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REVIEW

Activation of the Brain to Postpone Dementia: A Concept Originating from Postmortem Human Brain Studies

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Abstract Alzheimer's disease (AD) is characterized by decreased neuronal activity and atrophy, while hyperactivity of neurons seems to make them resistant to aging and neurodegeneration, a phenomenon which we have paraphrased as 'use it or lose it'. Our hypothesis proposes that (1) during their functioning, neurons are damaged; (2) accumulation of damage that is not repaired is the basis of aging; (3) the vulnerability to AD is determined by the genetic background and the balance between the amount of damage and the efficiency of repair, and (4) by stimulating the brain, repair mechanisms are stimulated and cognitive reserve is increased, resulting in a decreased rate of aging and risk for AD. Environmental stimulating factors such as bilingualism/multilingualism, education, occupation, musical experience, physical exercise, and leisure activities have been reported to reduce the risk of dementia and decrease the rate of cognitive decline, although methodological problems are present.

Keywords Dementia · Genes · Environmental stimulation · Brain activation · Cognitive reserve · Use it or lose it

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Introduction

Dementia and other brain disorders are by far the leading contributors to dependence. Worldwide, ~ 50 million people live with dementia, a figure that is thought to rise to 132 million by 2050 [1]. Alzheimer's disease (AD) is the most prevalent cause of dementia in the elderly. AD neuropathology is characterized by the presence of plaques containing amyloid beta (Aβ) and tangles consisting of hyperphosphorylated tau [2]. Based on the age of onset, AD can be divided into two subtypes: early-onset AD (EOAD), which starts before 65 years of age and represents only about 1% of all AD cases, and a late-onset type (LOAD), which begins after 65 years of age and represents 99% of all AD cases [3]. The contribution of the genetic component is much stronger for EOAD than for LOAD. Mutations in three different genes are well known to cause rare cases of EOAD in an autosomal dominant way: *APP*, *PSEN1*, and *PSEN2*. *APOEε4* is the most prevalent gene that increases risk in both EOAD and LOAD (reviewed in [4]). Genome-wide association studies have reported some 20 additional genetic risk loci for LOAD (reviewed in [5]). AD is generally based upon interactions between genetic and environmental factors. Environmental factors such as bilingualism/multilingualism, education, occupation, musical experience, physical exercise, and leisure activities have been reported to be associated with a postponement of AD, but definitive proof of such effects is lacking.

Our working hypothesis (Fig. 1) is that neurons sustain damage during their functioning, but that they have systems that efficiently repair most of this damage. The lifetime accumulation of damage that is not repaired is the basis for aging, and this is the main risk factor for AD. The balance between the amount of damage and the efficiency of repair determines the vulnerability to AD. Both extra

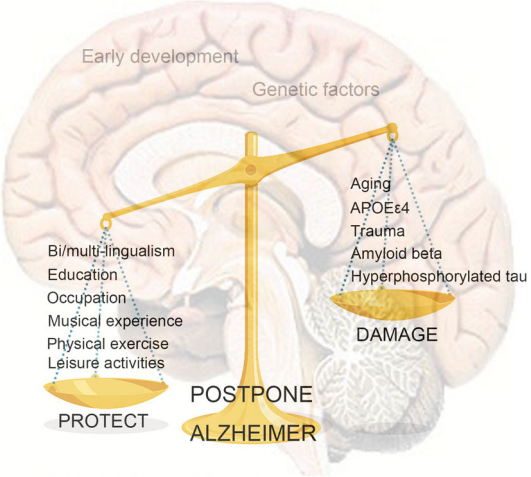

Fig. 1 Neurons are damaged by functioning, aging, trauma, and pathological changes like amyloid beta and hyperphosphorylated tau, and are more vulnerable due to some genetic factors, such as APOEε4. However, they have systems that efficiently repair most of the damage. Repair is stimulated by activating the brain. The balance between the amount of damage and the efficiency of repair determines the risk for Alzheimer's disease (AD). By stimulating the brain with environmental factors such as bilingualism/ multilingualism, education, occupation, musical experience, physical exercise, and leisure activities, repair mechanisms are thought to be stimulated and cognitive reserve is increased, resulting in postponing AD.

