific effects of each intervention type.

5.3 Aerobic training

Increased cerebral vascularization may constitute the hidden link between aerobic interventions, structural and functional brain changes, and cognitive functioning. The study by Maass and al. 2015 provided some evidence in this direction [40]. This hypothesis should be tested in the future using ASL, an fMRI approach for assessing tissue perfusion [130], together with functional and structural brain imaging for assessing GM and WM changes following aerobic training. Jonasson et al. (2016) [63] demonstrated that post-training increased aerobic fitness correlated with both increased cortical thickness of the hippocampus and general cognitive score improvements. In several of the studies covered in this review, CBF changes preceded or co-occurred with brain structural and functional training (see section 3.11.1). According to Ahlskog et al. (2011) [21], aerobic exercise may: 1) prevent age-related loss of synapses and neuropil; and 2) reduce vascular risk. However, stressful aerobic training (for instance interval training close to peak heart rate) may increase cortisol-levels and actually reduce beneficial neuroplastic adaptations [72, 108].

5.4 Non-aerobic training

More systematic neuroscientific research into non-aerobic training is required. The most promising types of non-aerobic training are those that integrate cognitive components and/or sensory enrichment. For instance, psychomotor training or TCC in combination with cognitive training would be ideal to provoke brain and behavioral changes [97, 98, 131, 132], and all the more if the cognitive trainings were multimodal [58, 94]. These studies should make use of functional MRI (including ASL) and structural MRI to fully grasp the underlying mechanisms. It should be noted that some real-life interventions, such as those involving music making or juggling, also combine physical non-aerobic exercise with cognitive training.

5.5 Real-life training

Direct comparisons between real-life interventions versus cognitive and physical training and combinations of these should disentangle their respective effects on brain and behavioral plasticity for countervailing age-related decline. Measures of motivation, appreciation, duration, and intensity

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[5] Method of Loci: serial word list learning using a strategy of episodic memory enhancement based on associations with familiar spatial environments

of training (including homework) should be part of the analyses. In the studies included in this review, these aspects were either overlooked or varied widely across studies.

5.6 Delayed measures

On the one hand, delayed measures raise certain ethical issues. For example, participants should not, for the sake of research, stop engaging in activities that, in principle, are stimulating and beneficial. On the other hand, these measures allow evaluating the persistence of plastic effects. One solution to the problem might be to enter into an agreement with participants, as part of the informed consent process, to deliberately pause the intervention for a certain lapse of time in return for the opportunity to pursue the activity at low cost after the study.

5.7 MRI studies and measurements

Looking forward, it is essential for RCTs on NPI to incorporate a comprehensive MRI approach in one study, analyzing structural (GM and WM), functional (fMRI and RS-fMRI), as well as metabolic measures, e.g. ASL and Magnetic Resonance Spectroscopic Imaging (MRSI) measures, with MRSI providing neurochemical profiling for a complete assessment. All these measurements need to be integrated within the same study allowing for a more comprehensive analysis of underlying mechanisms.

MRI sequence parameters should be adapted to strike an optimal compromise between a good signal-to-noise ratio and minimal time expenditure, especially considering the target population of older adults. Then, the fMRI tasks must be well-chosen to allow studying far-transfer effects, and out-of-scanner psychometric testing should be comprehensive, challenging, and varied to keep participants focused. Finally, study participants should be matched for age, gender, education level, and socioeconomic status before being randomized (stratified RCTs) in different groups to ensure that baseline measures are not significantly different. Test-retest effects should be minimized by using different test items at each measurement time point and by comparing results against those of an active or passive control group. Some authors have proposed such protocols [8, 133].

These comprehensive studies should be interspersed with more focused studies that concentrate on specific research questions about particular brain substrates and cognitive abilities. In such cases, the use of a concise set of MRI and psychometric measurements is not only more appropriate but also more time-efficient and cost-effective.

5.8 Use it or lose it

As we age, maintaining mental, physical, and social activity becomes crucial. Individuals should opt for activities that are both still feasible and personally motivating [134].

Instead of reducing our activities as we grow older, we should increase them to preserve or even develop our capabilities [111]. Learning new skills in a group setting, characterized by dynamic interaction, appears to be particularly effective for this purpose [19, 113, 135]. This conclusion is supported by studies in this scoping review, involving extended and relatively intensive programs combining complex cognitive and physical activities over several months in groups.

In an ideal world, all elderly persons should train their minds and bodies, separately or simultaneously, on a regular basis. Real-life regimens that can be implemented in ADL, according to individual tastes, seem optimally suited to ensure the longevity of beneficial effects by increasing the odds that individuals will keep training and doing so more frequently. This, in turn, would close the loop by having a positive impact on ADL.

To validate this hypothesis, a more comprehensive and coordinated research effort is essential. We anticipate that this scoping review will mark a step forward in that direction.

6. DESCRIPTION AND MAIN RESULTS OF EACH INDIVIDUAL STUDY

The description and main results of all interventions will be presented as a function of intervention type/NPI, characterized by the icons depicted below. The icons characterize the nature of the experimental interventions (not the active control interventions, if any), and the type of MRI measurements (structural or functional), but not the psychometric/behavioral measurements taken before, after, and sometimes during the interventions. The icons also provide information about the intensity and duration of the interventions.

6.1 Picturized characterization of interventions

⚙: Single-domain cognitive intervention

⚙⚙: Multi-domain cognitive interventions

🖥: Computerized training

🏃O_2: Physical aerobic training

🏃: Physical non-aerobic training

Intensity of training: ▁ Low Intensity – ▃ Moderate Intensity – █ High Intensity

Duration of training: $\xleftrightarrow{S}$ short – $\xleftrightarrow{I}$ intermediate – $\xleftrightarrow{L}$ long

☀☾: Activities of daily living (ADL) / real-life intervention

LI: low intensity: less than two hours per week

MI: moderate intensity: two to four hours per week or four times per week

HI: high intensity: at least four hours or five times per week

S: short: two weeks to two months

I: intermediate: two to four months

L: long > four months

Type of MRI

⊸s : Structural MRI (sMRI; gray matter (Voxel-Based Morphometry (VBM); Surface-based morphometry (SBM); Cortical Thickness (CT); segmentation); white matter (Diffusion Tensor Imaging (DTI))

⊸f: Functional MRI (fMRI, task-related & resting state fMRI; Arterial Spin Labeling (ASL))

6.2 Categories of NPI

Cognitive interventions, essentially laboratory regimens, either computerized or not, include various activities such as working memory exercises, serial word list learning, attention training, visuospatial skill development, reasoning tasks, executive function training, problem-solving techniques, second language acquisition, and more. We separated **1. *single-domain*** interventions 🧠, which essentially trained one cognitive domain, and **2. *multi-domain*** interventions 🧠 that train several ones.

Physical interventions include physical **3. *aerobic*** interventions 🚶O_2 : running outside or on a treadmill, endurance training, brisk walking, stationary cycling, etc. Nota bene, in HE aerobic interventions comprise all exercise inducing a heart rate of approximately 60-80% of maximal heart rate (HRmax) for a minimum of 15-20 minutes [136]. Another category consists of physical **4. *non-aerobic*** interventions 🚶: soft gymnastics, stretching, regular walking, moderate strength training, slackline training, coordination training, etc. The last two categories are **5. *Combined cognitive and physical aerobic interventions*** *and* ***6. Combined cognitive and non-aerobic physical interventions.***

Some interventions can be characterized as real-life and or artistic interventions that can become part of ADL, ☀☾: like dancing, juggling, music practice, TCC, BDJ, yoga, meditation, music listening, video-gaming, learning a new language, social activities, etc.

All studies focus on HE, therefore the population type not mentioned in general. Unless stated otherwise, studies are randomized controlled trials (RCTs) featuring baseline and post-training MRI measures and at least one behavioral variable.

The order of presentation of the articles within the six NPI categories is in principle alphabetical, like in Supplementary Tables 1-6 that provide detailed information in schematized form on each study. However, when closely related interventions are described together, for instance those based on the same englobing research, the first author's name that occurs will be used to determine the order of the presentation of the numbered subsections.

We refer to **Supplementary Tables 1–6 (SI-1 up to SI-6)** for details on the individual studies.

1. Single-domain cognitive interventions

1. 🧠 🖥 📶 $\xleftrightarrow{S}$ ⊸**s** ⊸**f** [VBM, ASL; Suppl. Table 1] [41]. Biel et al. (2020) combined computerized working memory training with watching novel (EG1 (experimental group 1) versus familiar movies (EG2) over four weeks, in three-weekly 36-minute sessions. The groups were compared with a passive control group (CON). Both experimental conditions only induced near behavioral transfer effects, without any additional novelty effect, and no gray matter (GM) volume changes occurred.

2. 🧠 🖥 📶 $\xleftrightarrow{S}$ ⊸**f** [Task fMRI; Suppl. Table 1] [52]. Brehmer et al. (2011) compared intensive adaptive computerized working memory training (experimental group(s); EG) to a CON (control group(s)) trained on the same working memory tasks, but at a stable low-level. The 5-week out-of-scanner cognitive training, five times per week 25 minutes, consisted of 7 working memory tasks, 4 visuo-spatial and 3 verbal ones. Before and after training task-related fMRI was measured during a spatial delayed-matching task [137], with low *vs.* high load working memory conditions. On the behavioral level, an "out-of-scanner" cognitive battery was applied before and after training, composed of two criterion tasks, similar to the fMRI tasks, two near transfer and four far transfer tasks. A criterion task measures performance compared to some standard outcome or criteria. No training related changes occurred post-training for the fMRI spatial delayed-matching working memory tasks.

However, compared to baseline, fMRI Blood Oxygenation Level Dependent (BOLD) activity decreased post-training in both EG and CON in widely distributed brain areas, but more strongly under high-load conditions in the EG in the dlPFC, superior temporal gyrus (STG), and lingual gyrus, compared to the CON. The activity decrease in the EG may indicate intervention-related increases in neural efficiency.

Scores of the working memory tasks trained over five weeks improved continuously from the first to the fourth week in the EG only. The cognitive battery measures after training also showed improvement in the EG only for working memory (near transfer) and sustained attention (far transfer). However, no direct associations occurred between behavioral improvements and fMRI activation decrease patterns.

3. 🧠 🖥 📶 $\xleftrightarrow{S}$ ⊸**f** [Task fMRI; Suppl. Table 1] [43]. Experiment 2 of this study by Dahlin et al. (2008) assessed pre- and post-training fMRI with 3 different tasks: a letter memory criterion task (near transfer), an n-back on numbers (far transfer), and a Stroop far transfer task, measuring interference inhibition. In between the baseline and post-training fMRI, a 5-week moderately intensive computer-based updating training took place (three times 45 minutes per week), consisting of a letter memory criterion task and 5 other updating tasks (EG). Compared to a passive CON, the EG showed increased post-training BOLD activity in the L striatum during the letter memory criterion fMRI task, together

with an increased effect size of the test scores (improved performance). Whether these results were directly correlated is not reported. So, the effect of the 5-week updating training limits in HE to a near transfer effect, as a similar task was part of the 5-week training in between the two fMRI measurements. Among the out-of-scanner trained tasks, only letter memory improved gradually from week one to week five. However, transfer only occurred when the criterion and transfer tasks engaged specific overlapping processing components and brain regions; therefore, this study induced only near transfer in HE. In contrast, training benefits extended to 3-back number tasks (far transfer) during fMRI in young adults, (Experiment 1, not discussed in detail) with increase in striatal regions for both tasks. HE also showed increase in striatal regions, but only for the letter memory criterion task, although at baseline fMRI, no striatal activation occurred, in contrast to the young adults. These results show a critical role for the striatum in mediating near transfer of learning after updating training in HE.

4. $\xleftrightarrow{I}$ / $\xleftrightarrow{L}$ S [DTI; Suppl. Table 1] [50]. De Lange et al. (2018) investigated the influence of intermittent word learning using the Method of Loci (see **Table 1**), alternating one hour of supervised word learning plus daily homework (10 weeks) versus rest (10 weeks) over a total of 40 weeks. They alternated 10-week blocks of rest and 10-week blocks of learning in two randomly composed EGs. EG1 started with a 10-week intervention period, EG2 with a 10-week rest period. The intermittent training induced an FA increase after each training period and FA decrease after each rest period in each both EGs. Mean, axial and radial diffusivity, (MD, AD and RD) showed the inverse pattern. These results evidence a direct relationship between the intensive intervention periods and positive WM changes[6] and show that intermittent cognitive training can induce dynamics of WMM plasticity. MD decrease in the inferior longitudinal fasciculus (ILF) and in the hippocampal cingulum bundle (HcCB) correlated with the California Verbal Learning Test (CVLT) scores. Memory enhancements persisted after the initial training session in both EGs, demonstrating that, unlike WMM, behavioral advantages do not require continuous training.

