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Physical Activity, Aging and Brain Health

Körperliche Aktivität, Altern und kognitive Fitness

REVIEW

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Summary

- **Physical activity** is a low-cost intervention in primary and secondary prevention of numerous chronic diseases (e.g., cardiovascular diseases, metabolic diseases, sarcopenia, cancer, dementia). Furthermore, several epidemiological, observational and randomized controlled studies have shown positive effects of physical activity on cognition and reduced risk of neurodegenerative diseases.
- **Industrial societies** are currently experiencing a tremendous demographic change with an unprecedented increase in absolute and relative numbers of elderly adults. This demographic change entails a plethora of challenges for the healthcare system. As the prevalence of many (neurodegenerative) diseases correlates with age, the number of persons affected by age-related diseases will rise.
- **In this context,** non-pharmacological concepts of healthy aging are becoming more attention. Especially lifestyle interventions (e. g. physical activity) are becoming increasingly important and could play a key role in healthy aging and prevention of neurodegenerative diseases. Recent research has shown that physical activity and/or physical exercise benefits cognition and brain plasticity across the lifespan.
- **In this review** we summarize (i) the effects of physical activity and/or physical exercise on brain plasticity, (ii) the role of physical activity and/or physical exercise in the prevention and therapy of dementia, and (iii) potential neurobiological mechanisms of physical activity-induced brain plasticity.

KEY WORDS:
Age-related Diseases, Brain Plasticity, Physical Exercise, Prevention

Zusammenfassung

- **Körperliche Aktivität** ist eine kostengünstige Intervention in der Primär- und Sekundärprävention von zahlreichen chronischen Krankheiten (z.B. Kardiovaskuläre Erkrankungen, Metabolische Erkrankungen, Sarkopenie, Krebs). Des Weiteren zeigen zahlreiche epidemiologischen Studien als auch randomisierte kontrollierte Interventionsstudien positive Effekte von körperlicher Aktivität auf kognitive Fähigkeiten und einen positive Effekt auf das Risiko von neurodegenerativen Erkrankungen.
- **Im Rahmen** des demografischen Wandels ist mit einem deutlichem Anstieg der Prävalenz von Demenzerkrankungen zu rechnen. Diese Entwicklung stellt die Gesellschaft im allgemeinen und das Gesundheitssystem im speziellen vor große Herausforderungen.
- **Diesbezüglich** gewinnen, bei aktuell noch fehlenden kausalen pharmakologischen Therapien, Präventionskonzepte zunehmend an Bedeutung. Unter anderem Lebensstilinterventionen (z. B. körperliche Aktivität) können in diesem Kontext einen wichtigen Beitrag zum gesunden Altern und der Prävention von neurodegenerativen Erkrankungen leisten. Insbesondere durch eine Reduktion von Risikofaktoren und verschiedener Maßnahmen und Interventionen (z. B. körperliches Aktivität) kann Neuroplastizität stimuliert werden.
- **In diesem Übersichtsartikel** analysieren wir (i) die Effekte von körperlicher Aktivität und/oder körperlichen Training auf Neuroplastizität, (ii) die Rolle von körperlicher Aktivität und/oder körperlichen Training in der Prävention und Therapie von dementiellen Erkrankungen und (iii) die zu Grunde liegenden neurobiologischen Mechanismen von durch körperlicher Aktivität induzierter neuronaler Plastizität.

SCHLÜSSELWÖRTER:
Altersbedingte Krankheiten, Plastizität des Gehirns, Bewegung, Prävention

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Introduction

Industrial societies are currently experiencing a tremendous demographic change with an unprecedented increase in absolute and relative numbers of older adults. This change is a consequence of two processes: on the one hand falling and/or low birth rates, and a continuously increasing life expectancy on the other hand. The demographic change entails a plethora of challenges for the healthcare system.

As the incidence of many (neurodegenerative) diseases correlates with age, the number of persons affected by age-related diseases will rise. In that respect, neurodegenerative diseases, such as Alzheimer´s Disease (AD) or Parkinson´s Disease (PD), with their severe cognitive deficits and potential loss of independent living constitute a major health problem and represent one of the largest global health issues.