damage due to environmental factors and deficient repair due to polymorphisms may result in an earlier onset of AD. In contrast, by stimulating the brain, the interaction between genetic and environment changes in such a way that cognitive reserve and/or the repair mechanism are increased, and so the rate of aging and the risk for AD are decreased. Indeed, decreased neuronal activity is an essential characteristic of AD, while increased neuronal activity seems to postpone AD changes, findings that have been paraphrased as 'use it or lose it' [6]. Interestingly, as was shown recently in the brains of hibernating animals, hypometabolism can trigger the hyperphosphorylation of tau [7]. Moreover, a larger brain size, suggesting increased brain reserve, goes together with a later age of onset of AD [8]. In a study of nuns 75–95 years of age, it was found that those who made more complex sentences in their letters at age 22 and thus had better functioning brains, were better protected against AD [9]. Recent epidemiological studies have shown that factors like bilingualism/multilingualism, education, occupation, musical experience, physical exercise, and leisure activities, correlate with a slower rate of memory decline during aging, a delayed onset of mild cognitive impairment (MCI), and/or a lower incidence of dementia. It is clear that the risk for AD is influenced by an interaction between genes and environment, while age is the major risk factor. Our hypothesis is that stimulation of brain function may favorably affect the interaction between genes and environment, increase repair and cognitive reserve, and thus slow brain aging and postpone AD. Arguments for this idea are presented in this review.

Cognitive Reserve and Neuronal Activation

Various reports indicate that extra brain reserve postpones AD. A larger premorbid brain size is correlated with a later start of AD [8]. Furthermore, IQ is positively correlated with premorbid brain size and negatively with brain atrophy in AD patients, where the disease presents with mild to moderate severity [10]. In contrast is a smaller brain size related to an earlier onset, a more rapid progression, and longer disease progression of AD [11].

A clear example of small brain size is Down syndrome (DS) [12], which is accompanied by a shorter life expectancy [13] and early cognitive decline [14]. All DS patients show AD-related neuropathology by age 40 [15], and develop dementia at a mean age of 55.5 years [14]. Also, the *APOEε4* allele is more frequent in DS individuals than in controls [16]. In contrast, the *APOEε2* allele has a protective effect against AD in adults with DS [17].

Neuronal activity is consistently decreased in AD. A positron emission tomography (PET) study showed a regional impairment of cerebral glucose metabolism in AD, especially in the temporal and parietal lobes [18]. Another PET study extended this finding by showing that *APOEε4* carriers have a more pronounced decline of metabolism in AD [19]. In addition, a significant negative relationship has been found between brain metabolism as measured by PET and plaque density in AD [20], as well as with the phosphorylated tau protein levels in the cerebrospinal fluid (CSF) in AD [21].

A decrease of cerebral glucose metabolism may precede cognitive impairment in patients with genetic risk factors. Reiman *et al*. [22] found that late middle-aged cognitively normal subjects who were homozygous for the *APOEε4* allele already had reduced glucose metabolism in those brain areas that were later affected by AD, in accord with Herholz's study [18]. Besides, pathological changes (i.e. Aβ) are associated with hypometabolism in cognitively normal controls before atrophy occurs [23].

Interestingly, increased activity has been reported in early/preclinical stages of AD in various brain areas. Higher metabolism has been found in the nucleus basalis of Meynert in MCI patients than in controls and late-stage AD patients [24]. Higher basal forebrain metabolism has also been found in MCI patients (Aβ positive or negative), while lower in patients with further cognitive decline [25]. In addition, cortical hypermetabolism has been reported in mostly Aβ-negative MCI patients [26]. Hypermetabolism in the hippocampus has been found in Aβ-positive MCI

patients [27]. Our micro-array study also showed neuronal hyperactivity in the prefrontal cortex in preclinical AD patients, as demonstrated by increased expression of a large number of genes [28, 29]. The hypermetabolism in some cognition-related areas in MCI patients suggests that the brain acts against the first functional impairments at the incipient stages of dementia. We are currently investigating a transcription factor (early growth response 1, Egr1) and microRNA-132 that may be responsible for the hyperactivity in the early stages of AD [30]. Indeed, in an AD mouse model, deficiency of this microRNA increases Aβ deposition and tau expression, phosphorylation, and aggregation [31–34].

There is also an increasing amount of literature indicating that metabolically very active neurons are less vulnerable to aging and AD, a phenomenon that we have paraphrased 'use it or lose it' [6, 35]. We have found various examples of such a relationship in the hypothalamus. Increased plasma vasopressin (AVP) levels are found in elderly subjects [36]. During aging, AVP neurons are activated in the supraoptic nucleus in women [37, 38], and these neurons remain intact in AD [39, 40]. The corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus are activated during aging in males and even more activated in AD (reviewed in [41]).

In contrast, a marked reduction in the number of AVP-expressing neurons and in the amount of AVP-mRNA was found in the suprachiasmatic nucleus (SCN) in aging, and even more so in AD. The SCN is the master biological clock, which regulates all circadian rhythms. In old rats, the diminished circadian sleep-wake amplitude can be restored by increasing the intensity of environmental light. In addition, the increased light input counteracts the age-related decrease in the number of AVP-expressing neurons in the SCN [42, 43]. In humans, we found by actigraphy that additional bright light improves the day-night rhythm in patients with intact vision, but not in patients with compromised sight [44]. We also found that the age-related decrease in melatonin secretion during the night, which is under the control of the SCN, is partly due to poor illumination as experienced by many elderly people, and can be restored using bright light [45]. Light is not a therapy for AD but rather a therapy for SCN function. However, it shows an important principle, i.e. that it is possible to re-activate neurons that are functionally affected in AD.

Early in the process of AD a phase of spontaneous activation has been found in different brain areas. Increased metabolic activity has been reported in the nucleus basalis of Meynert using the size of the Golgi apparatus as a measure of metabolic activity [24]. This spontaneous activation occurs in the phase of MCI, i.e. Braak stages III and IV, a result that confirmed later by *in vivo* PET [25]. In addition, we found activation of the expression of 865 genes in the prefrontal cortex in early, preclinical, AD (i.e. between Braak stages II and III), just before the accumulation of plaques and tangles. These activated genes are involved in synaptic activity, plasticity, and energy metabolism [28]. These studies suggest that a phase of spontaneous early activation occurs during the preclinical/early stages of AD that may temporarily compensate for the neuropathological changes and that seems to prevent cognitive impairment for some time.

Various *in vitro* studies have shown that neuronal activity can protect against cell death. One study showed that neural activation protects hypothalamic magnocellular neurons against functional axotomy-induced programmed cell death by the sodium channel blocker tetrodotoxin (TTX), both *in vivo* and *in vitro* [46]. Another study [47] found that prolonged suppression of spontaneous activity using TTX causes the death of cortical neurons in primary cell cultures, which may be mediated by Tissue-Type Plasminogen Activator [48]. Although these experiments are presumed to lead to a better understanding of slow neuronal death in neurodegenerative diseases, they are not directly AD-related. Recently, Akwa *et al.* found that synaptic activity protects against AD and frontotemporal dementia (FTD)-like tau-pathology by autophagic lysosomal degradation [49], indicating that neuronal activity may diminish AD pathology.

Only a few studies have shown that genetic factors affect the response of neuronal activity to environmental stimulation. One study indicated that the degree of cognitive improvement by combination training depends on dopamine-related genotypes: DRD3 Ser9Gly and COMT Val158Met polymorphism carriers benefit most from exposure to such training [50]. In addition, genes affect neuronal activity. It has been shown that nerve growth factor gene therapy triggers the activation of neuronal responses, i.e. axonal sprouting, cell hypertrophy, and activation of functional markers in AD patients [51].

Environmental Stimulation of Cognitive Reserve

Bilingualism and Multilingualism as a Stimulus for Cognitive Reserve

Several retrospective studies present evidence that bilingualism delays the onset of dementia by $\sim$ 4 years. Bialystok *et al.* first reported that bilingual patients with cognitive complaints show symptoms of dementia 4 years later than monolingual people, without a change in the rate of progression [52]. Later retrospective studies carefully controlled for multiple confounding variables (education, gender, cognitive and occupational levels, and immigration

status) also reported positive effects of bilingualism [53, 54]. Wilson *et al*. reported that a higher level of mastery of a foreign language is associated with a reduced risk of MCI [55]. However, the idea that bilingualism reduces the risk of dementia is still controversial, since other studies have not supported such a protective effect of bilingualism on age-related cognitive decline, nor on developing dementia [56–58] or a delay of onset of dementia [59–61]. However, the definition of bilingualism and the design and statistical structure of the studies varied [56, 59, 60]. Thus, well-controlled prospective studies are still lacking. Support comes, however, from the study of Klein *et al*. [62], who found a decline in the incidence of AD with an increase in population multilingualism, even after controlling for wealth and literacy. The overall picture still favors the conclusion that bilingualism protects against the symptoms of dementia.

Recent data seem to show an even stronger protective effect on cognition by multilingualism than bilingualism. In a retrospective nested case-control study consisting of participants with cognitive impairment without dementia and normal controls aged 65 and over, multilinguals presented a lower risk of cognitive impairment without dementia than bilinguals, after adjustment for education and age [63]. In another study [64], in which the study group consisted of immigrants and non-immigrants in Canada, it was found that multilingualism but not bilingualism in the overall group showed a delay of the age at diagnosis or age at onset of symptoms of almost 5 years, in agreement with the study of Bialystok *et al*. [52]. In a study of patients with dementia, Alladi *et al*. confirmed that bilingual patients develop dementia 4.5 years later than monolingual patients, while no additional benefit of speaking more than 2 languages was found [54]. It is thus at present not clear under what circumstances multilingualism provides more protection than bilingualism against the decline of cognition in AD. In addition, it is not yet known whether learning a second language later in childhood or even in adulthood without becoming bilingual, also results in extra cognitive reserve.

Bilingualism/multilingualism in relation to cognitive decline has also been studied with imaging techniques. A computed tomography study showed that bilingual patients with AD have more brain atrophy than monolingual patients [65]. Another study reported that multilingual MCI and AD patients have a thicker cortex than monolinguals [66]. Besides, bilingualism protects the brain against pathological changes. Early bilingualism is associated with lower CSF-tau [67]. The data indicate that bilingualism enhances cognitive reserve and enables bilinguals to function at a higher level than would be predicted from the level of the disease. So far, no systematic study of the association between bilingualism or multilingualism and the AD-related genetic background has been done.

Education and Cognitive Reserve

The risk of developing clinical cognitive AD changes has been found to be reduced in participants with higher education in most cohort studies [68–70], but not all [71, 72]. Some found that the association between education and AD is gender dependent [73], while various others found that the education effect is mainly present in the lowest education group [74–76].

Moreover, the role of education in predicting the clinical course of AD is not clear. On the one hand, a recent longitudinal cohort study based on a large data set of autopsy patients with confirmed AD demonstrated that a higher level of education is associated with a lower Clinical Dementia Rating Scale [77]. Some prospective studies found a significantly steeper rate of decline over time in cognitive performance among those with more education [78–80]. Patients with a higher education show a faster disease progression not only in LOAD, but also in EOAD [81]. The idea is that when AD clinically manifests in better-educated patients, the brain pathology is already quite advanced due to the greater brain reserve. This has indeed been confirmed in some imaging studies [82–84]. In contrast, one study of 482 patients with possible or probable AD, found a significantly slower rate of cognitive decline among those with more education [85].

Opinions differ when it comes to the association between the typical neuropathological changes in AD and education. While education has been reported to reduce the risk of dementia associated with a lower amyloid load [86], bigger head circumference [87], fewer neuritic plaques [88, 89], and a lower Braak stage [88], there are conflicting reports on an educational effect on brain atrophy [90], and on diffuse plaques [89] and tangles [86, 89, 91]. Moreover, education diminishes the cognitive consequences of severe but not of mild white matter pathology [92], while the opposite pattern occurs for tangles and neuritic plaques [88, 89, 91]. In addition, education is negatively associated with plasma tau levels in MCI and early AD [93].

One study has shown that education cancels out the genetic liability of *APOEε4* for cognitive decline, probably by enhanced reserve [94]. This is in accord with a study that was based on pooled data from three major population-based studies [95]. Higher education protects the brain from neuropathological AD changes in genetically risky subjects as well. A higher education is associated with lower amyloid in *APOEε4* carriers [96]. It should be noted, though, that the level of education is dependent on IQ and social factors and is confounded by self-selection, while for

obvious reasons randomized lifelong controlled trials cannot be performed on this topic.

Occupation and Cognitive Reserve

A population-based twin study suggested that greater complexity of work, especially with people, may reduce the risk of AD [97]. In addition, some cross-sectional studies associate the risk of developing dementia with lower occupational achievement [98–100], but this is not the case for all studies [101–103]. The differences may be caused by the interaction between the level of education and the risk of dementia [104]. Recurrent novelty at work seems to be a major stimulus for the brain [105]. Less complicated work such as manual labor is associated with earlier development of AD [106, 107] and complicated, intellectual work is associated with a reduced risk of AD [108]. Besides, occupational exposure to deleterious environments and substances such as metals, chlorinated solvents, and extremely low frequency magnetic fields increases the risk of AD [109].

Occupational complexity is correlated with better cognitive performance. However, the protection that occupation offers in terms of cognitive ability seems to disappear after retirement. Results from the Australian Longitudinal Study of Ageing showed that higher complexity of occupation is associated with greater speed, better memory, and better mental status at baseline in older individuals, but there are no associations of occupational complexity with rates of cognitive decline over time [110]. Finkels *et al.* even reported that a previously high level of complexity of a job that involves working with people is associated with a faster decline after retirement [111], in accord with the results of the Glostrup 1914 Cohort [112]. A recent study showed that high occupational attainment in individuals with MCI is an independent risk factor for a higher progression rate of MCI to AD, suggesting that the protective effect of high occupational attainment against cognitive decline disappears in the MCI stage [113]. Also, a later retirement age is associated with a later age at diagnosis of AD [114]. These studies illustrate that the cognitive protection brought about by occupation may need consistent occupation. The protective effect of occupation complexity led researchers to the hypothesis that occupational therapy might be helpful for AD patients. Multiple studies have indeed shown that occupational therapy delays the functional decline in AD patients (reviewed in [115]).

Measurements of hippocampal volume and brain atrophy suggest that occupational complexity enhances the cognitive reserve and reduces the adverse effects of neuropathology on cognition [116]. Occupation may protect cognition in *APOEε4* carriers as well. The onset of cognitive impairment in carriers with high lifetime intellectual enrichment occurs $\sim$ 8.7 years later than in carriers with low intellectual enrichment [117]. However, no significant difference was found between *APOEε4*-carriers and non-carriers in terms of the effect of occupation in another study [118]. Again, self-selection confounds studies on occupation. The effect of occupation on *APOEε4* carriers is thus far from settled. So far, there appears to be no systematic study about the association between occupation and AD-related pathological changes.