5,6. $\xleftrightarrow{S}$ S [SBM, DTI; Suppl. Table 1] [45, 46]. Engvig et al. (2010) [45] showed that after two months of intensive serial word list learning (one hour per week, plus 4 days of homework), using a spatial mnemonic encoding technique "Method of Loci" (see **Table 1**) [138], CT increased in R insula, bilateral fusiform gyrus and lateral orbitofrontal cortex (OFC). These CT changes directly correlated to improved verbal memory performance [45]. The passive CON displayed patterns of CT decrease in similar areas as the increase in the experimental group (EG).

DTI analyses of the same paradigm Engvig et al. (2012) [46] showed significant MD increase in frontal areas in the EG, as observed in normal aging [117], confirmed by a positive correlation with

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[6] Positive diffusivity results following training imply the occurrence of the opposite of age-related trends (see Appendix 2, section White matter).

age. However, fractional anisotropy (FA) increase in L anterior WM (peak voxel L anterior thalamic radiation) in combination with relatively stable radial diffusivity (RD) (*vs.* increase in the CON), revealed a positive effect of training, this frontal FA increase correlated positively with verbal memory scores exclusively in the EG.

7. 🧠 🖥 📶 $\overset{S}{\longleftrightarrow}$ ⊸f [Task fMRI; Suppl. Table 1] [47]. Erickson et al. (2007) applied adaptive (response time feedback) dual task (DT) and single task (ST) computerized training to an EG, that either detected colors *and* letters (dual task) or detected colors *or* letters (single task) during a two-to-three-week training (five times one hour per week). The DT and ST tasks were presented in randomized order. Compared to a passive CON, dual tasking compared to single tasking increased fMRI BOLD activation in L vlPFC and decreased activation in R vlPFC after training. The post-training observed combination of L vlPFC activity increase and R vlPFC decrease suggests that dual task training improves verbal and inner speech strategies relying on the L vlPFC.

The study comprised a group of young adults of which we do not discuss the results in detail here. However, performance improved for the dual tasks in HE, associated with an increase in hemispheric asymmetry, revealing a reduction in age difference in activation patterns compared to the young adults. No significant differences arose for scores of an out-of-scanner neuropsychological battery, indicating that no far transfer effects happened.

8,9. 🧠 🖥 📶 $\overset{S}{\longleftrightarrow}$ ⊸f [[Task fMRI; Suppl. Table 1] [35, 36]. In two studies by Heinzel and colleagues, both using the same training procedure, the authors investigated the effect of a moderately intensive computerized adaptive n-back working memory training over one month (three times 45 minutes per week) on far transfer effects and fMRI BOLD responses compared to a passive CON. Participants of the CON were matched to the EG for age, gender and education level, so this study is not a genuine RCT. The adaptive n-back training (EG) involved different working memory loads (0-1-2-3- up to 4-back on numbers) and decreasing ISIs (1500, 1000 & 500ms). During this adaptive training, task difficulty increased by higher working memory load and shorter ISI (interstimulus interval) as a function of success rate.

In the 2016 study [35], participants passed, before and after the training period, a large cognitive test battery and underwent fMRI comprising two different tasks: 1) the trained working memory task (near transfer) and 2) a far transfer task: a delayed recognition and updating "Sternberg task". The fMRI BOLD signal decreased post-training in both the trained n-back and in the updating condition of the untrained Sternberg task in R lateral middle frontal gyrus (MFG) and caudal superior frontal sulcus, compared to the CON. This BOLD decrease indicates a training-related increase in processing efficiency in working memory networks.

Regarding out-of-scanner battery tasks, an association emerged post-training between BOLD decrease in 1- & 2-back fMRI and improvement in Digit Symbol Substitution performance. So, on the behavioral level, working memory performance improved after training and far transfer occurred for executive functions (EF), processing speed, and fluid intelligence.

In the 2017 study [36], task fMRI before and after training only involved the trained n-back task. The results were analyzed in seven literature-based Regions Of Interest (ROIs) composing a working memory network (see Suppl. Table 1). Before and after training, the participants passed a visuo-auditory multimodal dual-task to assess far transfer effects. After training, the EG showed decreased BOLD responses in the working memory network during the task, and in the low-load condition (1-back) dlPFC activity decreased, predicting post-training auditory dual-costs in low-load conditions and visual dual-costs in high-load conditions.

10. 🧠 🖥 ▮ $\overset{S}{\longleftrightarrow}$ ⊸**s** [SBM; Suppl. Table 1] [44]. Kuhn et al. (2017) applied a 2-month computerized adaptive inhibition game intervention for minimum 15 minutes per day that induced increased CT in the pars triangularis of the R inferior frontal gyrus (IFG) associated with response inhibition. The R IFG increase was enhanced in participants who played more frequently and predicted response inhibition. The passive CON displayed patterns of CT decrease in similar areas as the increase in the EG.

11. 🧠 🖥 ▮ $\overset{S}{\longleftrightarrow}$ ⊸**f** [Task fMRI; Suppl. Table 1] [139]. Mikos et al. (2021) investigated the effects of a 6-week process-based object-location memory training (EG) versus an active CON on task-induced FC within the default mode network (DMN). Both adaptive trainings took place at home on the PCs of the participants 5 times 30-45 minutes per week. The EG engaged in process-based memory training involving object, shape, and landmark-location tasks with cued recall. Conversely, the CON group focused on visual perception tasks using the same visual material. Using fMRI, the authors analyzed changes in the dorsal and ventral DMN branches during an untrained object-location memory fMRI task across repeated measurements. The results revealed a significant increase of dorsal DMN deactivation in the training group compared to the control group particularly during encoding stages. However, this neural adaptation was not correlated with improvements in fMRI task performance.

12. 🧠 🖥 ▮ $\overset{S}{\longleftrightarrow}$ ⊸**s** ⊸**f** [VBM, ASL; Suppl. Table 1] [42]. Mozolic et al. (2010) trained participants individually over two months one hour per week in adaptive attentional tasks (EG). Stimuli were presented with Presentation software via LCD screen/overhead speakers; participants provided written or verbal responses (semi-computerized). The training provoked reductions in cross-modal interference and improvement in suppressing multisensory distraction during visual selective attention. The latter could be associated with marginally increased right inferior prefrontal Cerebral Blood Flow (CBF) ($p<.07$), but not with changes in GM volume, as compared to a CON, that followed health lectures.

13. 🧠 🖥 📶 $\overset{S}{\longleftrightarrow}$ ⊸f [Task & RS-fMRI; Suppl. Table 1] [48]. Ross et al. (2019) compared two types of moderately intensive cognitive training (EG1 and EG2) to a passive CON. EG1 underwent computerized adaptive Useful Field of View training (UFOVt) and EG2 various complex non-adaptive cognitively stimulating activities (paper-and pencil; reasoning, recall, and EF). UFOVt is an adaptive cognitive intervention that trains visual attention. Interventions took place twice per week for one hour over five weeks. EG1 outperformed the other groups for post-training FOV performance. The authors analyzed event-related fMRI activity in eight ROIs involved in effortful information processing, during an adapted Useful Field of View (UFOV) task. During this fMRI task reduced BOLD activity showed in EG1 post-training in six of the eight predetermined ROIs (anterior cingulate cortex (ACC) anterior insula (AI), dlPFC, inferior parietal lobule (IPL), supplementary motor area (SMA) & thalamus), whereas in EG2 activity decrease only showed in one region of interest (ROI), the AI. The activity decreases indicate efficiency increase, which was thus far larger in EG1 compared to EG2.

Exclusively in EG1, increased average network FC occurred after training. Specifically, activity increase occurred in four connections: AI-ACC, AI-visual cortex, AI-SMA & dlPFC-SMA. The authors do not report on direct correlations between functional brain plasticity and fMRI task performance.

14. 🧠 🖥 📶 $\overset{S}{\longleftrightarrow}$ ⊸f [Task fMRI; Suppl. Table 1] [49]. Using a slow event-related fMRI design, Scalf et al. (2007) compared the effects of an EG that received a computerized functional field of view (FFOV, see Table 1) training over five weeks (45 minutes per week), to a passive CON. Attrition in the passive CON was far superior to that in the EG (see Suppl. Table 1). The FFOV represents the spatial area in which a stimulus receives attention. The intervention comprised three conditions: central, peripheral, and dual FOV tasks, the latter also involved cognitive flexibility/switching. The fact that three different conditions were present during the training, involving a dual-task requiring cognitive flexibility/switching, may have enhanced learning. During pre-and post-training fMRI, all participants passed an adapted FFOV task (also the CON). In the EG, comparing the two time points, fMRI BOLD activation increased in the R IFG & R precentral gyrus, but no differences occurred when comparing the two groups over time. The two intensive behavioral testing sessions (T0: just after the fMRI and T1: just before the fMRI measurements) in between the two fMRI sessions may have induced learning in the CON. This may explain why a direct comparison between the two groups (EG vs. CON) did not show brain activity changes post-training. However, only in the EG BOLD activation increases correlated positively with accuracy in the FFOV test for all three conditions during fMRI.

15. 🧠 🖥 📶 $\overset{S}{\longleftrightarrow}$ ⊸s ⊸f [DTI, RS-fMRI; Suppl. Table 1] [7]. Strenziok et al. (2014) investigated cognitive and brain plasticity by comparing three different adaptive computerized cognitive trainings (video games) over six weeks: Brain Fitness (BF) involving adaptive auditory perception, Space Fortress (SF) involving visuomotor/working memory and Rise of Nations (RON) involving strategic reasoning. The intensive trainings consisted of three hours of supervised gaming

per week, supplemented with three hours of homework. The research team verified the hypothesis that the dorsal attention network (seed: right superior parietal cortex (R SPC)) may mediate far transfer effects of the computerized trainings to tests composing a cognitive battery (reasoning/problem-solving, comprising the Everyday Problems Test (EPT), episodic memory and working memory).

On the behavioral level, all three gaming interventions led to increased gaming scores after training (near transfer). SF showed the largest increase for working memory (the trained task) and BF for matrix reasoning. Both BF and SF provoked shorter test completion times for the EPT.

On the functional level [RS-fMRI], FC decreased between the R SPC (part of the dorsal attention network) and the L posterior inferior temporal lobe (ITL) from pre- to post-training more strongly in the SF group than in the RON group. FC between the R SPC and the L anterior ITL changed strongly in the BF group compared to the RON group. FC decrease between the R SPC and the L posterior ITL positively correlated to decrease of time to complete the EPT, indicating greater reasoning efficiency following SF. This shows that the dorsal attention network is implicated in BF training.

On the structural level, the main effect of group over time consisted in AD increase [DTI] in the L lingual gyrus and R thalamus. Following BF training, AD increased in occipito-temporal white matter, whereas AD reduced following SF and RON training. Thalamic AD increases, positively correlated to post-training working memory performance (far transfer). Additionally, a positive correlation between occipito-temporal AD increase and time to complete the EPT showed. Although decrease of AD in this study goes in the opposite direction as described by Beaudet et al. (2020) after 55y, we interpret this AD decrease positively from a functional point of view as it correlates positively with working memory performance and EPT completion time, suggesting a positive effect of training. Natural AD decrease after 55y of age is minor as compared to FA or RD development. This study is the only one not following the classical age-related trends.

2. Multi-domain cognitive interventions:

16. 🧠 📊 $\overset{\text{I}}{\longleftrightarrow}$ **f** [RS-fMRI; Suppl. Table 1] [53]. Bubbico et al. (2019), before and after four months (1h30 per week plus 30 minutes of homework, 120 minutes in total) of second language learning (EG) starting at beginner level, applied seed-based RS-fMRI. The intervention comprised working on vocabulary and grammar skills, acquiring knowledge on anglophone culture, speaking (communication), writing and reading. As the posterior cingulate cortex (PCgC) served as seed, the analyses concerned connectivity with the default mode network (DMN). A large test battery assessed cognitive performance. Compared to a passive CON, the EG showed FC increase of the PCgC with the right inferior frontal gyrus (R IFG), right superior frontal gyrus (R SFG) and left superior parietal lobule (L SPL). The FC increase was associated with improving general cognitive performance (Mini-Mental State Examination (MMSE) score). In fact, the CON showed superior MMSE performance at T0 and

decreased in performance post-training, whereas the EG group remained stable. No differences occurred for other cognitive tests.