Dementia in general is the most common neurodegenerative disorder. According to recent predictions, the global number of people affected by dementia will rise from currently around 50 million to 152 million by 2050 (51), whereby AD as the most common cause of dementia accounts for up to ›

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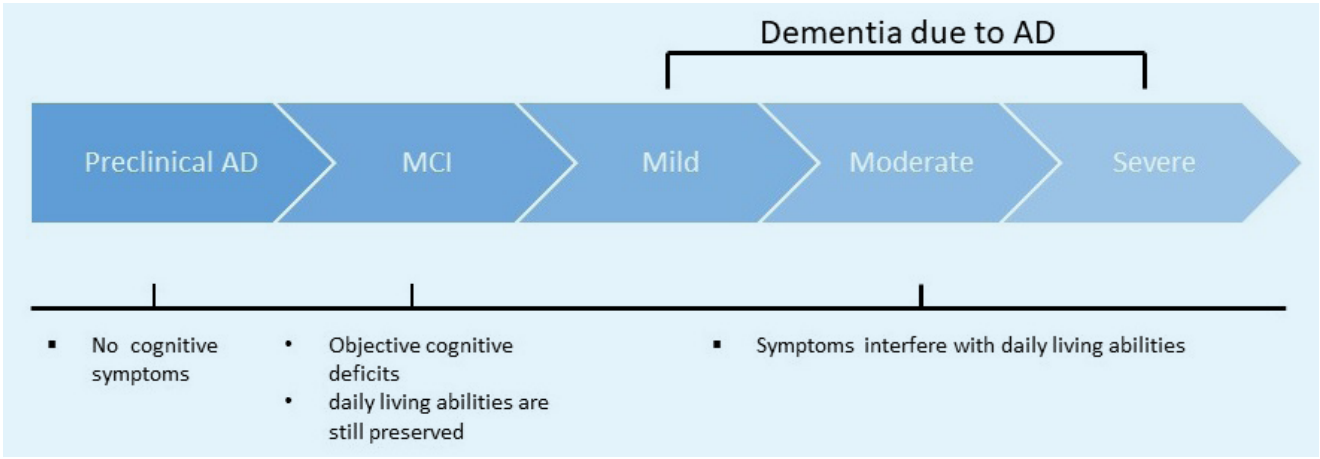

Figure 1

Alzheimer's disease (AD) continuum; Mild cognitive impairment (MCI).

75% of cases (36). Accordingly, methods for preventing, delaying the onset, slowing the progression, and improving the symptoms of dementia are urgently needed. However, in the last 30 years more than 200 clinical trials testing new, potential disease modifying drugs have failed (43).

In this context, non-pharmacological concepts of healthy aging are becoming increasingly important. Current research indicates that lifestyle factors, especially physical activity, could play a key role in healthy aging and prevention of neurodegenerative diseases (30).

Aging and Brain Health

Aging is a heterogeneous process and subject of intensive research, especially in the context of demographic change. However, there are several definitions (e.g., chronical age, biological age, successful aging) and theories of aging (e.g., cellular aging, genetic aging, physiological aging) (4). Molecular hallmarks of aging are telomere attrition, epigenetic alterations, mitochondrial dysfunction, loss of proteostasis, cellular senescence, and systemic chronic inflammation. These different mechanisms result in cardiovascular, pulmonal, renal, musculoskeletal, immune and cognitive alterations (for overview see (29).

Cognitive functions are crucial for successful healthy aging and self-independence of older adults. In general, levels of cognitive functions increase during childhood, peak at some point in adulthood and decline during aging. More specifically, cognitive abilities requiring effortful processing (e.g., visuospatial ability, fluid reasoning) decline throughout middle/late adulthood, whereas cognitive abilities requiring knowledge and/or experiences (e.g., autobiographical memory, semantic knowledge) peak in late adulthood (61). The research of age-related effects on cognition is dominated by cross-sectional comparisons between younger and older adults. However, cross-sectional studies are potentially confounded by cohort effects that may overestimate age-related differences in cognition. In contrast, longitudinal studies might underestimate potential age effects because of selective attrition (25).

Cognitive alterations are primarily attributed to structural and functional brain changes. Post-mortem and in vivo studies (using Magnetic Resonance Imaging, MRI) show age-related neural changes. These changes do not seem to result from neuronal loss, but rather from synaptic alterations in older adults (65). Age-related structural brain alterations occur in almost all cortical and subcortical regions, but most pronounced in prefrontal and temporal (including the hippocampus) brain regions. For example, structural MRI studies indicate an atrophy rate of the hippocampus of 2-3% per decade, which is accelerated to 1% yearly in old age (>70 years) (55). These brain regions are crucial for higher cognitive functions like memory and executive functions (e.g., working memory, cognitive flexibility, inhibitory control). Additionally, Diffusion tensor imaging (DTI) and T2-weighted MRI studies indicate decreased white matter integrity and increased white matter hyperintensities (WMH) during aging (10).

