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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.

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Results indicate that medium- and long-term interventions combining non-aerobic physical exercise and multi-domain cognitive interventions best stimulate neuroplasticity and protect against agerelated decline and that outcomes may transfer to 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.

## 1.1. 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.

## 1.2. 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  $\sim$ 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 the 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?

## 1.3. 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 yielded 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  $\geq$ 55 years<sup>22</sup> (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<sup>3</sup> (MRSI)

## 2.3. Information sources

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

## 2.3.1. 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.

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 2.3.2. 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.

 $<sup>^2</sup>$  According to the World Health Organization, old age begins at 55 (NIH Publication no. 11–7737).

<sup>&</sup>lt;sup>3</sup> MRSI, although related to MRI, primarily provides information about chemical composition and metabolites in tissues that have no direct relationship to behavior.

#### Table 1

Keyword classification and Data Items.

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

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.

## 2.3.2. Data charting process/data extraction

Our combined keyword research described in section 2.3.1 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 64 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.

## Table 2

Search examples.

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 "structural" OR "structural" OR "morphometry" OR "diffusion")) AND ALL=("cognit*" OR "structural" of "structural"	174

#### Table 3 Abbreviations.

ACC: anterior cingulate cortex ACM: adaptive capacity model

AD: axial diffusivity ADL: activities of daily living

AI: anterior insula

ASL: arterial spin labeling, a functional MRI method that assesses tissue perfusion BDJ: baduanjin

**BDNF**: Brain-Derived Neurotrophic Factor (growth factor)

BMLM: bayesian multilevel modeling

**BOLD:** blood-oxygen-level-dependent; fMRI imaging allows to observe brain activity in specific brain areas

CA: cornu ammonis

CASI: cognitive abilities screening instrument Cb: cerebellum

CBF: cerebral blood flow; CBV: cerebral blood volume; rCBF: regional cerebral blood flow; rCBV: regional cerebral blood volume CC: corous callosum

CEN: central executive network (refers to the same network as the ECN)

CMMSE: Chinese version of the Mini Mental State Examination

COGPACK: computerized multi-domain cognitive training http://www. markersoftware.com/USA/frames.htm

CON: control group(s)

CRF: cardiorespiratory fitness CT: cortical thickness

CTT: color trails test; CTT-1 measures visual processing speed/attention, CTT-2 idem plus cognitive flexibility CVLT: California Verbal Learning Test Cx: cortex

dACC: dorsal anterior cingulate cortex

dlPFC: dorsolateral prefrontal cortex

DMN: default mode network

 DSF-DSB: digit span forward – digit span backward
 DTI: diffusion tensor imaging
 EC: entorhinal cortex

ECN: executive control network (refers to the same network as the CEN)EF: executive function(s)

#### EG: experimental group(s)

FA: fractional anisotropy

FC: functional connectivity (derived from RSfMRI)

FD: fractal dimension (complexity of brain structures)

GM: gray matter HADS: Hospital Anxiety and Depression Scale Hc: hippocampus/hippocampal

Hc: hippocampus/hippocampal HcCB = hippocampal cingulum bundle

HE: healthy elderly persons hMT/V5: middle temporal area of the visual cortex

HRmax: maximal heart rate ICA: Independent Component Analysis

ICV: intracranial volume

IFG: inferior frontal gyrus

ILF: inferior longitudinal fasciculus IPC: inferior parietal cortex IPL: inferior parietal lobule ISI: interstimulus interval

**ITG**: inferior temporal gyrus **ITL**: inferior temporal lobe

L: Left

M1: primary motor cortex

MCI: Mild Cognitive Impairment

MD: mean diffusivity Method of Loci: serial word list learning, episodic memory strategy based on associations to familiar spatial environments MFG: middle frontal gyrus

MMSE: mini-mental state examination; MoCA: Montréal Cognitive Assessment Scale

MPRAGE/MP2RAGE: Magnetization Prepared (2) Rapid Gradient Echoes: optimized/common MRI sequence for high-resolution T1 mapping (=sMRI) mPFC: medial prefrontal cortex