17. $\overset{\text{L}}{\longleftrightarrow}$ f [Task fMRI; Suppl. Table 5] [37]. Carlson et al. (2009) divided community-dwelling African American women with low education, low income, and marginally low MMSE scores by means of extensive sociodemographic matching (no genuine RCT) in an EG and a passive CON. The EG was involved over six months in a multimodal "Experience Corps" activity program: a social service program designed to help elementary school children with reading achievement, library support, and classroom behavior, 15 hours per week. Before and after the program, the participants passed a flanker test measuring interference control (part of executive functions), during fMRI. After the program, the EG showed fMRI BOLD activity increase in L vlPFC, L dlPFC & ACC compared to the CON, in correlation with greater interference reduction.

18. $\overset{\text{I}}{\longleftrightarrow}$ s f [DTI, ASL, RS-fMRI; Suppl. Table 2] [54]. Chapman et al. (2015) compared complex cognitive training "gist reasoning" (strategy based, not content based), involving three distinct cognitive interventions (non-computerized) over three months, to a passive control group. Gist reasoning demands to continuously synthesize meanings and goals, and involves abstraction ability, a relevant skill in daily life [140]. One hour of supervised training per week was supplemented with 2h of homework. Measurements took place at baseline (T0), mid-term (T1, six weeks) and post-training (T2, three months). DTI results showed monotonic FA increase, representing increased WM integrity, from T0 to T1 to T2, in the L uncinate fasciculus. Nota bene, T0 (baseline) is called T1 in this study and so forth, we keep our nomination throughout the current scoping review: T0: baseline, T1: first point of measurement, T2: second point of measurement, etc.

ROI analyses [RS-fMRI] in the DMN: PCgC and middle frontal cortex and in the CEN (central executive network): dlPFC and IPC (inferior parietal cortex), comparing the EG to the CON, and T2 to T0, revealed enhanced FC in DMN and CEN, mirrored by increased Cerebral Blood Flow (CBF) (measured by ASL) in the same regions. Comparing psychometrics between the EG and CON after the full three months of training exhibited improved strategic reasoning and EF performance, which correlated positively to increased CBF in DMN and CEN.

19. $\overset{\text{I}}{\longleftrightarrow}$ f [RS-fMRI; Suppl. Table 2] [55]. Hardcastle et al. (2022) investigated associations within four higher-order resting state (RS) networks in participants undergoing multidomain adaptive cognitive training on attention, processing speed, and working memory (EG) compared to an active CON (watching National Geographic videos, answering related questions). Both trainings took place five times per week over 12 weeks. EG participants improved in seven out of eight tasks, most notably in a divided attention/speed-of-processing task called the Double Decision task that pertains to executive function. Post-intervention, only the frontoparietal control network demonstrated strengthened FC in the EG, correlated with improved Double Decision task

performance. These results suggest that the frontoparietal control network (similar to the CEN) may underpin divided attention and processing speed improvements following multidomain cognitive training.

20. 👤 🖥 📶 $\overset{S}{\longleftrightarrow}$ ⊸s ⊸f [VBM, RS-fMRI; Suppl. Table 2] [118]. Kawata et al., 2022 evaluated the effects of auditory and cognitive training over four weeks on cognitive function and auditory ability in HE. Participants were divided into 4 groups: auditory-cognitive training (AC, EG1), auditory training (A, EG2), cognitive training (C, EG3), and an active CON (steady low-level auditory and cognitive training). In all EG, training was adaptive: reducing sound intensity for AC and A group and adapting tasks to performance level in the C group. Pre- and post-training assessments included the cognitive tests Digit-Cancellation (attention, visual scanning; D-CAT), Logical Memory (verbal memory; LM), DSF and DSB, Pure-Tone Audiometry (PTA), and MRI scans. The AC/EG1 group showed differences in regional GM volume (rGMV) in specific brain areas (see Suppl. Table 2), compared to all other groups. Auditory training (AC and A) induced improved auditory measures (PTA) and increased rGMV and FC in the left temporal pole compared to non-auditory training groups. Cognitive training groups (AC and C) exhibited improved cognitive performance (LM and D-CAT) compared to non-cognitive training groups, and rGMV changes in specific brain areas (see Suppl. Table 2). No significant correlation between changes in auditory and cognitive measures over time and brain structural changes occurred.

21. 👤 🖥 📶 $\overset{I}{\longleftrightarrow}$ ⊸s [SBM; Suppl. Table 2] [56]. Kim et al. (2015) compared intensive 3-month robot-assisted and traditional multi-domain cognitive training (memory, calculation, language, EF and visuospatial training), five times 90 minutes per week. The robot group responded on a smart pad, the traditional training group provided oral or written responses. Both traditional and robot assisted interventions reduced CT thinning in bilateral medial prefrontal cortex (mPFC) and R middle temporal gyrus (MTG) compared to a passive CON. Robot assisted training induced additional decreased thinning in the ACC and R inferior temporal gyrus (ITG), possibly explained by the individual feedback provided in this group only, plus additional "winner of the months" announcements, enhancing motivation. This obscures the comparison to the control group. In the robot group, there was a positive correlation between CT changes in the L temporo-parietal junction (TPJ) & L ITG and EF scores. In the traditional intervention group, a positive correlation showed between CT changes in R ITG and R subgenual ACC and in visual memory scores.

22. 👤 🖥 📶 $\overset{I}{\longleftrightarrow}$ ⊸s ⊸f [VBM, SBM, DTI, RS-fMRI; Suppl. Table 2] [57]. Lampit et al. (2015) offered three weeks (intermediate measure) and finally three months of three-hour weekly computerized multi-domain cognitive training to the EG, involving attention, processing speed, memory, EF, and language tasks (from the computerized multi-domain cognitive training "COGPACK", see Table 1). The intervention yielded increased GM density in the R post-central gyrus gradually (~50% of total increase at three weeks with respect to the 3-month measures) compared to a CON

that watched videos. Global cognition performance also improved gradually over time and correlated positively to GM density increase in the post-central gyrus. CT also increased in the post-central gyri in the EG. DTI measures did not reveal any differences. Seed-based RS-fMRI (seeds: Hc and PCgG) revealed decreased DMN FC after three weeks between the PCgG (DMN) and the R SFG in the EG and increased FC between these regions in the CON. The observed DMN FC decrease correlated inversely with global cognition after training completion, or, in other words, DMN FC decrease corresponded to better cognitive scores. FC changes were significant after three weeks only, not after three months, but correlated with global cognition improvement after three months (post-training). Given the very small number of participants, reliability and validity cannot be ensured.

3. Physical aerobic interventions:

23,24. 🚶O_2📶 $\xleftrightarrow{L}$ s f [VBM, fMRI; Suppl. Table 3] [61, 109]. In two studies (2004, 2006), Colcombe and colleagues compared the effect of adaptive aerobic physical training (EG, walking on a treadmill) to non-aerobic physical training (toning and stretching, CON) over 6 months, both 3 times per week up to ~45 minutes for the 2004 study, and for one hour in the 2006 study, after an initial build-up in duration. Both interventions (EG and CON) were adaptive. In the 2006 study [61], comparing both groups over time, applying VBM analyses, gray matter volume increase showed in prefrontal (ACC & SMA, R IFG) and L superior temporal cortices, whereas WM increase emerged in the anterior corpus callosum. Cardiovascular fitness (VO_2max, see Table 1) increased significantly in the EG but not in the CON, without direct correlations to the brain data. In the 2004 counterpart [109], before and after training, an event-related fMRI design measured brain activations during a flanker test, involving inhibition of incoherent visual stimuli. Comparing the groups over time, stronger task-related BOLD activity occurred in attentional control areas (MFG, SFG, and SPL) in combination with reduced activity-level in the ACC in the EG. The EG improved in flanker performance over time, but no direct links to brain activation were reported. Reduced BOLD activity levels in the ACC, a region associated with conflict monitoring, may reflect increased efficiency to resist interference. Simultaneously the EG exhibited increased cardiovascular fitness, without direct relations to brain activity.

25,26,27. 🚶O_2📶 $\xleftrightarrow{L}$ s f [Automatized brain segmentation & BDNF levels, DTI, RS-fMRI; Suppl. Table 3] [62, 123, 141]. Erickson et al. (2011) [62], Voss et al. (2013) and Voss et al. (2010). compared the effects of a 12-month aerobic training program (EG, walking on a treadmill) to an active CON that received non-aerobic physical training (flexibility, toning, balance) on brain plasticity and cognition. Interventions took place three times per week for 40 minutes, after an initial build-up in duration.

[Automatized brain segmentation & BDNF levels] Erickson and colleagues (2011, Suppl. Table 3) [62] applied volumetric analyses of the Hc, thalamus and caudate nuclei, based on automatized brain segmentation. Aerobic training over twelve months (EG) induced a 2% increase of volume in bilateral anterior Hc, associated with increased BDNF serum levels (obtained via blood-sampling). In contrast, the CON displayed a 1.4% decrease of bilateral anterior Hc and of bilateral caudate nuclei. Exclusively the EG showed a positive correlation between spatial memory enhancement, Hc volume growth and BDNF serum levels, but spatial memory also improved in the CON. The EG showed stronger aerobic fitness increase post-training compared to the CON (VO_2max) without direct relationships to plasticity of brain and behavior.

[DTI] Voss et al. (2013, Suppl. Table 3) [141] evaluated the impact of the same interventions on WM integrity and executive control. No significant differences of FA, AD or RD occurred post-training between the groups. Although aerobic fitness training did not impact WM directly, enhanced aerobic fitness following the aerobic training correlated with enhanced WM integrity.

[RS-fMRI] Voss et al. (2010, Suppl. Table 3) [123] used resting-state fMRI to investigate the effect of the aerobic training on functional networks. Comparing the EG to the CON over the full training period (12 months), the EG exhibited increased FC within the DMN and a Frontal Executive Network (FEN). Comparing FC over time solely for the CON over the full training period, disclosed increased FC in a FPN (Fronto Parietal Network). No significant differences occurred between the groups for EF and verbal short-term memory. However, the increased FC in the DMN in the EG after 12 months of training correlated to greater improvement of EF.

28. 🚶O_2 📶 $\xleftrightarrow{S}$ **f** [RS-fMRI; Suppl. Table 3] [116]. In a study by Greeley et al. (2021), the EG performed high-intensity interval exercise "spinning" on a stationary recumbent bicycle two times per week for 23 minutes, followed directly by a motor task. The CON watched a documentary before the motor task. The interventions lasted 2.5 weeks. The motor task consisted of a serial targeting task with the non-dominant hand using a KINARM end-point robot (https://kinarm.com/kinarm-products/kinarm-end-point-lab/). FC was measured before the first and after the fifth day of practice (2.5 weeks). Comparing the EG to the CON over time by means of Independent Component Analysis (ICA), revealed increased FC between cerebellar, frontal-parietal, and dorsal attentional networks and bilateral putamen. Seed-based ROI analyses showed increased FC between brain regions that link the limbic system and the cerebellum (for details see Suppl. Table 3). So, bouts of high-intensity interval exercises over 2.5 weeks combined with motor learning during 5 sessions increased FC, but compared to the CON, the aerobic training did not show increased motor learning. Moreover, no motor learning appeared after a 5-week delay. At that time point, no brain data were acquired.

29. 🚶O_2 📶 $\xleftrightarrow{L}$ **f** [SBM; Suppl. Table 3] [63]. Jonasson et al. (2017) applied 6-month aerobic exercise (indoor walking or jogging and stationary cycling measuring seven different cognitive

constructs, resumable in a unit-weighted general cognitive score. The latter improved more in the EG compared to the CON across time. Both groups showed increased aerobic fitness post-training, with a stronger increase in the EG. Another interaction effect disclosed a positive correlation between general cognitive function and gain of dlPFC CT in the EG. Finally, higher aerobic fitness post-training correlated with increased CT of the Hc (both groups).

30. 🏃O_2 ▮ $\xleftrightarrow{I}$ f s [Perfusion MRI, Automated segmentation of the Hc, Suppl. Table 3] [40]. Maaß et al. (2015) provided the EG with individually adjusted 30-minute aerobic interval training three times per week for 12 weeks. The CON received two times 45 minutes of adaptive relaxation/stretching per week. The authors report a pseudo-randomized assignment to the EG and CON groups, matching for age, gender, Body Mass Index (BMI), self-reported activity level and verbal memory recall. No clear group differences over time (interaction) occurred, except for cardiovascular fitness which increased in the EG. Merging both groups together, after 3-month interventions, cardiovascular fitness was positively associated with Hc perfusion, both positively correlating to early spatial recall and recognition scores.