Normal Aging, MCI & Dementia

The transition between normal and pathological aging, namely dementia, is smooth and clinically often difficult to detect. In this regard, "mild cognitive impairment" (MCI) (52) is a transitional stage between normal aging and dementia in which patients present with subjective and objective cognitive deficits. Unlike in dementia, daily living abilities are still preserved. MCI is associated with an increased risk for Alzheimer's disease, especially when memory functions are affected (amnestic MCI). A meta-analysis (38) reports an annual conversion rate from MCI to dementia of 5-10%. However, accordingly, not all MCI patients will progress to dementia.

Dementia is a syndrome, diagnosed when objective cognitive deficits are present over a period of at least 6 months that cannot be explained by delirium or other psychiatric disorders and the inability to function at work and/or usual daily activities (in contrast to MCI) (37). The most common cause of dementia is AD (up to 75% of all cases). AD is a chronic disease with a long preclinical and prodromal phase (20 years). Based on the continuum of AD (Clinical trajectory from preclinical AD, MCI to Dementia, Figure 1), in 2018 the "National Institute on Aging -Alzheimer`s Association (NIA-AA) Research Framework" (28) purposed a biological definition of AD including ß amyloid deposition, pathologic tau, and neurodegeneration [AT(N)] using different biomarkers (imaging and biofluids). Thus, the diagnosis is not restricted on clinical symptoms (e.g., memory deficits). Currently, the NIA-AA AD definition is especially used in research contexts and trials because a preclinical diagnosis of AD could provide a critical opportunity for therapeutic interventions (including physical exercise interventions).

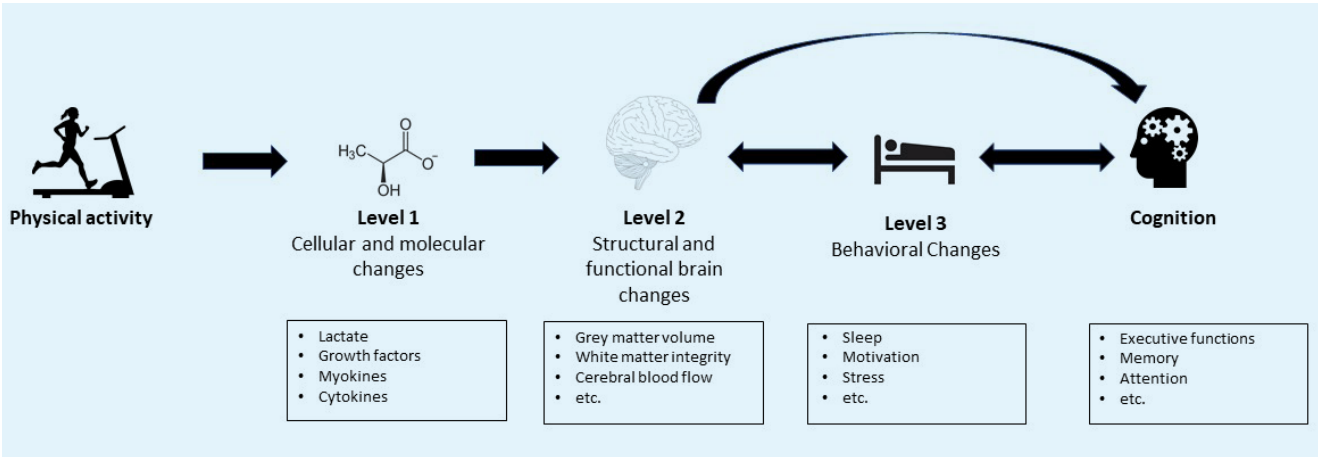

Figure 2

Level model of neurobiological mechanisms of exercise induced brain plasticity.

Correspondingly, the pathophysiological hallmarks of AD are ß amyloid plaques and abnormal tau tangles (5). In recent years, neuroinflammation has emerged a third core feature of AD which might provide a link between ß amyloid and abnormal tau tangles (26).

The main risk factor for dementia, especially AD, is age: 3% of people aged 65-64 years, 17% of people aged 75-84 years, and 32% of people aged 85 years and older are diagnosed with AD (24). However, current research indicates an unequivocal downtrend in the prevalence and incidence of dementia associated with prevention investments (e.g., improved education, vascular health). These results highlight the urgent need for primary and secondary prevention strategies.

