

Physical Activity and Sports in the Prevention and Therapy of Neurodegenerative Diseases

Körperliche Aktivität und Sport in der Prävention und Therapie neurodegenerativer Erkrankungen

Thanks to numerous medical, hygienic and technical advances, life expectancy in Germany has increased from just over 30 years in the 19th century to the current more than 80 years. Demographic data say that every second child born these days will live to be 100 years old. This positive development, however, is accompanied by an increase in age-associated diseases of the metabolic system (Diabetes mellitus Type 2, adiposity, etc.), of the cardiovascular system (coronary heart disease, hypertension, etc.), of the locomotor system (sarcopenia, arthrosis, etc.) and the central nervous system (dementias, amyotrophic lateral sclerosis, Parkinson's, etc.). The increase in neurodegenerative diseases (especially dementias) is a serious challenge for the health system.

Neurodegenerative Diseases

Neurodegenerative diseases is the generic term for disease patterns characterized by progressive nerve cell destruction. The most frequent neurodegenerative diseases are dementias (such as Morbus Alzheimer, Frontotemporal dementia, vascular dementia), which account for 60-70%. Other neurodegenerative diseases include Morbus Parkinson (second most-frequent neurodegenerative disease), Huntington's Chorea and motoneuron diseases (such as Amyotrophic lateral sclerosis). Age is the main risk factor for the development of neurodegenerative diseases. Among other things due to the high incidence and prevalence, the research focus on neurodegenerative diseases is presently on dementias. According to health insurance and survey data, an increase from currently 1 to 1.5 million to up to 3.5 million in 2050 is to be expected in Germany.

Dementia in turn is a generic term for diseases characterized by a loss of memory and other cognitive capabilities. Dementias can be differentiated into primary and secondary dementias, whereby primary dementias are based on a neurodegenerative pathomechanism and secondary dementia arises out of another (usually organic disease (such as hyponatremia, vitamin deficiency) or intoxication. Although secondary forms of dementia account for only 2% of all dementias, knowledge of them and their diagnostics is elementary, since they are often reversible by treatment of the underlying disease. Primary

forms of dementia are Alzheimer's Dementia (the most frequent form accounting for 50-70%), frontotemporal dementia, Lewy-Body dementia, vascular dementias and mixed dementia forms. To date, there are no causal-effective pharmacological therapies for the treatment of dementias: the current acetylcholinesterase inhibitors (galantamin, donepezil and rivastigmin) and the NMDA receptor (N-methyl-D-aspartate receptor) antagonist memantin can only slow the progress of the disease (10,11). In this context, preventive intervention approaches are gaining in importance. The starting point for preventive measures are the modifiable risk factors, like lack of exercise, depression, overweight, hypertension and Diabetes mellitus. In Germany (and other Western countries), physical inactivity has the highest prognostic influence on dementias. Current projections assume that a 10 to 50% reduction in modifiable risk factors could reduce the number of dementia diseases in Germany by 23,000 to 130,000 cases.

Especially the long asymptomatic preclinical phase (ca. 20 years) of Alzheimer's Dementia offers great potential for targeted preventive intervention by means of changed lifestyle and sports training (9).

Sport-Induced Neuroplasticity

The influence of physical activity and sports training on cognition has been a central focus of research in neurosciences for decades. In this respect, the current study situation shows that both a single sports session (acute exercise) (2) as well as regular physical activity and sports training (chronic exercise) (3) have positive effects on cognitive capabilities. The human brain can adapt structurally and functionally to exertion even at advanced age, a capacity which is termed neuronal plasticity. Neurobiological mechanisms of neuroplasticity are, among others, the new formation of nerve cells (neurogenesis), the formation of new vessels (angiogenesis) and the formation of new contact sites between the nerve cells (synaptogenesis).

One aspect, which is controversially discussed in neuroscience is adult neurogenesis. Up to the 1990s, medicine and neuroscience maintained the dogma that no new nerve cells can be formed in the human brain after birth. In 1998, Erickson et al. could demonstrate for the first time the

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new formation of nerve cells in the adult hippocampus, a central structure for memory functions (5). Studies in animal models have shown that especially physical activity and an environment full of variety promoted the number of newly-formed nerve cells and their integration in the existing neuronal networks. In the past two years, however, several studies have been published – among others in the magazine *Nature* – that deny adult neurogenesis (18). With respect to this, the question arises of the extent to which physical activity and sports training induce neurogenesis or whether the positive effects are mediated via other neurobiological mechanisms (angiogenesis, synaptogenesis, etc.). In this context, however, it must be stated that the neurobiological mechanisms of sports-induced neuroplasticity are hardly understood (8). Potential molecular and cellular mechanisms of action are, among others:

- Growth factors (such as brain-derived neurotrophic factors [BDNF], vascular endothelial growth factor [VEGF], insulin-like growth factor 1 [IGF-1])
- Increased cerebral perfusion
- Reduced systemic inflammation (22,23).