31. 🏃O_2 ▮ $\xleftrightarrow{I}$ s f [VBM, cerebral metabolism; Suppl. Table 3] [64]. In the study by Matura et al. (2017), 3 months of aerobic cycle training, three times per week for 30 minutes, preserved cerebral choline concentrations, whereas in the passive CON choline concentrations decreased. Comparing the EG to the CON over time, resting heart rate and maximum heart rate (HRmax) during exercise improved. However, no changes in gray matter, in cognitive performance, nor in VO_2max occurred across groups and time.

32. 🏃O_2 ▮ $\xleftrightarrow{I}$ f [Task MRI; Suppl. Table 3] [66]. Nocera et al. (2017) found that three months of stationary bicycle spinning three times a week (adaptive from 20 to 25 minutes per day) improved verbal fluency compared to a CON that did simple balancing training. Comparing the groups across time, the EG displayed decreased post-training BOLD activity in the R IFG (pars triangularis) during the task-related fMRI semantic fluency task, indicating greater neural efficiency. Increased aerobic fitness (VO_2max) across time and verbal fluency increased in the EG and correlated inversely to R IFG activity.

33,34,35,36. 🏃O_2 🏃 ▮/▮ $\xleftrightarrow{L}$ f s [sMRI, manual and automatized brain segmentation, DTI; Suppl. Table 3] [70-73]. All four publications are MRI substudies of the Generation 100 Study [69, 106], spanning 5 years. This study compares two exercise regimens: EG1 involved twice-weekly high-intensity interval training (HIIT) with four sets of four minutes at 90% peak heart rate, separated by three-minute rest periods. EG2 consisted of 50-minute moderate-intensity continuous training (MICT) sessions at 70% peak heart rate. The EG1/ HIIT group exercised at a higher intensity, but exercise frequency and duration were similar across groups. Supervised indoor and outdoor training options for both EG included walking, running, and aerobics; participants could also exercise individually. The active control group (CON) followed Norwegian national guidelines, engaging in at least 30 minutes of moderate physical activity five days a week. Cardiorespiratory fitness (CRF) was measured by peak oxygen uptake (VO_{2peak}). Measures were taken after 1, 3 and 5 years. Participants were highly educated on average.

[SBM; automatized segmentation; Suppl. Table 3] [72]. Pani et al. (2021) analyzed 5-year training effects on gray matter (GM) brain plasticity. Surprisingly, EG1 compared to the CON showed increased Hc atrophy, and EG2 greater thalamic atrophy. CRF increased in all three groups during the first year only. However, CRF at baseline correlated positively with cortical volume at all later time points. So higher CRF at baseline reduced 5-year cortical atrophy rate in HE. Strikingly, following the Norwegian physical activity guidelines of minimum 30 minutes of daily moderate physical activity (CON), yielded the lowest hippocampal and thalamic atrophy rates.

[DTI; Suppl. Table 3] [71]. In Pani et al. (2022a) the analyses focused on white matter microstructure. Despite the absence of group-time interaction or group effect, both higher CRF and exercise intensity co-occurred with enhanced WMM during the intervention period. However, this effect diminished progressively over time. Different aspects of physical activity influenced WM metrics tracts in distinct ways, with the most pronounced and intersecting impacts observed in the corpus callosum. EG2 (MICT) didn't demonstrate a long-term benefit exceeding two years. Although EG1 (HIIT) enhanced CRF more than EG2 (MICT), no significant group or time interaction effect was observed on FA or MD. A positive relationship was identified between CRF, training intensity, and FA i.e. in the corpus callosum. Altogether, fitness and exercise intensity affect WM tracts, indicating a complex relationship with cognitive health that should be further explored.

[sMRI, automatized brain segmentation; Suppl. Table 3] [70]. Pani et al. (2022b) investigated the effects of a 5-year exercise intervention on Fractal Dimension (FD) that reflects brain structural complexity, a biomarker of brain health [142]. Group membership did not affect FD over time. However, there was a significant positive correlation between CRF levels and increased FD in cerebral and temporal lobe gray matter, indicating that maintaining high CRF potentially protects against loss of structural complexity in brain regions susceptible to aging and related pathologies (temporal lobe GM). This was not observed with cortical thickness measurements; thus, FD might be a more sensitive marker for detecting structural changes.

[sMRI; manual and automatized brain segmentation; Suppl. Table 3] [73]. Arild et al. (2022) explored growth of WMH. Contrary to the initial hypothesis, neither EG1 (HIIT) nor EG2 (MICT) attenuated WMH growth compared to the CON. No group-by-time interactions were observed for WMH, periventricular WMH (PWMH), or deep WMH (DWMH). However, a significant group by time interaction for PWMH volume showed a larger increase in the combined EG1&2 (MICT&HIIT) compared to the CON, indicating that exercise did not protect against the negative aging indicator of PWMH growth. Additionally, cardiorespiratory fitness (measured as VO_{2peak}) increased in all groups initially but returned to baseline at the final follow-up. Cardiorespiratory fitness was not associated, three times 30-60 minutes per week) compared to an active CON (toning and stretching). They did not find significant CT changes between the groups across time. Additionally, they applied a comprehensive neuropsychological battery

with any changes in WMH volumes over time. Therefore, participating in either aerobic exercise group did not offer advantages in slowing WMH progression compared to adhering to national physical activity guidelines.

37. 🚶O_2 🚶 📶 $\xleftrightarrow{L}$ ⊸S [sMRI, automatized brain segmentation; Suppl. Table 3] [114]. In this 1-year study, Tarumi et al. (2022)) randomized HE in either an adaptive aerobic exercise group (EG) or stretching-and-toning program (active CON) to assess the effects on cognitive function and cerebral structure. Both interventions led to improved cognitive composite scores over time, although the groups did not differ. Test-retest effects cannot be excluded. Moreover, both groups experienced reductions in total brain volume and mean CT over time. Interestingly, the stretching group exhibited less hippocampal volume reduction than the aerobic group. A notable finding was the positive correlation between increased CRF and improvements in both cognitive score and regional CT in the L IPL. The study suggests that both interventions can enhance cognitive performance but might not inhibit general age-related brain volume loss.

38. 🚶O_2 🚶 📶 $\xleftrightarrow{L}$ ⊸S [Task-fMRI; Suppl. Table 3] [67]. Using an fMRI flanker task, measuring interference control, Voelcker-Rehage et al. (2011) compared the influence of 12 months of adaptive aerobic walking (EG1) to non-aerobic fine and gross-motor whole body coordination (EG2) and an active CON (relaxation and stretching). All three interventions were provided three times an hour per week. Measurements were taken at T0, T1 (6 months) and T2 (12 months) and included the fMRI flanker task, another out-of-scanner visual search task (measuring perceptual speed), and different fitness assessments. Significant interaction Group x Time (T2 *vs.* T0) exhibited for the incongruent condition of the Flanker test in different frontal, parietal and sensorimotor areas, with fMRI BOLD increases for EG1 and decreases for EG2 and the CON. Comparing EG1 to the CON between T2 and T0 (interaction), showed *decreased* activation during the flanker task in L SFG, L MFG and bilateral medial frontal gyrus, L ACC, L para-Hc gyrus, R STG and R MTG. Comparison of T2 *vs.* T0 solely for EG2 for the flanker task showed *increased* activations in the IFG, thalamus, caudate and in the SPL. EG1&2 improved in accuracy for the flanker test, whereas in the CON group performance was unchanged after 12 months. Only in the EG1, cardiovascular fitness improved (VO_2 max). In both EG, feet-tapping and one-leg stand improved. EG2 showed improved visual search at T2. Task-related BOLD activation decrease in EG1 may reflect increased neural efficiency and seems mainly driven by increase of VO_2 max.

Nota bene, T0 (baseline) is called T1 in this study and so forth, we keep our nomination throughout the current scoping review: T0: baseline, T1: first point of measurement, T2: second point of measurement, etc.

4. Physical non-aerobic interventions:

Also consider the study by Voelcker-Rehage et al. (2011) [67] described above, that compared aerobic to non-aerobic training. The studies that used combined non-aerobic and cognitive training should also be considered (see 6. Combined cognitive and physical non-aerobic interventions [58-60, 86, 87, 94].

39. 🚶 ▮ $\xleftrightarrow{L}$ ⊸s [VBM; Suppl. Table 4]. [76]. Demnitz et al. (2022) examined the impact of a one-year training program on physical function and brain structure in 247 community-dwelling HE over a span of four years. The study, part of the larger LISA project [143], divided participants into 3 groups: high-intensity resistance training EG2/HIT, moderate-intensity resistance training EG2/MIT, and a passive CON. Both trainings were adaptive. EG1/HIT performed 3h of supervised training, EG2/MIT 1h supervised, and 2*1h home training; this disbalance is a weakness of the study. MRI was acquired at baseline and after four years, but no activities were offered in the intervening 3 years. Therefore, the results provide information on sustained changes three years after training completion. Lower limb motor function measured by chair stand performance [144] and GM volume did not differ between the three groups over four years. However, baseline performance at the chair stand predicted GM increase after 4 years in cerebellar regions. Controlling for chair test performance at baseline, thus separating subgroups as a function of progress, not training assignment, showed gray matter differences R SMA and dlPFC between improvers vs. maintainers/decliners. In conclusion, chair stand baseline performance and progress better predicted GM after 4 years than training group assignment. However, the 3-year pause between training completion and MRI measurements may have washed out the effects.

40. 🚶 ▮ $\xleftrightarrow{L}$ ⊸f [fMRI; Suppl. Table 4] [74] Liu-Ambrose et al. (2012) divided participants (only women) in three experimental conditions. Two EG received adaptive resistance training over 12 months, EG1 twice per week and EG2 once per week for 60 min. (10 min. warm-up, 10 min. cool-down), whereas a CON participated in twice-weekly balance and toning training. So, two different intensities of resistance training were compared. Task-related fMRI measured BOLD responses during a flanker test evaluating interference control before and after training. Contrasting EG1 to CON over time, EG1 showed greater percent BOLD signal change post-training in L AI extending into the L MTG in conjunction (no direct relationship) with significant interference reduction (flanker task) Contrasting EG2 to CON did not yield significant fMRI or behavioral differences.

41. 🚶 ▮ $\xleftrightarrow{S}$ ⊸s ⊸f [VBM, RS-fMRI; Suppl. Table 4] [75]. In Magon et al. (2016), six weeks of slack line training (3 times 90 minutes per week) in which participants must maintain their balance

on a nylon cable, did not induce whole brain level GM or FC results over time compared to a CON that received educational sessions with similar frequency. However, the balance performance (single-leg slackline standing performance) increased in the EG only. When performing analyses exclusively on EG participants that improved their balance performance, seed-based correlation revealed FC decrease between the striatum (caudate, putamen) and widely distributed frontal and parietal brain areas, most likely reflecting increased striatal network efficiency positively impacting balance.

5. Combined cognitive and physical aerobic interventions

42. O_2 $\xleftrightarrow{L}$ S [DTI; Suppl. Table 5] [82]. In Burzynska et al. (2017), four groups of low-active HE participated in 6-month lifestyle interventions (three hours per week): 1) adaptive dancing (EG1), 2) brisk walking and brisk walking plus nutrition supplements (regrouped in one EG: EG2) that were compared to an active CON (strength/stretching/balancing). Both EGs consisted of aerobic activity. Only EG1 was adaptive, learning more complex steps over time, thus comprising a cognitive constituent. Despite the lifestyle interventions, WM integrity declined in all groups in widely distributed brain regions, exhibiting as FA decrease and RD, AD and MD increase. However, in the adaptive dancing group only, FA increased in the fornix, known to be involved in episodic memory [145]. However, no correlations between the FA changes and cognitive behavior manifested. Some advantages for processing speed manifested in all groups.