MRI: Magnetic Resonance Imaging

MRSI: Magnetic Resonance Spectroscopic Imaging

MTG: middle temporal gyrus NPI: Non-Pharmacological Interventions

OFC: orbitofrontal cortex

PALT: paired associative learning test

PCgC: posterior cingulate cortex

**PFC:** prefrontal cortex **PPC:** posterior parietal cortex

R: Right

RD: radial diffusivity **ReHo:** regional homogeneity, evaluates local temporal synchronizations of spontaneous low frequency BOLD signals **ROI:** region of interest **RS-fMRI:** resting state functional magnetic resonance imaging; **RS:** resting state **SBM:** surface-based morphometry **SFG:** superior frontal gyrus

SMA: supplementary motor area SMART: Strategic Memory Advanced Reasoning Training sMRI: structural MRI (cf. MPRAGE/ MP2RAGE) SN: salience network

SPC: superior parietal cortex SPL: superior parietal lobule SSRS: social support rating scale STG: superior temporal gyrus

T0: baseline T1: 1st post-training timepoint

T2: 2nd post-training time point

T3: 3rd post-training time point

TBSS: Tract-Based Spatial Statistics (tool for voxel-wise analysis of diffusion data) TCC: tai chi chuan TICV/TIV: total intracranial volume

TMT: trail making test

**TPJ**: temporoparietal junction **UFOVt**: Useful Field of View training

VBM: voxel-based morphometry

VCAP: Virginia Cognitive Aging Project battery VLMT: Verbal short- and long-term memory; German adaptation of the *Rey Auditory Verbal Learning Test (RAVLT)* VO<sub>2max</sub>: maximum rate of oxygen consumption during incremental exercise VO<sub>2peak</sub>: peak oxygen uptake VO<sub>2vAT</sub>: oxygen consumption at the ventilatory threshold vlPFC: ventrolateral prefrontal cortex

WM: white matter; WMH: WM hyperintensity; PWMH: periventricular WMH; DWMH: deep WMH WMM: WM microstructure WMS-CR: Wechsler Memory Scale-Chinese Revision

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	RBANS: Repeatable Battery for the Assessment of
stimulus may receive attention)	Neuropsychological Status measures cognitive decline or
UFOV useful FOV=FOV	improvement via 5 index scores: Immediate Memory,
FFOV: functional FOV = area where visual	Visuospatial/Constructional, Language, Attention, and
information is effectively processed	Delayed Memory
FPN: frontal parietal network	RCT: randomized controlled trial

#### 2.4. Collating, summarizing, and reporting results

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

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. multidomain 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.

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.

			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		

# Table 4Organization of Supplementary Tables 1–6.

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#### 3. Discussion

In this discussion section, all studies are first discussed according to the six types of intervention (3.1 upto 3.6). 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 3) wordlist training, Engvig's two-month study and de Lange's  $4 \times 10$  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 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 <u>subsection 3.11.1</u>): 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 min 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 and 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<sup>4</sup> [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<sup>5</sup> at baseline better predicted 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.

<sup>&</sup>lt;sup>4</sup> Slackline training involves balance-centric exercises performed on a taut line.

<sup>&</sup>lt;sup>5</sup> A person's time to rise from a seated position to a standing position without the use of their arms for assistance.

#### 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 engagement as well as to music listening. Dancing requires 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 Refs. [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

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#### 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 the 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 only the dominant hand 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 min 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, and particularly so 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

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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) sufficed 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 requires support from studies that combine measurements of 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



**Fig. 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.

aerobic exercise, as shown in the Generation 100 study [70-73].

Fig. 1 depicts the relative impact of the six NPI types 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.

#### 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 <b>Appendix 2)</b>, 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 again 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 a car) [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<sub>2</sub>max. 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 after 18 months of training (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 6–10 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 min 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 min 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 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 min 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 welltrained 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<sub>2</sub>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 12month 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 involving cognitive training that reinforced learning were challenging and motivating, and involved associative approaches (like the Method of Loci<sup>6</sup>) [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 in HE [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 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.