In this regard, Norton et al. (49) postulate that one third of global AD is related to modifiable risk factors. Modifiable AD risk factors are: 1. Low educational attainment; 2. Physical inactivity; 3. Depression; 4. Overweight; 5. Midlife hypertension; 6. Smoking; and 7. Diabetes mellitus.

These factors open up an opportunity for various preventive strategies. According to a computational model, a reduction of 10% of these risk factors per decade could lead to a decrease of 8.3% of the global Alzheimer's prevalence by 2050 (49). Hence, the aim of primary/secondary prevention is to delay the onset or slow the progression of AD pathophysiology. A 5-year delay in the onset of AD could reduce the number of patients by over 50% (58).

Effects of Physical Activity and Exercise on Brain Plasticity

Physical activity and/or physical exercise is a low-cost intervention in primary and secondary prevention for numerous chronic diseases (e.g., cardiovascular diseases, metabolic diseases, cancer, sarcopenia) (64). Furthermore, physical activity has several positive effects on brain health, can stimulate brain plasticity and reduces the risk of neurodegenerative diseases (e.g., dementia) (23).

In this regard, "physical activity" is defined as any muscle-induced bodily movement which increases energy expenditure above ~ 1.0/1.5 metabolic equivalent of task (MET, 1 MET = 1 kcal (4,184 kJ) × kg–1 × h–1), whereby "physical exercise" is a specific, planned and structured form of physical activities (11). Additionally, physical exercise can be divided into acute physical exercise (single bout) and chronic physical exercise (physical exercise training). Current guidelines of the World Health Association (WHO) recommend a minimum of 150 minutes moderate-intensity or 75 minutes vigorous-intensity aerobic activity and strength training per week (22).

Recent research has shown that physical activity and/or physical exercise benefits cognition and brain plasticity across the lifespan (60). A current systematic review concludes moderately strong evidence that moderate to vigorous physical exercise enhances cognition, especially memory and executive functions (19). However, results from randomized controlled trials report some inconsistent findings and high inter-individual differences in response to physical exercise interventions (46). In consequence the National Academies report summarize that evidence from human studies are insufficient to recommend physical exercise for preventing cognitive decline (17). For a detailed analysis of the National Academies report we recommend a perspective article by Voss et al. (63). Hence, more clinical intervention studies are needed with long-term follow-up assessments and more specific and sensitive tasks to evaluate exercise-induced brain plasticity (e.g., hippocampal dependent mnemonic discrimination) (63).

Neurobiological Mechanisms of Exercise Induced Brain Plasticity

Despite several animal and human studies showing that physical exercise can enhance brain plasticity, the underlying neurobiological mechanisms of exercise induced brain plasticity are still largely unknown. Given that physical exercise affects numerous organ systems, it seems likely that physical exercise effects on brain plasticity operate via multiple pathways, mechanisms and levels (Figure 2). Stillman et al. (59) propose a level model: cellular and molecular changes (Level 1) initiate structural and functional brain (Level 2) and/or behavioral (Level 3) changes resulting in cognitive enhancement.

Effects of Acute Exercise on Brain Plasticity

Even a single bout of physical exercise (acute exercise) can enhance cognition with strongest effect sizes for executive functions (13). A meta-analysis has suggested greatest enhancements occur within 15 minutes following acute exercise. Results from van Dongen et al. (62) even show long-term memory enhancement for up to 48 hours after a single bout of physical exercise. Moreover, using functional MRI (fMRI) they found that performing physical exercise four hours after encoding improved memory retention and increased hippocampal pattern similarity during retrieval. In contrast, exercising immediately ›

after learning/encoding did not lead to any improvements. Furthermore, results from animal research indicate that a single bout of treadmill running can enhance object recognition for up to 21 days through hippocampal noradrenergic mechanisms (15).

Potential mechanisms of acute exercise on cognition are catecholamines (e.g., norepinephrine), neurotrophic factors (e.g., Brain-derived neurotrophic factor, BDNF) and cerebral blood flow (54).