43. O_2 $\xleftrightarrow{S}$ S [sMRI, automatized segmentation; Suppl. Table 5] [146]. Castells-Sanchez et al. (2022) describe a 12-week RCT, a substudy of the Projecte Moviment RCT [147], in healthy middle-aged and older adults. In this study, the cognitive impacts and underlying mechanisms of different interventions were investigated, including progressive intense aerobic exercise (AE, EG1), adaptive computerized multimodal cognitive training (CCT, EG2), and a combination of both (COMB, EG3), in comparison to a waitlist control group (CON). EG1&2 exercised ~45 minutes per day five days per week, EG3 did both, thus trained two times 45 minutes daily, biasing group comparisons. Biomarkers (TNF-α, ICAM-1, HGF, SDF1-α levels, not explained here, refer to the article), BDNF levels, and targeted cytokines were measured via blood sampling, CRF with the Rockport 1-Mile Test, and physical activities using the Minnesota Leisure Time Physical Activity Questionnaire. Despite the absence of differences in molecular biomarker concentrations in any group over time or compared to the CON, ICAM-1 and SDF1-α changes were inversely correlated with increase in physical activity in the AE and COMB groups. Concerning brain volume, only EG2 exhibited a significant increase in the precuneus. Sex appeared to moderate brain volume changes in EG1 and EG3, with greater benefits for men. However, these molecular and brain volume modifications did not correlate with previously reported cognitive benefits [148] for EF in EG1, and attention-speed in both EG1 and EG3.

44. 🧠 🌅🌙 📶 ⟷ 🧲f [ASL, RS-fMRI; Suppl. Table 5] [20]. This study by Chapman et al. (2017), compared Strategic Memory Advanced Reasoning Training (SMART, non-computerized, strategy based not content based, see Suppl. Table 5), to aerobic training (treadmill walking/stationary cycling), and to a passive control group by means of CBF (measured with ASL) and seed-based RS-fMRI. No intervention was provided that combined both cognitive and aerobic elements. Both SMART and aerobic regimens involved three hours of training per week over three months. Measures comprised innovative cognitive behavior, brain FC and their relationships. The seed-based RS-fMRI focused on the DMN (FC between OFC and PCgC) and on an ROI analysis for two CEN regions: i) whole brain cross-correlation/FC of bilateral dlPFC and ii) of IPC. The SMART training groups showed, post-training and compared to the two other groups, increased CBF in medial OFC and bilateral PCgC (two nodes of the DMN). Additionally, the SMART groups improved strongly from baseline to mid-training for innovative cognition (superior innovation scores from the Multiple Interpretations Measure (MIM)). Most importantly, in the SMART group, innovation performance positively correlated with FC in the CEN, and negatively with FC in the DMN.

Nota bene, T0 (baseline) is called T1 in this study and so forth, we keep our nomination throughout the current scoping review: T0: baseline, T1: first point of measurement, T2: second point of measurement, etc.

45. 🧠 vs. 🚶O_2 📶/📶 ⟷ 🧲f [RS-fMRI; Suppl. Table 5] [85]. This study by Gu et al. (2021), compared the effect of multi-domain cognitive training (EG1) vs. aerobic training (EG2) on FC. Both regimens took place twice weekly over 12 weeks; the approaches were not combined. EG1 received an hour of varied cognitive training (see Supplementary Table 5 for details). EG2 engaged in aerobic training (brisk walking), for up to 40 minutes. The fact that EG2 received shorter training biases comparison. EG1, EG2, and a CON received lectures on healthy living. The authors investigated differences in FC of the entorhinal cortex (from now on EC-FC) comparing EG1, EG2, and the CON, at 12 months after intervention completion, representing a delayed measure (T1). The entorhinal cortex situated in the medial temporal lobe is a hub for memory, navigation, and time perception, one of the first structures to degrade with Alzheimer's disease [149]. Comparing EG2 to EG1, increase in EC-FC for EG2 (aerobic training) showed in bilateral MTG, R supramarginal gyrus, L angular gyrus and R postcentral gyrus. Comparing EG1 with the CON showed decreased EC-FC in the R Hc, R MTG, left angular gyrus, R postcentral gyrus and increased EC-FC with the bilateral pallidum. Comparing EG2 to the CON displayed increased EC-FC with the R mPFC, bilateral pallidum and R precuneus. At baseline, EC-FC correlated with R mPFC and with the visuospatial/construction index score of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, see Table 3). Comparing T1 (12-month delayed measure) to T0 for EG1, EC-FC increase with the R Hc negatively correlated with improved RBANS delayed memory index score, indicating improved efficiency, demanding fewer

resources. Comparing T1 to T0 for EG2, EC-FC increase with the L angular gyrus positively correlated with the improved RBANS attention index scores, indicating enhanced verbal memory and attention. So, both cognitive training and aerobic exercise modified FC of the EC after a delay of 12 months, but through different neural pathways.

46. 🏃O_2 🧠 📶 $\xleftrightarrow{L}$ ⊸s [DTI; Suppl. Table 5] [150]. Mendez Colmenares et al. (2021) compared aerobic walking (with and without nutritional supplements, merged into one group; EG1), and aerobic adaptive dancing (EG2), the latter comprising cognitive and social components (four dances learned per session) to a non-aerobic active CON (flexibility, strength, and balance). All interventions lasted six months and took place three times per week for one hour (building up gradually over the first six weeks). EG1 and EG2 together compared to the CON showed an increase of total WM volume (whole brain), and in the genu of the corpus callosum (CC) and less decrease in the splenium of the CC, forceps minor, cingulum and superior longitudinal fasciculus. Compared to the control group (CON), EG1 (aerobic walking) had a more positive impact on white matter (WM) regions than EG2 (see Supplementary Table 5 for details). However, this apparent advantage could be attributed to EG1's larger sample size (n=86) after merging, compared to EG2's smaller sample size (n=51), leading to increased statistical power. For EG1 only, improved episodic memory (part of the Virginia Cognitive Aging Project (VCAP) battery), correlated to total WM volume and volume of the genu of the CC. No significant correlations with cardiorespiratory fitness or WM manifested. In the CON a consistent pattern of WM decline occurred.

47,48,49.🏃O_2 🧠 🌅☾ 📶/📶 $\xleftrightarrow{L}$ ⊸s ⊸f [VBM, automated segmentation, BDNF plasma levels; Suppl. Table 5] [79-81]. Muller (2017) and Rehfeld and colleagues (2017, 2018), compared the effects of six to eighteen months of adaptive dance training (EG1) to a sports group (EG2) that received fitness strength, flexibility, and endurance training. Training (90 minutes) took place twice a week for the first six months, and once a week for the last twelve months. In the EG2 20 minutes on 90 minutes concerned endurance training, thus involving a certain level of aerobic exercise. Different analyses were applied, at two time points: six months (T1) and eighteen months (T2) after training onset.

[VBM, BDNF plasma levels] Muller et al. (2017) [79]), comparing EG1 to EG2 showed that the L precentral gyrus's GM volume (VBM) increased in EG1, then remained stable between T1 and T2. Increased BDNF plasma levels at T1 probably drove this GM structural plasticity effect, as BDNF returned to pre-intervention level at T2. Between T1 and T2, the dancers' right parahippocampal gyrus exhibited a supplementary increase in GM volume. Then, in both groups 1) cardiovascular fitness levels remained constant over time and 2) verbal long- and short-term memory scores (VLMT) increased consistently over time. There were no correlations between neuroplasticity and behavioral measures.

[VBM, automated segmentation] In Rehfeld et al. (2017) [80], after 18 months, applying VBM with a Hc mask [automated segmentation], GM volume increase occurred exclusively in EG1 in the R Hc. ROI analyses in four subfields of the Hc, showed a mean effect of time, with GM volume increase in both groups in the L cornu ammonis (CA1), L CA2, R subiculum and L CA4/dentate gyrus. Post-hoc t-tests for each group separately over time (T2 *vs.* T0) revealed that EG1 exhibited GM increase in the L CA1, L CA2, L CA4/dentate gyrus and bilateral subiculum. For EG2 GM increases showed in L CA1, L CA2 and L subiculum. Comparing groups over time (T2 *vs.* T0) only disclosed an increased composite balance score for EG1. Correlation analysis between all Hc subfields and balance yielded no significant results irrespective of whether the groups were analyzed separately or jointly.

[VBM, BDNF plasma levels] Rehfeld et al. (2018) [81], only analyzed the first 6-month period (T1). Because attrition occurred after six months, these analyses enclosed more participants (see Suppl. Table 5), providing greater statistical power. The analyses now also comprised an extensive neuropsychological battery. Also, a more recent voxel-based morphometry analysis for pairwise longitudinal group comparison was applied. Comparing EG1 to EG2 over time, stronger increase of GM volume in frontal and temporal cortices, ACC, medial cingulate cortex, L insula, L STG, SMA, L pre- and post-central gyrus showed in EG1. Comparing EG2 to EG1 over time revealed specific GM volume increase in EG2 in occipital and cerebellar regions. White matter changes (VBM) over time in EG1 showed increase in the truncus and splenium of the corpus callosum and in bilateral frontal and R parietal WM. For EG2, there was greater WM volume increase in R temporal and occipital regions over time. Like in Muller et al (2017), BDNF levels rose in EG1 after six months. In these new analyses over six months on more participants, enhanced aerobic fitness reached significance for both groups post-training (T1). For cognition, only one test out of the psychometric battery, visuospatial memory, displayed enhanced scores after training in both groups. No correlations between neuroplasticity and cognitive behavior expressed.

Notably, as these three studies rely on the same experimental plan, it is probable that Muller et al. (2017) [79] and Rehfeld et al. (2017) [80] did not report on the extensive neuropsychological battery, because there were no significant results. In the Rehfeld 2018 study [81], with more participants following less attrition, only one out of many tests showed a significant difference for merged EG1 and EG2.

50. 🧠 🖥 🏃O_2 📊 ↔ S f [VBM, DTI & Task fMRI; Suppl. Table 5] [65]. Takeuchi et al. (2020) compared the effects of a 3-month computerized working memory training simultaneously performed with aerobic training on a recumbent ergocycle (EG, dual-task; three times an hour per week), to working memory training (CON1) or aerobic training alone (CON2). They analyzed WM & GM brain structure with DTI and functional brain activations during a 2-back working memory fMRI task using numbers. Comparing the EG to the two CON over time, no GM volume differences nor significant results concerning FA occurred. However, MD [DTI] decrease showed in the dual-task group

compared to the two single-task groups in widely distributed brain areas (R OFC, L Hc, midbrain areas, L basal ganglia, areas nearby R dlPFC and dorsal anterior cingulate cortex (dACC)), however, without correlation to general cognitive functions. Compared to the other two groups, the dual-task group showed increased fMRI BOLD activity in attentional reorientation regions (R TPJ and R STG) associated with better 2-back accuracy (during fMRI) and to improved EF (out-of-scanner).

6. Combined cognitive and physical non-aerobic interventions

51. 🚶 🧠 ⌒ ☾ ▯ ⟷ ⊸s [VBM; Suppl. Table 6] [111]. Boyke et al. (2008) investigated whether HE can still learn to juggle with three balls for at least 60 seconds over a period of three months and whether this is accompanied by transient selective structural plasticity like in young adults [151]. On an initial 44 non-juggler HE only 25 met the inclusion criterion of minimum 40-60 seconds of successful juggling with three balls. The participants trained daily. This group was compared to an equal size passive CON (n=25). Comparison of the groups over time, directly after training (three months), showed GM concentration (density) increase in middle temporal area of the visual cortex (hMT/V5), L frontal and cingulate cortices, R precentral gyrus and L Hc; there was also GM increase in R Hc and bilateral nuclei accumbens. After a 3-month delay however, these plasticity effects disappeared. Only 23% of the HE succeeded in juggling for > 60 seconds, whereas in an earlier study 100% of 20-year-olds achieved this goal [152]. Nevertheless, the (transient) plasticity results after three months comparing HE vs. young adults, were remarkably similar concerning GM changes in the hMT/V5, despite the differences in behavioral success rate. The improvement in juggling performance did not correlate to the GM changes.

52,53,54,55. 🧠 🚶 ▯ ⟷ ⊸s ⊸f [DTI, RS-fMRI; Suppl. Table 6] [59, 60, 86, 87]. An intervention applying four different types of analysis investigated the effect of a moderately intensive 3-month non-computerized multi-domain cognitive intervention (memory, reasoning, problem-solving and visual-spatial skill training (map reading)), combined with additional handicraft and other non-aerobic physical training (whole body stretching). Interventions took place for one hour, twice per week. All final analyses concerned measures taken one year after training completion (delayed measure).