<sup>&</sup>lt;sup>6</sup> Method of Loci: serial word list learning using a strategy of episodic memory enhancement based on associations with familiar spatial environments.

#### 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.

 $\mathbf{\dot{\chi}O}_2$ : Physical aerobic training.

🗴: Physical non-aerobic training.

Intensity of training: Low Intensity – Moderate Intensity – High Intensity.

Duration of training:  $\stackrel{S}{\longleftrightarrow}$  short –  $\stackrel{I}{\longleftrightarrow}$  intermediate –  $\stackrel{L}{\longleftrightarrow}$  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 **4**, which essentially trained one cognitive domain, and **2**. *multi-domain* interventions **4** that train several ones.

*Physical interventions* include physical **3**. *aerobic* interventions  $\mathbf{\dot{\chi}O}_2$ : 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 min [136]. Another category consists of physical **4**. *non-aerobic* interventions  $\mathbf{\dot{\chi}}$ : 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,  $\mathbf{x}$ : 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

2. **P S S C 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 min, 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.

 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.  $\bigcirc$  [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 1 h 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<sup>7</sup> 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. **C** [SBM, DTI; Suppl. Table 1] [45,46]. Engvig et al. (2010) [45] showed that after two months of intensive serial word list learning (1 h 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 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.

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.

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) dIPFC activity decreased, predicting post-training auditory dual-costs in low-load conditions and visual dual-costs in high-load conditions.

10.  $\mathbb{Q} \subseteq \mathbb{Q}$  [SBM; Suppl. Table 1] [44]. Kuhn et al. (2017) applied a 2-month computerized adaptive inhibition game intervention for minimum 15 min 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. 🔮 🖾 👖 👗 🛋 [Task fMRI; Suppl. Table 1] [139]. Mikos et al. (2021) investigated the effects of a 6-week

<sup>&</sup>lt;sup>7</sup> Positive diffusivity results following training imply the occurrence of the opposite of age-related trends (see Appendix 2, section White matter).

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 min 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.

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.

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. **Q** [IS-fMRI; Suppl. Table 2] [53]. Bubbico et al. (2019), before and after four months (1h30 per week plus 30 min of homework, 120 min 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.

18. **Q C I C I C I C I C D I**, 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.

21. **W 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 min 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. **W S I I I S S S C** [VBM, SBM, DTI, RS-fMRI; Suppl. Table 2] [57]. Lampit et al. (2015) offered three weeks (intermediate measure) and finally three months of 3-h 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 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.  $\mathbf{\dot{C}O}_{2}$   $\mathbf{\dot{C}O}_{2}$ 

25,26,27.  $\mathbf{\dot{x}O_2} = \mathbf{\dot{x}O_2} = \mathbf{\dot{x}$ 

[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<sub>2</sub>max) 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.  $(Q_2 \cup S)$   $(Q_2 \cup S)$ 

29.  $\mathbf{\dot{c}O_2} \prod \mathbf{\dot{c}} \mathbf{\dot{c}O_2} \prod \mathbf{\dot{c}} \mathbf{\dot{c}O_2} \prod \mathbf{\dot{c}O_2} \mathbf{\dot{c}O_2} \prod \mathbf{\dot{c}O_2} \mathbf{\dot{c}O_2} \prod \mathbf{\dot{c}O_2} \mathbf$ 

30.  $\mathbf{\dot{\xi}O_2} \square \mathbf{\dot{f}} = \mathbf{\dot{f}} = \mathbf{\dot{f}} \mathbf{\dot{f}}$ 

31.  $\mathbf{\dot{C}O}_2$   $\mathbf{\dot{C}O}_2$ 

32.  $\mathbf{\dot{\chi}O_2}$  [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 min 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<sub>2</sub>max) across time and verbal fluency increased in the EG and correlated inversely to R IFG activity.

33,34,35,36.  $\mathbf{\dot{x}O_2} \mathbf{\dot{x}} \mathbf{\dot{n}} \mathbf{\dot{k}} \mathbf{\dot{k}} \mathbf{\dot{k}O_2} \mathbf{\dot{k}} \mathbf{\dot{k}} \mathbf{\dot{k}O_2} \mathbf{\dot{k}O_2}$ 

[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 min 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<sub>2peak</sub>) increased in all groups initially but returned to baseline at the final follow-up. Cardiorespiratory fitness was not associated, three times 30–60 min 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.  $\dot{\chi} O_2 \dot{\chi}$  [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.  $\mathbf{\dot{x}O_2}$   $\mathbf{\dot{x}}$   $\mathbf{\dot{n}}$   $\mathbf{\dot{x}}$   $\mathbf{\dot{x}}$ 

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. X I 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 dIPFC 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.  $\star$  I (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. X I S S S F [VBM, RS-fMRI; Suppl. Table 4] [75]. In Magon et al. (2016), six weeks of slack line training (3 times 90 min 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.  $\mathbf{O}_2$   $\mathbf{O}_2$ 

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.  $\mathbf{\dot{v}}_{\mathbf{0}}$   $\mathbf{\dot{v}}_{\mathbf{0}}$   $\mathbf{\dot{v}}_{\mathbf{0}}$   $\mathbf{\dot{v}}_{\mathbf{0}}$   $\mathbf{\dot{v}}_{\mathbf{0}}$   $\mathbf{\dot{v}}_{\mathbf{0}}$   $\mathbf{\dot{v}}_{\mathbf{0}}$   $\mathbf{\dot{v}}_{\mathbf{0}}$   $\mathbf{\dot{v}}_{\mathbf{0}}$   $\mathbf{\dot{v}}_{\mathbf{0}}$  [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 min per day five days per week, EG3 did both, thus trained two times 45 min daily, biasing group comparisons. Biomarkers (TNF- $\alpha$ , ICAM-1, HGF, SDF1- $\alpha$  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- $\alpha$  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. A factor of the end of the en

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.  $\mathbf{\dot{x}O_2}$   $\mathbf{\dot{x}O_2$   $\mathbf{\dot{x}O_2}$   $\mathbf{\dot{x}O_2}$   $\mathbf{\dot{x}O_2}$   $\mathbf{\dot{x}O_2}$   $\mathbf{\dot{x}O_2}$   $\mathbf{\dot{x}O$ 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 min. 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.  $\mathbf{\dot{k}O_2} \ \mathbf{\dot{Q}} \ \mathbf{\dot{k}} \ \mathbf{\dot{k}O_2} \ \mathbf{\dot{k$ 

47,48,49.  $\mathbf{\dot{c}O_2} \cong \mathbf{\dot{c}O_2} \oplus \mathbf{\dot{c}$ 

[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.

6. Combined cognitive and physical non-aerobic interventions

 non-aerobic physical training (whole body stretching). Interventions took place for 1 h, 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 dIPFC). 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 dIPFC (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 lateralization effects, more similar to young adults, in HE after training compared to the CON. No behavioral results were reported.

56.  $4 \times 1$  [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 inscanner behavioral scores. No significant Group  $\times$  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.

[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. 61,62. 61,62. 61,62. 61,62. 61,62. 61,62. 61,62. 61,62. 61,62. 61,62. 61,62. 61,62. 62, 64]. 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; 3 h per week) as well as body-mind (TCC) training (an additional 3 h per week) along with weekly group counseling (90 min per week). So, the interventions occupied 7.5 h 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.

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[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. Q 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 min 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.

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.

#### 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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#### **CRediT** authorship contribution statement

**C.E. James:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Conceptualization. **D.M. Müller:** Investigation. **C.A.H. Müller:** Investigation. **Y. Van De Looij:** Writing – review & editing, Methodology, Investigation. **E. Altenmuller:** Writing – review & editing. **M. Kliegel:** Writing – review & editing. **D. Van De Ville:** Writing – review & editing, Investigation, **D. Marie:** Writing – review & editing, Investigation, Conceptualization.

## Declaration of competing interest

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.

#### 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 Ref. [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 gray-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 Refs. [130,199].

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26674.

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