BDNF is a neurotrophic growth factor and crucial for neurogenesis, growth of dendritic spines, synaptogenesis, and long-term potentiation (6). Several studies have shown that exercise induced neuroplasticity is associated with BDNF. A meta-analysis concludes that acute exercise can increase peripheral blood BDNF levels in humans. Additionally, meta-regression analysis has shown that greater exercise duration was associated with greater increases in BDNF levels (16). Regarding exercise intensity, Saucedo Marquez et al. (56) have reported that shorter bouts of high intensity exercise are more effective than continuous moderate-to-high-intensity exercise in elevating BDNF levels. Moreover, potential effects of high intensity exercise on brain plasticity may be linked to lactate. Indeed, increased peripheral lactate levels (following high intensity exercise) are associated with increased peripheral BDNF levels (for review see (42)). Furthermore, Schiffer et al. (57) have shown that lactate infusion at rest can increase peripheral BDNF levels in humans.

Another potential molecular mechanism of exercise induced brain plasticity could be the PGC-1α1 mediated kynurenine metabolism. Kynurenine is a metabolite of the amino acid tryptophan which can cross the blood-brain barier (BBB) and promote (neuro-) inflammation and neuronal cell death (12). Agudelo et al. (1) have shown that exercise can increase skeletal muscle PGC-1α1, thus enhancing the conversion of kynurenine to kynurenic acid which cannot cross the BBB. In turn, reduced plasma levels of kynurenine may protect the brain from neurodegenerative changes.

Using mass spectrometry Morville et al. (39) identified plasma metabolome profiles of resistance and endurance exercise in humans showing different effects of exercise type on human physiology. Mass spectrometry-based metabolomics can measure up to hundreds of metabolites and help to understand the mechanisms of exercise induced brain plasticity. Lactate and the ketone body β-hydroxybutyrate (BHB, e.g., 3-hydroxybutyrate) were among the highest induced metabolites following resistance or endurance exercise, respectively. BHB may strengthen neuronal connectivity through increased hippocampal and cortical BDNF expression.

Studies investigating structural and functional brain changes following acute exercise are still limited. A recent systematic review of acute exercise studies using fMRI reports profound changes in brain activation, especially in the frontal and temporal regions following exercise (27). In this regard, functional brain activation could depend on fitness level, exercise protocol, and sex. However, most studies are performed in young, healthy adults. For example, using arterial spin-labelling (ASL) Pontifex et al. reported no effects of acute exercise on cerebral blood flow in pre-adolescent children (mean age 10.2 ±1.0) (53).

Effects of Regular Physical Exercise on Brain Plasticity

Several epidemiological, observational and randomized controlled studies demonstrate that regular physical activity and/or physical exercise can improve brain structure and function, as well as cognition across the lifespan. (19, 45). However, various randomized clinical trials failed showing benefit effects of exercise on brain plasticity (31).

Though, which type of exercise (e.g., aerobic, resistance, motor-coordinative) is most effective in inducing brain plasticity is unclear. Most studies have investigated the effects of aerobic exercise with changes on structural and functional brain plasticity, neurotrophic growth factors (e.g., BDNF) and cognition.

In a landmark cross-sectional study, Colcombe et al. (14) have shown that cardiorespiratory fitness is associated with reduced brain tissue loss in aging humans. Furthermore, Erickson et al. (20) reported that cardiorespiratory fitness is associated with hippocampal volume and spatial memory in older adults. Following up these findings in a randomized controlled trial, Erickson et al. (21) were able to show that one year of aerobic exercise training can increase the size of the hippocampus and improve memory in older adults. In this regard, changes in BDNF levels and cardiorespiratory fitness were associated with hippocampal volume plasticity. Furthermore, Maass et al. (35) reported vascular hippocampal plasticity following a three-months aerobic exercise intervention in older adults using perfusion MRI.

Although few studies have investigated the effects of resistance training on brain plasticity showing improvements in cognition, increased levels of IGF-1 and increased hemodynamic activity using fMRI (34). A systematic review concluded that resistance training has positive effects on cognition, especially executive functions (33). Considering the findings of Moreville et al. (39) that lactate levels are greater after resistance training suggests a need to further investigate the effects of resistance training on brain structure, function and cognition.

Furthermore, motor-coordinative exercise interventions (e.g., dancing) have been shown to enhance brain plasticity. Following 18-months of dance intervention Müller et al. (44) reported increased parahippocampal grey matter volume, BDNF levels and improved verbal memory. Burzynska et al. (9) investigated young expert female dancers showing lower anisotropy in corticospinal tract and altered functional connectivity of the action observation network in comparison to healthy young controls, but no differences in brain volume and cognition. The potential neurobiological mechanisms of motor-coordinative exercise are in particular synaptogenesis and neurotrophic factors.