[DTI; Suppl. Table 6] [59]. X. Cao et al. (2016) compared this multi-domain cognitive and physical training (EG1) to a single-domain cognitive intervention (EG2, reasoning training) and a control group (CON). All three groups received some lectures on healthy living. Baseline behavioral/cognitive performance and brain measures were compared to delayed post-training measures, a full year after training completion; no measures were taken directly after training completion (three months). Cao et al. (2016b) reported decrease of AD and stable MD, RD and FA in EG1 at the delayed post-training measures, and increased CMMSE scores (Chinese version of the MMSE), but no direct correlations arose between brain and behavioral data. Comparing EG1 directly to EG2 revealed positive effects in posterior parietal WM (decreased RD in the corona radiata) for EG1, positively correlating to the Color Trials Test-1 (CTT-1) performance (evaluating visual processing speed). The CON showed FA decrease in temporal areas, and MD and RD increase.

[RS-fMRI; Suppl. Table 6] [86]. Deng et al. (2019), using the same experimental settings and time-points as Cao et al. (2016) [59], reported more integrated local FC in HE, more similar to that of young adults, at the delayed post-training measure in both EGs. So, in contrast to the preceding analysis, multi-domain training did not provoke stronger results. A subcortical cerebellar (Cb) network showed the strongest training merging EG1 and EG2, vs. control effects. At baseline, local FC integration was positively correlated with educational level. No brain-behavior relationships established as a function of training.

[RS-fMRI; Suppl. Table 6] [87]. In W. Cao et al. (2016), the 3-month multi-domain cognitive intervention (EG) was compared to the CON. The time-points of data collection were identical. The authors applied seed-based RS-fMRI in three higher order brain networks: the DMN (seed: PCgC), the SN (seed: R AI) and the CEN (seed: R dlPFC). They observed increased FC comparing the EG to the CON before and after training (delayed measure) in all three networks. In the EG, comparing baseline to the delayed measure, RBANS performance and FC between R dlPFC (CEN) and R SFG correlated positively. RBANS stands for Repeatable Battery for the Assessment of Neuropsychological Status and measures cognitive decline or improvement (see Table 3).

[RS-fMRI ; Suppl. Table 6] [60]. Luo et al. (2016) also only compared the multi-domain group (EG1) to the CON. The time-points of data collection were the same. This sub-study analyzed lateralization in 10 common resting-state fMRI networks. Notably, some resting-state networks are symmetrical (DMN, sensorimotor network, etc.), while others like the frontoparietal and attention networks are asymmetrical in healthy young adults. The so-called laterality cofactor quantifies the lateralization. Two networks, the R and L frontoparietal networks showed better-conserved lateralization effects, more similar to young adults, in HE after training compared to the CON. No behavioral results were reported.

56. 🧠🚶🌅🌙📶 ⟷ f [Task fMRI, RS-fMRI; Suppl. Table 6] [38]. Guo et al. (2021) compared a 4-month music instrument (32-key keyboard harmonica) weekly training provided in large groups (n=15; EG), plus daily homework ("as much as possible"), to a passive control group (wait list). The participants were initially musically naïve. Behavioral measures involved lifestyle, general cognition (MMSE), memory (digit span forward – digit span backward (DSF-DSB); the Wechsler Memory Scale Logical Memory (WMS-LM I; immediate verbal recall & WMS-LM II delayed verbal recall)), manual dexterity, as well as a well-being and a distress scale.

Post-training findings from the fMRI visual working memory task (0- and 1-back face stimuli) in the EG revealed a decline in brain activation in the R SMA, L precuneus, and bilateral PCgG during the 1-

back task. However, these changes were not correlated with in-scanner behavioral scores. No significant Group x Time Interaction occurred for the in-scanner behavioral results, potentially because of a ceiling effect for the simple visual 1-back face stimuli task.

Among all behavioral measures (n=13), only WMS-LM II (delayed verbal recall) showed stronger improvement in the intervention group than in the CON over time.

Comparing the EG to the CON, results from the seed-based RS-MRI showed decreased FC over time between R PCgG (seed, DMN) and L MTG, and between L putamen (seed) and R STG, during the 1-back visual working memory task.

Moreover, comparing EG post-training to baseline revealed improved memory performance (DSF-DSB and WMS-LM II), linked to reduced FC between the L putamen and R STG .

57,58,59,60. 🧠 🚶 🌅🌙 📶 $\overset{L}{\longleftrightarrow}$ **S** [DTI, SBM, VBM; Suppl. Table 6] [90-93]. Jünemann et al. (2022 [90]), Worschech et al. (2022 and 2023 [92, 93]), and Marie et al. (2023 [91]) all pertain to the same research project [8]. After stratified randomization at two sites (Switzerland, Germany; over 150 musically naïve HE either learned to play the piano (EG1) or received musical culture lessons (EG2; analytical listening, learning about music) over twelve months. Each analysis comprised slightly different numbers of participants, due to missing data. A limitation of the study is the absence of a passive control group.

[DTI; see Suppl. Table 6] [90]. Junemann et al. (2022) examined white matter in 121 participants over a six-month period. Utilizing Fixel-Based Analysis, eight specific neural pathways, or Tracts of Interest (TOIs)—including the corpus callosum (CC), fornix, left and right acoustic radiations, left and right corticospinal tracts, and left and right arcuate fasciculus—were investigated. The study found that Experimental Group 1 (EG1) exhibited stable microstructural integrity in the body of the fornix, as indicated by subvoxel-level results from Fixel-Based Analysis [153]. In contrast, Experimental Group 2 (EG2) showed a significant decline in the same area. In EG1, microstructure volume in the body of the fornix correlated positively to practice intensity (homework amount in minutes per week). For both groups taken together, volume increase of microstructure in the body of the fornix over six months correlated to an improved score on the delayed Rey Auditory Verbal Learning Test (long term memory for wordlists). Playing a simple 5-tone scale with all five fingers of the right hand on the piano keyboard [154] improved more over time in EG1 than in EG2.

[SBM; see Suppl. Table 6] [92]. Worschech et al. (2022) analyzed 134 participants' data using Bayesian Multilevel Modeling (BMLM). Interaction between the groups over time revealed CT increase in EG1 in L anterior Heschl's gyrus, L planum polare, bilateral superior temporal sulcus, and R Heschl's sulcus compared to EG2. EG2 displayed the opposite pattern, with CT decrease in these five auditory areas. Speech in noise performance (International Matrix Test [155]) at baseline -in all participants- could predict CT of R anterior Heschl's gyrus and several other of the auditory ROIs. A former behavioral analysis [115] within the same research project could show speech in noise perception improvement in both groups when the stimuli were presented in both ears, whereas an advantage for the piano group showed when the stimuli were presented in the left ear (thus essentially processed in the right auditory cortices).

[VBM see Suppl. Table 6] [93]. In another analysis, Worschech et al. (2023) examined the influence of the musical training regimens on fine motor skills, and its connections with cognition and gray matter brain changes in three bilateral motor-related areas (M1 (primary motor cortex), thalamus, putamen), at both the 6-month and 12-month (end-of-training) intervals using BMLM. No distinct gray matter volume changes in the ROIs occurred in both groups over time (interaction effects). At T2 compared to T0, EG1 showed, compared to EG2, superior improvement in fine uni and bimanual motor skills (Purdue Pegboard) and working memory (DSB). Specifically, within EG1, unimanual fine hand motor skills and contralateral M1 gray matter volume were simultaneously enhanced over the 6–12-month period. In EG1, largely distributed cortico-basal ganglia-thalamus coupling occurred between ipsilateral R ROIs and L ROIs; in EG2, this effect was much less widely spread.

[VBM] Marie et al. (2023) [91] could show an improvement of tonal working memory [156] in participants from both music education groups, after six months, associated with gray matter volume increase in bilateral Cb (Lobule VIII and IX). Additional increase in gray matter in the L caudate nucleus & R Rolandic operculum could not be associated with working memory. Other explanatory variables for the improved tonal memory score were the total number of lessons followed, practice intensity (minutes per week), and amount of sleep. Another measure of auditory working memory, DSB scores, also improved but did not relate to the brain changes. Additionally, in EG1, a segment of the right primary auditory cortex (the koniocortical field) exhibited preserved gray matter volume over the span of six months, whereas the control group experienced a significant reduction in volume. Despite these specific positive results, generalized fronto-temporo-parietal gray matter volume atrophy occurred in remaining cortices, consistent with the literature. In summary, these findings indicate that both practicing the piano and engaging in analytical listening can enhance working memory and the related neural structures in HE.

61,62. 🧠 🌅🌙 🖥 🚶 📶 $\xleftrightarrow{S}$ f [RS-fMRI; Suppl. Table 6] [58, 94]. Li et al. (2014) [58] compared the effects on regional FC within the DMN of an EG to a CON. The EG received intensive 6-week multimodal cognitive (associative memory (i.e. Method of Loci) and computerized EF interventions (computerized; three hours per week) as well as body-mind (TCC) training (an additional three hours per week) along with weekly group counseling (90 minutes per week). So, the interventions occupied 7.5 hours per week. The CON received two lectures on health and aging during the same 6-week period. Before and after training, all participants passed a large psychometric battery, including social parameters. The multimodal training strongly increased regional FC between the mPFC (DMN) and the L paraHc complex compared to the CON. The level of FC between mPFC and L paraHc complex correlated with individual trail making test (TMT) scores (evaluating attention, processing speed, and switching). This multimodal intervention integrating cognitive, body-mind training and social support (group counseling) strengthened resting-state FC between the mPFC (part of the DMN) and the L paraHc complex (medial temporal lobe).

[RS-fMRI; Suppl. Table 6] [94]. Using the exact same experimental plan, Zheng et al. (2015) compared regional homogeneity (ReHo) that evaluates local temporal synchronizations of spontaneous low frequency BOLD signals. After the intervention period, the EG showed increased ReHo maps in the L STG & and in the L posterior Cb versus decreased ReHo maps in L MTG. In contrast, the CON displayed the opposite pattern: decreased ReHo maps in L STG & L posterior Cb, and increased ReHo maps in bilateral MTG. Regression analyses in the EG revealed that local spontaneous resting-state activity (BOLD activity) in L STG and R MTG predicted verbal category fluency and associative learning respectively.

In both studies [58, 94], in comparison to the CON, the EG achieved higher scores in the paired associative learning test (PALT), the social support rating scale (SSRS) and in physical vitality after the intervention without correlation to brain data.

63,64. 🚶 ☀☾ 📶 ↔ ⊙f [RS-fMRI; Suppl. Table 6] [97, 98]. Liu (2019), Tao (2016) and colleagues examined whether two different body-mind techniques TCC versus BDJ exerted a distinct effect on resting-state functional connectivity and memory function. In both studies. EG1 received TCC exercise [27], EG2 BDJ exercises [157] and a passive CON just some basic health education at the beginning of the experiment. Baduanjin is a similar, but less physically and mentally demanding practice than TCC. The training lasted three months and was intensive: 1h per day, five times per week. Behavioral testing consisted in measuring different memory functions using the Wechsler Memory Scale-Chinese Revision (WMS-CR, mean score MQ: memory quotient).

[RS-fMRI; Suppl. Table 6] [97]. Liu et al. (2019), applying seed-to-voxel analyses, evaluating EG1 development over time, found increased FC between PCgC (seed) and R putamen/caudate, and between mPFC (seed) and R temporal gyrus. Evaluating EG2 over time, decreased FC showed between mPFC and R orbital prefrontal gyrus and the putamen. PCgC and mPFC seeds are both part of the DMN. Comparing EG1 to EG2 over time displayed increased FC between mPFC and putamen/caudate, the opposite comparison did not yield significant results. Both groups improved their MQ scores. However, no relationships between MQ scores and FC changes manifested.

[RS-fMRI; Suppl. Table 6] [98]. Tao et al. (2016), also used seed-to-voxel analyses. Seeds now were the R and L Hc. Like in Liu et al., behavioral testing consisted of the WMS-CR. As this is the same study as Liu and al., improved MQ scores are reported again for both groups. Comparing the EG1 to the CON over time resulted in FC increase between bilateral Hc and mPFC. A direct comparison between EG1 and EG2 yielded no significant FC differences. FC increase between bilateral Hc and mPFC was positively associated with the memory quotient across all subjects, but the FC increase was only significant for the TCC training that thus seems to exert a stronger effect on functional brain plasticity.

65.66. 🧠 🖥 🚶 📶 ↔ ⊸s [SBM, manual segmentation & DTI; Suppl. Table 6] [100, 101]. In Lovden et al. (2012) [101] and Wenger et al. (2012) [100], four months of moderately intensive (50 minutes every other day) spatial navigation training in a virtual environment while simultaneously walking on a treadmill *in men only* (EG), was compared to walking on a treadmill alone (CON). In both groups walking was non-aerobic, participants walked at a comfortable speed.