Physical Activity and Sports in the Prevention of Dementia Diseases

Numerous epidemiological, cross-sectional and interventional studies indicate that physical activity and sports training can significantly reduce the risk of dementia (12). A metaanalysis by Hamer & Chida in 2009, which included 16 prospective studies, concluded that physical activity reduces the dementia risk by 28% and the risk of Alzheimer's dementia up to 45% (6). A positive relationship between physical performance capacity (determined by Vo2max), the hippocampal volume and cognitive capability has been shown in several cross-sectional studies (12). Some randomized interventional studies, on the other hand, show mixed results (1). In a landmark study in 2011, Erickson et al. could demonstrate that 1-year aerobic endurance training led to an increase in the hippocampal volume and an improvement in memory performance (4). A current Cochrane Review (based on 12 studies with 754 participants) reported, however, no evidence for positive effects of aerobic endurance training on cognitive capabilities in elderly people (21). Potential causes could be too-small samples, too-short intervention periods at too-low intensity, test batteries with low sensitivity or other things. Due to the sometimes inconsistent research situation, no guidelines on the importance of physical activity and sports in the prevention of dementia diseases have been issued. In this respect, Voss et al. recommend plans for future research in order to accelerate the creating of guidelines (20). In this context, the focus should be among other things on hippocampal memory capacity (for example using pattern separation).

Due to the multifactorial genesis of dementia diseases, the influence of multidimensional intervention concepts on the prevention of dementia has been increasingly examined (9). Completed studies with a number of subjects greater than 1000 include FINGER (Finland, n=1260), PreDIVA (Netherlands, n=3526) and MAPT (France, n=1680). Results of the FINGER study have shown that a 2-year multidimensional intervention (sports, nutrition, cognitive training, vascular monitoring) can hinder cognitive degenerative processes in people with an elevated risk of dementia (14). Results of the 5, resp. 7-year follow-up examinations are currently being prepared.

The primary result of the MAPT and the PreDIVA studies were less impressive. Secondary analyses have, however, also shown in these two studies that especially people with an elevated risk of dementia profit from the intervention. Rosenberg et al. draw three central conclusions from the multidimensional approaches thus far. It is (i) elementary to examine the right target group (especially persons with an elevated risk of dementia), (ii) as early as possible (highest potential for prevention in cognitively-healthy and younger seniors) and (iii) by means of intensive intervention (17). A world-wide FINGERS study is currently running based on the positive results of the Finish FINGER study (<https://alz.org/wwfingers>).

Physical Activity and Sports in the Therapy of Dementia Diseases

The number of randomized, controlled interventional studies on the effects of sports in dementia diseases, mild cognitive impairment) is currently lower than in cognitively-healthy seniors. A current metaanalysis (based on 13 randomized, controlled interventional studies on 673 dementia patients) reports that physical activity and sports can improve cognitive capabilities and activities of daily living. The effect size and evidence situation are, however, low.

Another important aspect in the context of dementia diseases are neuropsychiatric comorbidities. Metaanalyses report a prevalence of neuropsychiatric symptoms (depression, psychomotor restlessness, anxiety, aggression, sleep disorders) of 60 to 90%. These are a serious cleft in the patients' autonomy and quality of life. The Danish ADEX study showed in this respect that moderate to high-intensity sport intervention leads to a significant improvement in neuropsychiatric symptoms in dementia patients.

Physical Activity and Sports in the Prevention and Therapy of Other Neurodegenerative Diseases

Morbus Parkinson is the second most-common neurodegenerative disease. The pathophysiological mechanism of Parkinson's is nerve-cell destruction of dopaminergic neuron in the Substantia nigra. Clinically Parkinson's manifests with the classical triad of akinesia, rigor and tremors at rest along with postural instability. Epidemiological studies indicate that physical activity can significantly reduce the risk of Parkinson's. Randomized controlled interventional studies have shown positive effects of physiotherapy and sports on motoric capabilities and neuroplasticity in Parkinson patients (15) and, according to current S3 Guidelines of the DGN (Deutsche Gesellschaft für Neurology / German Neurology Society) they should be part of the therapy. Which training form (endurance training, strength training, dance training, etc.) at which intensity constitutes the optimal therapy form must be verified in further interventional studies.

The research situation is inconsistent with respect to the effects of physical activity and sports on the prevention and therapy of less-common neurodegenerative diseases (such as ALS (amyotrophic lateral sclerosis), Huntington's chorea) (24). Several case-control studies with small numbers of patients with ALS and Huntington's chorea indicate a relationship between physical activity and the risk of disease, resp. the progression of the disease. In ALS, a European

case-control study (on 652 ALS patients) could, however, determine no negative effect of physical activity (16). Animal-experimental and human studies with low numbers of patients indicate that low-to-moderate physical training can improve the performance capability of ALS patients (24). However, clear guidelines are missing for sports-medical practice on the use of exercise and sports in the prevention and therapy of less-common neurodegenerative diseases. Randomized controlled interventional studies are therefore urgently needed.

Conclusion & Outlook

Research interest has increasingly grown over the past years with respect to the effects of physical activity and sports on neurodegenerative diseases. Physical activity and sports are low-cost intervention forms with low to no side effects, which offer positive health benefits over the whole span of life. Current studies show that both physical activity and sports play a central role, especially in the prevention of dementia diseases. The effects of training interventions in patients with mild cognitive impairments (MCI) and dementia are considerably lower. This implies that an early intervention is necessary. From the point of view of neuroscience and sports-medicine, life-long physical activity and sport training are optimal for the prevention of dementia diseases. However, clear guidelines for sports-medical practice are lacking for the use of exercise and sports in the prevention and therapy of neurodegenerative diseases.

Future studies should investigate the dose-effect mechanism of various forms of intervention (7, 19), the potential of personalized sport interventions (13) and the neurobiological mechanisms of sport-induced neuroplasticity. ■

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