Musical Experience and Cognitive Reserve

Musical experience has the capacity to engage auditory, cognitive, motor, and emotional functions and remains relatively preserved with aging. Elderly people who underwent long-term musical training earlier in life do better in a wide range of auditory processing tasks [119–121]. They also show faster performance and timing in language tasks [122], enhanced auditory attention [123], music-related motor abilities [124], and executive functions [125]. Moreover, music training in early life seems to have a beneficial effect that continues into late adulthood [126, 127]. Musical training in elderly people seems to be beneficial for cognition as well. Piano lessons for older adults result in enhanced cognitive flexibility, general processing speed, and working memory [128], as well as executive functions, attention, visual scanning, and motor ability [129]. It should be noted, however, that these conclusions are not based upon formal randomized well-controlled tests. It can, therefore, not be excluded that those persons who have chosen voluntarily to follow a musical training are different from non-musicians by self-selection.

Playing a musical instrument by elderly of 75 years of age reduced the risk of developing dementia in a 5-year follow-up [130]. Another study showed that music lessons in childhood and adolescence are associated in old age with a lower risk of developing MCI, but not with a slower rate of cognitive decline [55].

Possibly because of the relative neuropathological preservation of medial frontal and limbic areas in AD [131], music-induced emotions and memories are preserved even in the more advanced stages of AD [132, 133]. This enables the application of music therapy in all stages of dementia. Stimulating background music has been reported to temporarily enhance awareness [134], episodic memory [135–137], and verbal fluency [138]. The "Index music" method, in which the subjects have to describe a memory of their choice related to the music presented to them, has been found to increase the autobiographical memory quality scores of AD patients [139]. Both singing and listening to music may help to maintain general cognition and executive function and alleviate depression [140]. Singing is more effective than listening to music or

standard care for patients for enhancing working memory and episodic memory, especially in patients with mild dementia, and for reducing the psychological stress and burden experienced by caregivers [141]. In addition, singing in a choir improves cognition and visuospatial processing in AD patients [142] and 6-months of karaoke-singing improves psychomotor speed and mood in AD patients [143]. However, another study reported a lack of improvement of verbal memory after 12 weeks of singing in AD patients [144]. Moreover, playing a musical instrument enhances cognition as measured by the Mini-Mental State Examination scores in MCI patients [145]. So far, however, there is no study trying to explain the differences in observations on the basis of associations between musical experience and genetic background.

Physical Activity and Cognitive Reserve

A large number of studies have consistently shown a relationship between more physical activity and a reduced risk of dementia. A review which analyzed 20 longitudinal epidemiological studies suggested a significant and independent preventive effect of physical activity on cognitive decline or dementia, after adjustment for various confounders [146]. In a meta-analysis of 16 prospective epidemiological studies, people engaged in a baseline level of physical activity had a 28% lower risk of developing any type of dementia and a 45% lower risk of developing AD, even after controlling for confounding variables [147]. Leisure-time physical activity clearly reduces the risk of AD. However, the risk reduction is less clear for types of physical activity related to occupation and commuting. The only study separating occupational from commuting activities, and distinguishing them from leisure-time activities, did not find a relationship with AD risk [148], suggesting that work-related physical activity is not enough to protect against AD.

It has been suggested that physical activities at any time in life protect against cognitive impairment [149], while early/mid-life physical activity confers stronger protection than late-life exercise. Mid-life physical activity appears to protect against dementia late in life [150]. A population-based case-control study [151] shows that those who take moderate exercise during mid-life have a lower risk for MCI than those who take it late in life. While teenage physical activity is most strongly associated with lower odds of late-life cognitive impairment among all four stages of life [149], it seems that earlier physical activity has a stronger protective effect on cognitive impairment. However, it is never too late to increase physical activity for cognitive protection.