[SBM; Suppl. Table 6] [100]. In Wenger et al. (2012), the EG showed less cortical thickness (CT) decrease in the right middle frontal gyrus (R MFG) after training completion compared to the CON, but after a 4-month delay, this training advantage faded.

[fMRI, Manual segmentation, DTI; Suppl. Table 6] [101]. Lovden et al. (2012) applied region of Interest (ROI) analyses in bilateral Hc and showed that after the 4-month training GM remained stable in bilateral Hc in the EG, remaining quite stable also after the 4-month delay, whereas the active CON showed progressive decline consistent with longitudinal estimates of age-related decline. Mean diffusivity (MD) [DTI] decreased in the R Hc in the EG post-training, also a positive training effect, but returned to baseline after the 4-month delay. In the active CON, GM atrophy also manifested in the R MFG after training completion and no MD changes occurred. Although navigation performance improved after training completion, no significant relationships arose with other cognitive tests, CT change in the R MFG, Hc volume, or MD.

In both studies [100, 101], gain in spatial navigation partially persisted after the 4-month delay, whereas the active control group showed progressive decline.

67. 🧠 🚶 ☾ 🖥 📶 ↔ ⊸f [Task-fMRI; Suppl. Table 6] [39]. In McDonough et al. (2015), high-challenging digital real-life adaptive interventions (EG) were compared to low-challenging non-adaptive ones (CON). The EG was divided in three subgroups: a) digital photography, b) quilting (on computerized sewing machines), and c) both "dual group". The active CON consisted of two subgroups supposed not to contain an active learning component: a) social themed activities (cooking, traveling related topics, etc.), & b) placebo group (music listening, playing simple games, watching movies). All groups exercised at least 15 hours per week over 14 weeks. Participants were randomly assigned to the EG or CON subgroups, but within the EG, participants could refuse one of the three sub-conditions (the study is thus a quasi-RCT). Both groups were committed to the activities for 15 hours per week. An fMRI semantic classification task (living *vs.* non-living) comprised two levels of difficulty (easy *vs.* hard). Behavioral out-of-scanner tasks evaluated verbal recall and fluency.

Contrasting the three EG (grouped) to the two CON (grouped) comparing post-training to baseline, and the hard to the easy fMRI condition, the EG showed activation increases in 11 clusters in frontal, temporal, and parietal cortices. Comparing EG to CON over time in each of those 11 clusters exhibited increased activation in the EG in L intraparietal sulcus, L MTG, R ITG, L mid cingulate gyrus & R precuneus. No post-hoc group differences manifested for the fMRI task. But in the EG, the relative fMRI BOLD increases resulting from the comparison of hard to easy fMRI task items, correlated with training time, age, and cognition (verbal fluency). Then, increase in verbal fluency in the EG correlated to brain activity increase in R ITG.

A delayed fMRI test one year after training completion on approximately two-thirds of the population demonstrated remaining BOLD increases in the EG in the L intraparietal sulcus, the L MTG & R ITG.

68. 🚶 🧠 📶 $\overset{S}{\longleftrightarrow}$ ⊸f [fMRI; Suppl. Table 6] [102]. Naito et al. (2021) studied whether complex bimanual digit training (EG1), comprising simultaneous divergent finger movements with the right and left hand, thus involving a cognitive constituent, could improve right hand/finger dexterity in HE, as compared to right-hand digit training alone (EG2). Complex bimanual exercises may train the interhemispheric inhibitory system, and thus improve deteriorated hand/finger dexterity in HE. Before and after training right-hand finger dexterity was measured using a peg task. During fMRI (before and after training), blindfolded participants experienced a kinesthetic illusory movement of the right-hand (via muscle afferent input) without performing any motor tasks, for measuring ipsilateral motor-cortical inhibition. After training, only EG1 showed a right-hand finger dexterity improvement correlated with a reduction in ipsilateral motor-cortical activity. So, decline of sensorimotor and associated cognitive function of the right hand can be improved by bimanual complex training tasks facilitating interregional brain communications, but not by right-hand training alone.

69. 🧠 🧘 ☾ 📶 $\overset{S}{\longleftrightarrow}$ ⊸f [RS-fMRI; Suppl. Table 6] [103]. Shao et al. (2016), compared meditation (EG) to relaxation (CON) training over eight weeks, approximately three times 90 minutes per week, using seed-based (PCgC/precuneus) FC RS-fMRI, and a behavioral out-of-scanner emotion processing task (valence and arousal). The aim of the study was to investigate the influence of meditation on brain FC and affective regulation. Meditation also involves mastery of bodily position and breathing. Comparing both groups over time, the EG showed increased FC between the PCgG /precuneus (seed; part of the DMN) and the pons. Comparing the groups over time for the emotion processing task disclosed less extreme valence ratings in the EG: more positive ratings of negative pictures and fewer positive ratings of positive pictures. Moreover, the same interaction effect showed decreased arousal ratings in the EG. Changes in FC between the PCgC/precuneus and pons predicted changes in affective processing after meditation training.

70. 🧠 🖥 🚶 📶 $\overset{L}{\longleftrightarrow}$ ⊸s [VBM; Suppl. Table 6] [51]. West et al. (2017) compared a 3D video game intervention (Super Mario 64, Nintendo Wii) to computerized piano training and a passive CON over six months [51]. Both EGs received five times 30 minutes training per week. GM density analyses

performed within three ROIs, the Hc, dlPFC and Cb, revealed that Super Mario video-gaming increased GM in bilateral Hc and L Cb compared to computerized music (piano) training. In comparison, the music group showed specific GM increase in the R dlPFC and R Cb compared to the passive CON. In contrast, in the passive CON GM decrease manifested in bilateral Hc, R dlPFC and bilateral cerebellum. Finally, only in the gaming group, a positive correlation between GM increase in the L Hc and improvement of short-term memory performance appeared.

DATA AVAILABILITY STATEMENT

The data used to write this scoping review consists of the 70 discussed publications. All findings of this review are available within the article and its supplementary materials.

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Appendix 1

CONCEPT DEFINITIONS

To facilitate the reading of this scoping review to a broad readership, including different professionals potentially not familiar with psychological or neuroscientific concepts, we provide some elementary concept definitions.

Transfer of learning involves the influence of past learning on present functioning. It consists of the partial or total carryover of abilities, skills, and knowledge learned in one circumstance to another [158]. A distinction should be made between near and far transfer, even if the two mechanisms may overlap to some extent. No agreement exists about the exact essence of far transfer, which simply means that improved skills stretch beyond the limits of the trained domain [159]. In contrast, near transfer takes place between closely linked abilities. Interventions aiming to address age-related degeneration of function, focus on far transfer of learning to ADL [7]. An example of near transfer is improved bimanual fine finger dexterity in children after learning to play string instruments in a group setting over two years, an example of far transfer improved abstract reasoning in the same children [89]

Adaptive training is a form of individualized training, which adapts the stimulus or task as a function of the participant's performance or provides feedback on that performance. It may, e.g., concern task complexity, or ISIs (interstimulus intervals). As a result, it offers effective and individualized learning paths to motivate each participant throughout the learning process and maintains a challenging learning environment at all stages.

Experience-driven brain plasticity involves an adaptation of brain substrates following new and enduring experiences. For gray matter, such plasticity in elderly adults is essentially due to changes of neuropil. Neuropil is the complex net of axonal, dendritic, and glial branchings as well as capillaries, which together form the bulk of the central nervous system gray matter of the brain in which the nerve cell bodies are embedded [160, 161]. However, intrinsic cell mechanisms driven by epigenetic information storage may also play an important role [162], but this kind of mechanism transcends the scope of this publication.

Plasticity of white matter, not considered part of neuropil, principally derives from changes in the brain's myelin distribution [163, 164]. These two types of morphological brain changes (gray *vs.* white matter) are typically analyzed independently. Yet, they represent distinct facets of the same neuroplastic processes and are thus fundamentally entangled in a complex manner [12].

These structural changes may be accompanied by modulation of task-related functional brain activity (fMRI), resting-state functional connectivity (RS-fMRI), and plasticity of behavior [10, 165]. The macroscopic analyses in the studies discussed in this scoping review do not allow drawing any valid conclusions on the precise underlying microscopic mechanisms that drive brain plasticity. For an outline of the relationship between macroscopic measurements and fundamental physiology, see [13].

Appendix 2

To facilitate the reading of this scoping review to a broad readership, including different health professionals, we provide a short introduction to the MRI techniques and measures used in the discussed studies.

Structural brain plasticity

Gray matter

Brain morphometry of gray matter (GM) operates on structural images acquired with T1-weighted high-resolution 3D sequences, for instance, a T1 weighted gradient echo pulse sequence, an MPRAGE (magnetization-prepared rapid acquisition of gradient echoes) [166] or the more advanced (improved grey-white matter contrast and higher resolution) MP2RAGE [167, 168]. T1 (longitudinal relaxation time) is the time constant that determines the rate at which excited protons return to equilibrium that differs across different tissue types.

In essence, two techniques are relevant for this review [169]. First, voxel-based morphometry (VBM) compares GM density or concentration (probabilistic) or GM volume (quantitative) of distinct populations. It is well-established for evaluating learning effects [170], but has also been applied in very different domains of activity such as juggling, learning to golf, making music, driving taxis, developmental language disorders, schizophrenia, etc. [111, 171-179]. Nowadays, manual brain segmentation and automatized voxel-based morphometry GM volume measurements, provide highly similar results [180].

Second, surface-based morphometry (SBM) can extract cortical thickness (CT), which is confounded in VBM measures, yet, volume and thickness are independent neuroanatomical traits [181, 182]. Cortical thickness has been used to evaluate neuroplasticity following learning in longitudinal studies [183-185].

White matter

Diffusion weighted imaging (DWI) is a magnetic resonance imaging modality used to assess the properties of water diffusion (diffusivity) within the brain. Due to the ease with which water moves down the cytoplasm of long cylindrical neural axons, water diffusion occurs along the axons in white matter (WM). This allows measuring axon tract directions and delineating WM regions, resulting in white matter orientation and volume measurements.

Diffusion tensor imaging (DTI) is one popular way that DWI data can be summarized into classical diffusivity characteristics (FA, MD, AD, RD, see next paragraph), it is essential considering the development of various diffusivity parameters over the lifespan, to correctly interpret changes following interventions in HE. This WM plasticity results in an increase of myelin sheet thickness and alignment of myelinated nerve fibers.

For fractional anisotropy (FA), and mean, axial, and radial diffusivity (MD, AD, RD), different patterns of development occur over the lifespan [117]. Moreover, patterns of decline (increase or decrease) may be region-specific. Nevertheless, globally after 55y, a marked decrease in FA and increase in RD manifests, as well as a minor increase in AD and moderate increase of MD.

Tract-based Spatial Statistics (TBSS), a suite of tools for analyzing diffusion data using a tensor-fitting method, may be used to extract diffusion data [186].

WM can also be measured using VBM, automated or manual brain segmentation [170, 187].

Novel approaches, like fixel-based analyses, allow modeling multiple fiber populations within the same voxel providing microscopic information, identifying sub-voxel entities dubbed "fixels" [153, 188].

Functional brain plasticity

Task-related fMRI

Task-based functional MRI (fMRI) is widely used nowadays in longitudinal studies to identify brain plasticity of regions that are activated during a specific task [189]. Due to neurovascular coupling, when neuronal activity increases, the vascular system overcompensates the demand in oxygen by increased blood flow to the active regions. Hemoglobin is diamagnetic when oxygenated; however, it is paramagnetic when deoxygenated. Due to this difference in magnetic properties, the MR signal of blood varies slightly with oxygenation level. The blood-oxygenation-level-dependent (BOLD) signal that is picked up by fMRI is then acting as a proxy for neuronal activity [190].

RS-fMRI

Resting-state functional MRI (RS-fMRI) probes the brain's functional architecture and connectivity patterns by investigating spontaneous fluctuations of the BOLD signals. This technique has been used to identify a repertoire of resting-state networks (RSNs) that regroup spatially distinct areas of the brain that exhibit coherent fluctuations at rest [191]. RS-fMRI allows investigating the intrinsic segregation or specialization of brain regions/networks on a functional level [192]. The most used measure is FC.