As mentioned above, several studies have shown positive effects of physical exercise on the hippocampus, a crucial region for memory consolidation, learning and spatial navigation (18). Additionally, animal and human studies indicate that physical activity can improve hippocampal dependent pattern separation, the ability to discriminate among similar or ambiguous experiences (63). However, no randomized controlled trials have investigated the effects of exercise on pattern separation so far.

Potential mechanisms of regular physical activity and/or exercise on cognition and brain plasticity are neurotrophic factors (e.g., BDNF), myokines (e.g., irisin, cathepsin b) and metabolites (e.g., lactate, BHB), changes in the gut-brain axis, a modulation of (neuro-) inflammation and/or a reduction of risk factors (e.g., obesity, hypertension) (for review see (47)). Especially, the synergetic effects of physical activity on risk factors are to be emphasized.

Role of Physical Activity and Exercise in the Prevention and Therapy of Dementia

A large body of epidemiological and observational studies demonstrate that physical activity (mostly assessed using questionnaires) can reduce dementia risk. A meta-analysis including

16 prospective studies (163.797 participants without dementia at baseline) reported a 45 % reduction in risk of AD related to physical activity (23). A recent review concludes that regular exercise can attenuate cognitive decline in patients at risk for dementia (50). However, most studies do not consider different dementia causes (with different underlying neuropathological mechanisms) in their participant recruitment.

Some research results indicate that exercise interventions in preclinical dementia and MCI could be more successful, as opposed to in mild to moderate dementia (7). For example, Lautenschlager et al. (32) reported in a randomized controlled trial cognitive improvements in patients with subjective and/or mild cognitive impairment following moderate aerobic exercise intervention. In contrast, the Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with mild to moderate dementia showing no effects on cognition and/or other clinical outcomes (only improved physical fitness) (31). In this context, more large-scale randomized controlled trials are necessary to estimate the potential role of physical exercise in the prevention and therapy of dementia (40).

Given the multifactorial aetiology of dementia several current research trials utilize multidomain lifestyle interventions for dementia prevention. In the past years, results from three large multidomain trials (FINGER, PreDIVA & MAPT) have been published (30). So far, only the FINGER trial has revealed beneficial intervention effects on cognitive functions among participants at risk of dementia (48). However, in a post-hoc subgroup analysis participants with brain amyloid deposition showing less cognitive decline during follow-up in the multidomain lifestyle intervention group compared to the control group within the MAPT trial (3). Furthermore, Brown et al. (8) have reported in APOE4 carrying older adults that higher physical activity levels are associated with lower brain amyloid deposition. Hence, future trials should investigate biomarker based exercise interventions.

Conclusion and Perspective

In summary, recent research indicates prevention of age-related cognitive decline and dementia by physical activity (Table 1). Especially, epidemiological evidence supports this notion. However, results from randomized controlled trials are highly variable. On the one hand, this heterogeneity may originate from the fact that there are "responders" and "non-responders" with respect to the impact of physical exercise on cardiorespiratory fitness and brain plasticity. In this regard, some studies indicate that the non-responder status can be mitigated by increasing the exercise intensity and/or dose which underpinning the necessity of tailored exercise prescriptions (e.g., personalized exercise interventions) (46). On the other hand, physical exercise studies show a high variability regarding the exercise protocol (e.g., intensity, duration) and/or the control of external factors (e.g., mood, lifestyle factors, circadian rhythm). Understanding the response variability will be important for preventing potential side-effects, treatment failures, and enhancing exercise efficacy.

Additionally, the current COVID-19 pandemic could have disastrous consequences for dementia prevention because physical inactivity levels have increased due to contact restrictions and home confinements by up to 30% (2). Therefore, dementia research must consider COVID-19 into future prevention strategies (e.g., developing app-based lifestyle interventions) (41).

Table 1

Practical recommendations for brain plasticity.

PRACTICAL RECOMMENDATIONS FOR BRAIN PLASTICITY
-physical active lifestyle across lifespan
-combination of endurance, resistance and motor-coordinative exercise
-reduction of risk factors (e.g., obesity, systolic blood pressure, smoking)
-lifelong learning of new movements (e.g., juggling, dancing)
-social & cognitive active lifestyle (e.g., traveling, learning new languages)
-situation- and target group-specific flexible adaptation of exercise intervention (e.g., development of app-based training)

Conflict of Interest

The authors have no conflict of interest.

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