The intensity of physical activity is also a factor in the protection against cognitive impairment. A recent prospective cohort study derived from the a population-based study [152] found that physical activity at a moderate intensity in mid-life among MCI participants decreases the risk of dementia. In a meta-analysis based on 15 prospective studies, Sofi *et al.* [153] reported a consistent protection by all levels of physical activity against cognitive decline, with stronger protection in the high-level exercise group than individuals in the low-to-moderate level exercise group. A large cohort study was carried out in individuals of 65 years or older and showed after 5 years that higher levels of physical activity are associated with a reduced risk of cognitive impairment, AD, and other dementias [154]. A recent study quantified the intensity of physical activity and showed that physical activity over a specific range (0–2000 kcal/week or 0–45 metabolic equivalent of task h/week) is associated with a risk of AD in an inverse linear dose–response manner, such that an increase in physical activity by 10 metabolic equivalent of task h/week or 500 kcal/week is associated with a $\sim$ 13% decrease in the risk for AD [155]. Physical activity has been found to protect against cognitive decline, while the protection level differs for different types of physical exercise. Many programs, including physical exercise, have been carried out for aged adults to protect them from cognitive decline. One program explored the effects of an "everyday" activity. The participants tended to show improvements in executive function and memory relative to matched controls ($P < 0.10$), with impaired baseline executive function showing the greatest improvement compared to non-impaired controls [156]. In addition, a combination of fun-recreational activities as well as cognitive, aerobic, and sensory stimuli counteract aging-related cognitive decline [50]. However, a meta-analysis on walking for non-demented sedentary elderly revealed that walking improves set-shifting (task-switching) and inhibition (Stroop Color and Word Test) without improving cognitive impairment. Specifically, no improvements were found in executive functioning [157].

Even though it seems that physical activity may have a protective effect on cognition in non-affected elderly, the role of physical activity for individuals already experiencing cognitive impairment is less clear. One may wonder, of course, whether physical activity is able to reverse the pathophysiological process of dementia during the latest stages of the disease. A recent meta-analysis suggested that physical exercise, aerobic exercise in particular, benefits global cognition in MCI patients [158]. This is in accordance with an earlier meta-analysis of 30 trials with 2,020 participants [159], which reported beneficial effects of physical activity on physical fitness and cognitive function in adults with cognitive impairment (MCI and dementia), while the mean time required to achieve these results was in most cases < 4 months. As reviewed by

Rolland *et al.* [146], physical activity brings about significant improvements in AD patients in psychological and/or physical performance, mobility, balance, strength, gait speed, sleep, agitation, mood, and cognitive function. Another meta-analysis of 16 trials with 937 participants provided evidence that exercise programs significantly improve the ability to perform activities of daily life and possibly also improve cognition in people with dementia, although some caution was advised in interpreting these findings [160]. This result is in accord with a meta-analysis which focused on cognitive-physical interventions [161]. However, there are also studies that showed no effects of physical activity on cognition in a cognitively-impaired population [162], except for depression [163]. Although this field is in its infancy, it appears that physical activity is a feasible way to postpone, and to a lesser degree treat cognitive decline, even in the presence of AD. Continued research on strength, consistency, and the dose-response relationship is needed to safely disseminate physical activity as a treatment for cognitive impairment. In particular, more prospective research, including the genetic background of patients, is needed to evaluate the therapeutic effect of physical exercise in older adults with AD.

When it comes to the association between physical activity and the APOE genotype, few studies have been performed. One study found that moderate and low levels of midlife leisure-time physical activity were associated with a higher risk of dementia, while high levels of such activity were related to a lower risk of dementia. More benefits of midlife leisure time physical activity have been shown in *APOEε4* non-carriers [164]. This conclusion is the opposite of that of another study, which suggested stronger protective effects of physical activity on the risk of dementia in *APOEε4* carriers than in non-carriers [165]. A third study has demonstrated that carriers of dopamine-related genotypes, like the DRD3 Ser9Gly and COMT Val158Met polymorphisms, have the greatest benefits from exposure to combination training of sensory stimuli and fun-recreational activities [166]. So it is not yet clear how gene-environmental interactions influence the effect of physical activity on cognition and dementia.