A few of the canonical RSNs relevant for our review include the default mode network (DMN), the central executive network (CEN; also called executive control network (ECN)), and the salience network (SN), which are three of the most investigated large-scale brain functional networks [193]. The mPFC, the posterior cingulate cortex (PCgC) and the inferior parietal lobule (IPL) are the DMN's primary nodes. The DMN is the largest network and critical for a variety of self-referential emotional and cognitive functions [194, 195]. The CEN, responsible for higher executive and cognitive functions, mainly consists of the dlPFC and the posterior parietal cortex (PPC). The SN’s main nodes are the insular cortex and the anterior cingulate cortex (ACC). This network is critical for identifying significant information and for switching between the CEN and the DMN [193, 196-198]

Arterial Spin Labeling

Arterial Spin Labeling (ASL) is another functional MRI method that assesses and quantifies tissue perfusion and collateral blood flow in the brain by using a freely diffusible intrinsic tracer, usually water. For an extensive review, we refer to [130, 199].

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Captions:

Figure 1. Neuroprotection against aging. This diagram illustrates the influence of various NPIs on ADL. In this visual representation, Each NPI type is represented by a circle, with the circle's diameter indicating the general influence of the NPI on brain and behavioral changes, while the extent of overlap with the ADL domain signifies the strength of transfer effects following the interventions. Cognitive interventions are depicted in yellow, physical interventions in blue and combined interventions in green.

Table 1: Keyword classification and Data Items

Table 2: Search Examples

Table 3: Abbreviations

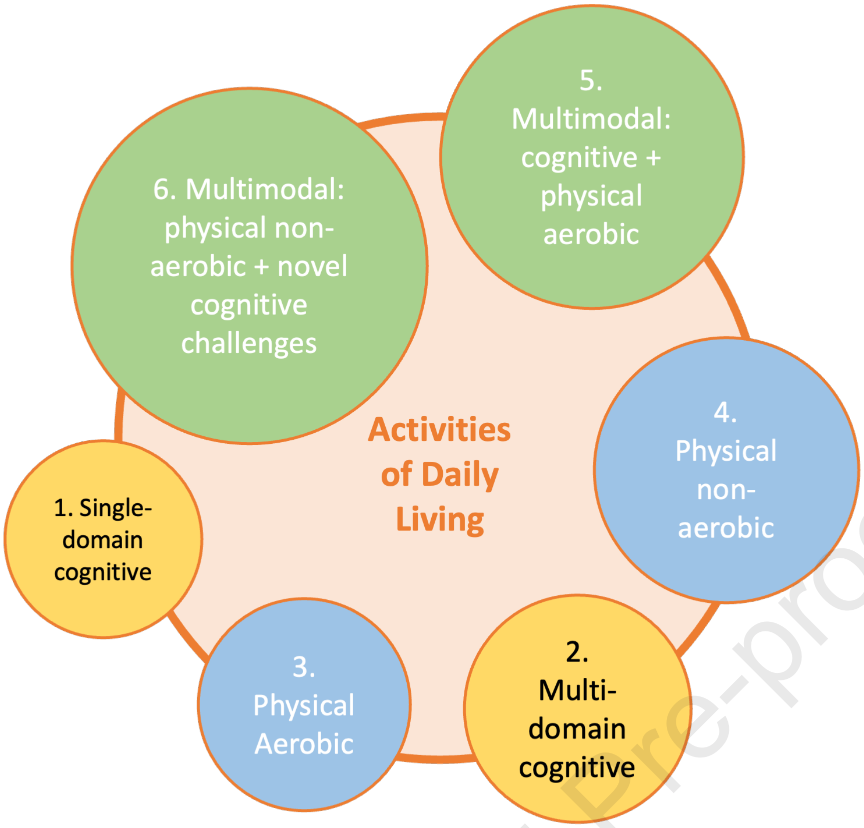
Table 4: Organization of Supplementary Tables 1-6

1. AGE • aging/ageing • healthy older adult • older adult • senior • elderly • healthy elderly • retirement/retired • adult • healthy	**4. TYPE OF ACTIVITY** • physical training • aerobic • non-aerobic • cognitive training • computerized training • real-life training • lifestyle • natural training • body-mind training	**6. BRAIN** • brain • networks • brain networks • brain plasticity • plasticity • functional brain changes • functional brain plasticity • functional brain connectivity • structural brain changes • structural brain plasticity • structural brain connectivity
2. METHOD • randomized • randomised • randomized controlled trial randomised controlled trial • rct • longitudinal	**5. SPECIFIC ACTIVITY** • dancing • music • music(al) practice • music(al) listening • tai-chi • baduanjin • yoga • chess • video game/gaming • serious game	**7. BRAIN MEASURE OR DERIVATE** • MRI/Magnetic Resonance Imaging • functional MRI/fMRI • structural MRI/sMRI • Resting State fMRI/RS-fMRI • Voxel based Morphometry/VBM • Surface based Morphometry/SBM • Cortical thicknessi/CT • Diffusion Tensor Imaging/DTI
3. ACTIVITY • intervention • training • regimen		**8. DOMAIN/EFFECTS** • cognitive • sensorimotor • perception • transfer • near transfer • far transfer

Search examples	**Number of publications**
ALL=("older adult") AND ALL=("randomized" OR "randomised") AND ALL=("training" OR "intervention") AND ALL=("brain" OR "MRI") AND ALL=("cognit*")	34
ALL=("older adult") AND ALL=("randomized" OR "randomised") AND ALL=("training" OR "gam*" OR "computer*") AND ALL=("brain" OR "MRI") AND ALL=("cognit*")	23
ALL=(("aging" OR "ageing" OR "older adults") AND ("healthy")) AND ALL=("randomi*") AND ALL=("training" OR "regimen") AND ALL=("danc*" OR "music*" OR "physical" OR "aerobic" OR "body-mind" OR "computerized") AND ALL=(("brain" OR "MRI" OR "fMRI") OR ("connectivity" OR "networks" OR "structural" OR "morphometry" OR "diffusion")) AND ALL=("cognit*" OR "sensorimotor*" OR "perception")	174

ACC: ant		
ACM: adaptive capacity model	**Hc**: hippocampus/hippocampal	**ReHo**: regional homogeneity, evaluates local temporal synchronizations of spontaneous low frequency BOLD signals
AD: axial diffusivity	**HcCB** = hippocampal cingulum bundle	**ROI**: region of interest
ADL: activities of daily living	**HADS**: Hospital Anxiety and Depression Scale	**RS-fMRI**: resting state functional magnetic resonance imaging; **RS**: resting state
AI: anterior insula	**HE**: healthy elderly persons	**SBM**: surface-based morphometry
ASL: arterial spin labeling, a functional MRI method that assesses tissue perfusion	**hMT/V5:** middle temporal area of the visual cortex	**SFG**: superior frontal gyrus
BDJ: baduanjin	**HRmax**: maximal heart rate	**SMA**: supplementary motor area
BDNF: Brain-Derived Neurotrophic Factor (growth factor)	**ICA**: Independent Component Analysis	**SMART**: Strategic Memory Advanced Reasoning Training
BMLM: bayesian multilevel modeling	**ICV**: intracranial volume	**sMRI:** structural MRI (cf. MPRAGE/MP2RAGE)
BOLD: blood-oxygen-level-dependent; fMRI imaging allows to observe brain activity in specific brain areas	**IFG**: inferior frontal gyrus	**SN**: salience network
CA: cornu ammonis	**ILF:** inferior longitudinal fasciculus	**SPC**: superior parietal cortex
CASI: cognitive abilities screening instrument	**IPC**: inferior parietal cortex	**SPL**: superior parietal lobule
Cb: cerebellum	**IPL**: inferior parietal lobule	**SSRS**: social support rating scale
CBF: cerebral blood flow; **rCBF:** regional cerebral blood flow; **rCBV**: regional cerebral blood volume	**ISI**: interstimulus interval	**STG**: superior temporal gyrus
CC: corpus callosum	**ITG**: inferior temporal gyrus	**T0**: baseline
CEN: central executive network (refers to the same network as the ECN)	**ITL**: inferior temporal lobe	**T1**: 1st post-training timepoint
CMMSE: Chinese version of the Mini Mental State Examination	**L:** Left	**T2**: 2nd post-training time point
COGPACK: computerized multi-domain cognitive training http://www.markersoftware.com/USA/frames.htm	**M1:** primary motor cortex	**T3**: 3rd post-training time point
CON: control group(s)	**MCI**: Mild Cognitive Impairment	**TBSS**: Tract-Based Spatial Statistics (tool for voxel-wise analysis of diffusion data)
CRF: cardiorespiratory fitness	**MD**: mean diffusivity	**TCC**: tai chi chuan
CVLT: California Verbal Learning Test	**Method of Loci**: serial word list learning, episodic memory strategy based on associations to familiar spatial environments	**TICV/TIV:** total intracranial volume
CT: cortical thickness	**MFG**: middle frontal gyrus	**TMT**: trail making test
CTT: color trails test; CTT-1 measures visual processing speed/attention, CTT-2 idem plus cognitive flexibility	**MMSE**: mini-mental state examination;	**TPJ**: temporoparietal junction
Cx: cortex	**MoCA**: Montréal Cognitive Assessment Scale	**UFOVt**: Useful Field of View training
dACC: dorsal anterior cingulate cortex	**MPRAGE/MP2RAGE**: Magnetization Prepared (2) Rapid Gradient Echoes: optimized/common MRI sequence for high-resolution T1 mapping (=**sMRI**)	**VBM**: voxel-based morphometry
dlPFC: dorsolateral prefrontal cortex	**mPFC:** medial prefrontal cortex	**VCAP**: Virginia Cognitive Aging Project battery
DMN: default mode network	**MRI:** Magnetic Resonance Imaging	**VLMT**: Verbal short- and long-term memory; German adaptation of the *Rey Auditory Verbal Learning Test (RAVLT)*
DSF-DSB: digit span forward – digit span backward	**MRSI:** Magnetic Resonance Spectroscopic Imaging	**VO_2 max**: maximum rate of oxygen consumption during incremental exercise
DTI: diffusion tensor imaging	**MTG**: middle temporal gyrus	**$VO_{2\ VAT}$**: oxygen consumption at the ventilatory threshold
EC: entorhinal cortex	**NPI**: Non-Pharmacological Interventions	**VO_{2peak}**: peak oxygen uptake
ECN: executive control network (refers to the same network as the CEN)	**OFC**: orbitofrontal cortex	**vlPFC**: ventrolateral prefrontal cortex
EF: executive function(s)	**PALT:** paired associative learning test	**WM**: white matter; **WMH**: WM hyperintensity; **PWMH:** periventricular WMH; **DWMH**: deep WMH **WMM:** WM microstructure
EG: experimental group(s)	**PCgC**: posterior cingulate cortex	**WMS-CR**: Wechsler Memory Scale-Chinese Revision
FA: fractional anisotropy	**PFC**: prefrontal cortex	
FD: fractal dimension (complexity of brain structures)	**PPC:** posterior parietal cortex	
FC: functional connectivity (derived from RS-fMRI)	**R:** Right	
FEN: frontal executive network	**RAVLT**: Rey Auditory Verbal Learning Test; German adaptation VLMT. verbal short- and long-term memory test	
FOV: field of view (spatial area in which a stimulus may receive attention) - **UFOV** useful FOV= FOV - **FFOV** functional FOV = area of FOV where visual information is effectively processed	**RBANS**: Repeatable Battery for the Assessment of Neuropsychological Status measures cognitive decline or improvement via 5 index scores: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory	
FPN: frontal parietal network	**RCT**: randomized controlled trial	

NPI classes 1-6						
Categories						
Author/year & Research question	**Population & Design**	**Nature and duration of intervention(s)**	**MRI measures/derivates; behavioral variables; time points**	**Main findings: brain plasticity**	**Main findings: behavior & relation to brain changes**	**Conclusions/ remarks**
Characteristics of NPI						
Reference	Sample size; Age range	Intervention description	Brain measure; computed derivates; Timepoints T0, T1, T2, etc.; delayed measures	Comparisons between groups and over time of brain derivates	Comparisons between groups and over time of behavioral variables	General conclusions, (critical) remarks
Research question	Randomization; Groups	Duration of intervention; Intensity of intervention	Behavioral tests description		Relationships between brain and behavioral measures	
Full references						


5. Multimodal: cognitive + physical aerobic
6. Multimodal: physical non-aerobic + novel cognitive challenges
Activities of Daily Living
4. Physical non-aerobic
1. Single-domain cognitive
3. Physical Aerobic
2. Multi-domain cognitive

Randomized Controlled Trials of Non-Pharmacological Interventions for Healthy Seniors: Effects on Cognitive Decline, Brain Plasticity and Activities of Daily Living—A 23-year Scoping Review

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: