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Physical Activity and Neurodegenerative Diseases: Potential Role in Prevention and Therapy

Körperliche Aktivität und neurodegenerative Erkrankungen: Mögliche Rolle bei Prävention und Therapie

CLINICAL REVIEW

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Summary

- **Physical activity and exercise** are low-cost interventions in primary and secondary prevention of several noncommunicable disease (e.g. cardiovascular diseases, chronic kidney disease, neurodegenerative and neurovascular disease).
- **In the context of demographic change,** the relative and absolute numbers of patients with neurological, especially neurodegenerative disease, will increase. Based on missing causal therapies and high costs, non-pharmacological (e.g. physical activity) approaches for healthy aging are gaining attention.
- **Epidemiological, observational, and randomized controlled studies** have shown that physical activity can enhance brain plasticity and improve cognitive vitality over lifespan. However, the underlying neurobiological mechanisms are still largely unknown. Physical activity can influence different risk factors for neurovascular and neurodegenerative diseases (e.g. arterial hypertension, obesity). Moreover, physical activity can induce cellular and molecular changes (level 1) followed by structural and functionals brain changes (level 2) and/or behavioural adaptations (level 3).
- **In this clinical review** we summarize the role of physical activity in the prevention and therapy of neurological disease.

KEY WORDS:
Exercise, Dementia, Prevention, Intervention, Arterial Hypertension, Obesity

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Introduction

Physical activity and exercise are low-cost interventions in primary and secondary prevention for numerous non-communicable diseases (e.g., cardiovascular diseases, arterial hypertension, metabolic diseases, cancer, dementia) (45) which have several positive effects on brain health and possibly stimulate brain plasticity across lifespan reducing the risk of several neurological diseases (e.g. dementia, Parkinson's disease) (5, 30). In this regard, physical activity is defined as any movement associated with energy expenditure and exercise as a specific, structured, and planned form of physical activity (4).

An essential feature of healthy brain aging is the lifelong ability to adapt to external and internal stimuli, a process called brain plasticity (also known as neuroplasticity). Molecular and cellular mechanisms of brain plasticity are among other things neurogenesis, synaptogenesis, axon sprouding, glial changes, angiogenesis, and myelin remodelling (48).

In this clinical review, we summarize the potential role of physical activity and exercise in prevention and therapy of neurodegenerative disease. Due to space limitations here, we can only provide a broad overview. For more information, relevant guidelines and/or review articles on the respective topic are to be referred.

Neurological Diseases and Physical Activity

Dementia, Alzheimer´s Disease, and Vascular Cognitive Impairment

Dementia is a clinical syndrome, characterized by objective cognitive deficits over a period of at least 6 months that cannot be explained by other causes (e.g. depression, hypothyroidism) and impairs activities of daily living. Dementia is the most frequent neurodegenerative disease. According to current calculations the number of patients with dementia will rise from around 50 million to 152 million by 2050 (9).

The most common cause of dementia is Alzheimer's disease (AD) with a proportion up to 75% (35). The second most common cause of dementia is vascular cognitive dementia (VCI) (42). Moreover, current research indicates that alterations of vasculature (especially microvascular dysfunction) contribute up to 65% of all dementia cases (2). This highlights the role of cerebral small vessel disease (CSVD) in dementia.

40% of all dementia cases are related to modifiable risk factors (e.g. physical inactivity, hypertension, diabetes mellitus, overweight) (23). This highlights the fundamental role of prevention strategies. According to a computational model, a reduction of 10% of these modifiable risk factors per decade could lead to a decrease of 8.3% of the global dementia prevalence by 2050 (32).

Several epidemiological, observational, and randomized controlled studies have shown that physical activity can enhance cognition, reduce the risk and might slow progression of dementia (26, 29, 30, 41). For example, Hamer & Chida (15) reported a 45% reduction of dementia risk related to physical activity. However, several studies do not consider different dementia causes (with different underlying neuropathological mechanisms) in their participant recruitment. ›

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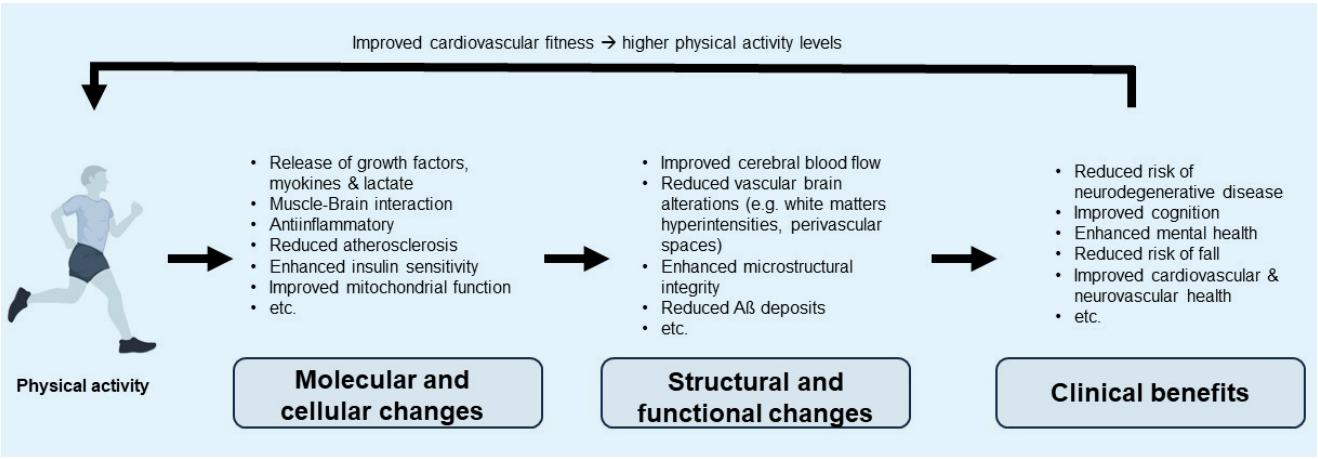

Figure 1

Effects of physical activity on molecular & cellular changes, structural & functional changes and resulting clinical benefits.

Additionally, results from randomized controlled trials report some inconsistent findings and high inter-individual differences in response to physical exercise interventions, mainly when only caloric expenditure is considered (40). Hence, more clinical intervention studies beyond endurance training involving other motor and non-motor demands are needed with long-term follow-up assessments and more specific and sensitive tasks to evaluate exercise-induced brain plasticity and the underpinning neurobiological mechanisms (44).

Furthermore, up to 90% of all dementia cases exhibit neuropsychiatric comorbidities (e.g. sleep disorders, depression, anxiety). Physical activity can improve neuropsychiatric symptoms in dementia cases (21).

Despite the overall positive evidence, the current German S3-guideline for dementia recommends that physical activity can be considered for therapy in dementia and mild cognitive impairment (class B recommendation, (8)).

Parkinson‘s Disease (PD)

PD is the second most-common neurodegenerative disease and characterized by the presence of bradykinesia and at least one more motor symptom (rigidity or resting tremor) (33). Pathophysiological mechanisms of PD include loss of dopaminergic neurons in the substantia nigra and intracellular aggravation of α-synuclein.

Experimental models and epidemiological studies indicate that higher physical activity levels are associated with reduced PD risk (46). In a meta-analysis, physical activity has been associated with a 34% PD risk reduction (47) . This effect was predominantly demonstrated in males with less effects in females. The reasons for this gender effect remains to be elucidated. Preventative effects were even larger, when the same amount of energy was spent by vigorous activity / exercise (10).

In addition to primary or secondary prevention, several randomized controlled trials indicate that physical activity can improve motor and non-motor symptoms (e.g. fatigue, sleep, depression, cognition) in PD patients. Moreover, physical activity and specific types of exercise can be used to differentiatedly improve gait, balance and strength, and reduce cardiovascular comorbidities in PD (24).

The current S2k guideline recommends that patients should be physically active (class A recommendation, (17)).

Stroke

After myocardial infarction, stroke is the second most cause of mortality. Stroke can be classified into ischaemic stroke and haemorrhagic stroke. With a proportion of up to 85%, ischaemic stroke caused by arterial occlusion is the most common type (19). Modifiable risk factors for stroke are hypertension, atherosclerosis, smoking, physical inactivity, and diabetes.

Many observational and interventional studies report an inverse relationship between physical activity levels and stroke risk. Thus, physical activity is associated with a 25-30% risk reduction of stroke (13).

A current Cochrane review summarizes that physical exercise is safe and can reduce disability in stroke patients. Moreover, cardiorespiratory improvements following exercise are associated with reduced hospitalisation rate (1, 38).

The German S3-guideline recommends physical activity and structured exercise interventions for stroke patients (class A recommendation, (6)).

Multiple Sclerosis

Multiple sclerosis (MS) is the most common neuroinflammatory and neurodegenerative disease in young adults (11). Pathophysiological hallmarks are demyelinating lesions in the brain and spinal cord. Up to date, the causes of MS are still largely unknown. Epidemiological studies indicate a potential role of lifestyle (e.g. smoking, obesity) and environmental factors (e.g. vitamin D levels). Current results from Mendelian randomization studies suggest that physical activity levels could reduce the risk of MS (22).

In patients with MS, physical exercise interventions can improve clinical symptoms and quality of life (25). A meta-analysis demonstrated a reduction of relapses by 27%. However, recent research concludes sparse and inconclusive evidence for physical exercise on neuroprotection in MS patients, most likely due to the absence of large, long-term (≥1 year), and well-designed studies (18).

The German S2k guideline recommends physical activity and exercise for MS patients (class A recommendation, (7)).

Amyotrophic Lateral Sclerosis (ALS)

ALS is characterized by the degeneration of both upper and lower motor neurons. Clinically, ALS is associated with progressive muscle weakness. ALS has been reported with higher prevalence in some professional athletes. Epidemiological case–control studies report inconsistent results regarding the role of physical activity and ALS risk (16). However, a European case-control study reported no associations between physical activity levels and ALS risk (34).

Experimental data and human studies (with small sample sizes) indicate that low-to-moderate physical exercise training can improve clinical symptoms in ALS patients (49).

Physical Activity Recommendations in Neurodegenerative Disease

Most guidelines for prevention and therapy recommend a minimum of 150 minutes moderate-intensity or 75 minutes vigorous-intensity aerobic activity and additional strength training per week on the basis of the WHO guidelines (3, 14). However, specific personalized exercise prescriptions are missing.

In general, most studies have investigated the role of endurance exercise interventions. Additionally, animal studies have shown that a combination of endurance and cognitive intervention could be most effective for brain plasticity (43). In humans, more complex types of sports like dancing, variability of exercise with involvement of several motor demands and other (affective and social) factors and/or addition of neurocognitive challenges (dual task) could be an ideal intervention to enhance brain plasticity, improve cardiovascular fitness, and fall prevention (28, 36).

Optimal specific exercise prescription parameters for neuroprotection are still largely unknown (e.g. FITT principle frequency, intensity, time, and type of exercise). Future studies are needed to investigate personalized exercise prescriptions (31).

In patients with neurodegenerative disease or at-risk we strongly suggest sports medical examination and performance diagnostic before starting or resuming new exercise training. The sports medical check-up should identify individual risk factors (especially for cardiovascular disease and falls) and enable the safety of exercise intervention, possibly even by adjustments of the preferred type of sports (for example walking football or sit volleyball instead of football or volleyball).

Additionally, we suggest individualized exercise prescriptions. These should be adjusted to the needs and comorbidities (e.g., cognitive-motor training) of the patients. The exercise training should be optimally based on a shared decision-making process between physician and patient, optimally also involving trainers and therapists.

Neurobiological Mechanisms of Physical Activity

Despite several animal and human studies showing physical activity to be associated with brain plasticity, the underlying neurobiological mechanisms are still largely unknown. In general, physical activity induces cellular and molecular changes (level 1) followed by structural and functionals brain changes (level 2) and/or behavioural adaptations (level 3) (39).

Physical activity and exercise are associated with pleiotropic effects. For instance, physical activity can enhance neurotrophic factors (e.g. BDNF (brain derived neurotrophic factor)), release myokines (e.g. irisin, cathepsin B), reduce systemic inflammation, improve cardiovascular fitness and brain perfusion, and modulate risk factors (e.g. hypertension, obesity) (12, 27, 30). Interestingly, animal models with enriched environments are likely to be very beneficial when combined with endurance training, and should be investigated in future studies (19, 37).

Conclusion and Perspectives

Epidemiological studies indicate that physical activity is associated with a reduced risk of neurodegenerative disease. However, based on small sample sizes, the evidence for specific and differentiated physical activity interventions in therapy of neurodegenerative diseases is lacking. Randomized controlled trials indicate positive effects on neuroprotection and other clinical parameters (e.g., cardiorespiratory fitness, fall prevention, improvement of neuropsychiatric symptoms). In this regard, most guidelines recommend physical activity in the therapy of neurodegenerative disease. However, especially in less-common neurodegenerative diseases (e.g. ALS) the evidence regarding the role of physical activity in prevention and therapy is limited. Future studies investigating the effects of physical activity and exercise (which should not be restricted to endurance) interventions (e.g. personalized exercise) are urgently needed. Additionally, currently running multidomain intervention studies (e.g. world wide FINGER-study (20)) will enhance our understanding of potential prevention and therapy approaches.

Conflict of Interest

The authors have no conflict of interest.

Summary Box

Physical activity and exercise are low-cost interventions in primary and secondary prevention. Current guidelines recommend physical activity for prevention and therapy of neurodegenerative and neurovascular diseases (e.g. dementia, Parkinson's disease (PD), and stroke). However, specific personalized exercise prescriptions are missing.

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