The association between physical activity and the AD pathological (Aβ/tau) burden has been the topic of a few cross-sectional studies. When measured *in vivo* either by PET or by CSF analysis [167], a negative association between physical activity level and Aβ load has been found in cognitively intact elderly. A similar relationship was found between physical activity and CSF tau in another study, which disappeared, however, after controlling for cardiovascular risk factors, *APOEε4* status, and depressive symptoms [168]. In healthy late-middle-aged adults, engagement in moderate physical activity is associated with higher CSF Aβ42, lower total tau/Aβ42, and lower phosphorylated tau/Aβ42. In contrast, neither light nor vigorous physical activity is associated with any of the biomarkers [169]. In addition, a relationship was found between high levels of physical activity and reduced amyloid as determined by PET *in vivo* in *APOEε4*-positive individuals [170]. However, such a relationship is difficult to interpret because the brain changes may cause diminished physical activity. Without well-controlled, randomized longitudinal studies, it is difficult to judge what is cause or effect, especially in at-risk individuals.

Leisure Activity and Cognitive Reserve

Various studies have reported effects of leisure activity on the risk of cognitive decline/impairment and on the risk for AD (for reviews see [171] and [172]). The results from these studies are, however, inconsistent. Some studies reported a protective effect of social activities on the risk of cognitive decline/impairment [173–175], while others did not find a significant effect [175–177]. However, a recent meta-analysis showed significant associations between cognitive leisure activities and diminished risk of cognitive impairment and dementia [178]. Prospective studies have shown a protective role of leisure activity against dementia as well. A recent study, which examined a sample of 1,475 elderly ($\geq$ 65 years) who were dementia-free at baseline, over a follow-up period of up to 15 years, revealed that higher levels of "Total activity" and "Social activity" are associated with a decreased risk of dementia [179], in accord with a prospective study of Swedish twins [180], as well as with another 20-year cohort study [181]. Some studies have reported not only that life-long leisure activity has a protective effect, but also that late-life leisure activity reduces the risk of dementia [130, 182, 183]. One longitudinal study showed that stimulating activity, either mentally- or socially-oriented, may protect against dementia [184]. This is in accord with a recent longitudinal study which showed that late-life leisure activities protect against cognitive impairment among elderly Chinese, while the protective effect is more profound for educated elderly [185]. Another study found significant differences in the level of social activity at baseline between those with stable MCI and those who had progressed to dementia, indicating that social activity affects the further prognosis in MCI in a positive way [186]. However, two other studies did not find a significant protective effect of late-life social support activities [187] or of midlife social engagement [188] on the risk of dementia. The overall image is that leisure activity, during one's whole life or just in late life, seems to be accompanied by a reduced risk of dementia.

The effect of leisure activities on cognitive function appears to be domain-specific. One study reported that participation in political activities is related to better

cognition. This appears, however, not to be the case for social-cultural or organizational activities [189]. Another study reported that reading, watching TV and listening to radio, may diminish the decline in perceptual speed, but not in verbal fluency or performance, whereas no effect was found of social or religious activities on any of the cognitive domains [176]. Leisure activities that have demonstrated pro-cognitive effects include reading, discussion groups, computer usage, participation in card and board games, solving puzzles, playing musical instruments, and learning a second language. Social activities that have demonstrated pro-cognitive effects include traveling, going to the theater, concerts or art events, participating in social groups, socializing with family, and dancing [190].

The potential impact of leisure activity/cognitive training in late life in older adults has been a topic of increasing interest. A meta-analysis of 7 randomized clinical trials (RCTs) in healthy older adults showed that interventions with cognitive exercise have an average effect size of 0.6 on neuropsychological performance, which is consistent with the findings from observational studies [191]. The effect size for RCTs does not depend on the duration of the follow-up. However, the quality of reports is generally low. The overall findings indicate that multi-domain cognitive training has the potential to improve cognitive function in healthy elderly and slow down the decline in affected individuals [192]. The effect of mental activity/cognitive training is preserved in cognitively impaired elderly according to a cross-sectional study [193].

However, few RCTs have focused on the effects of social and other types of activity on improving cognitive function in cognitively impaired individuals, since they are difficult to perform. Moreover, it would be unrealistic to do an RCT for every single activity. The reported RCTs found just focused on one leisure activity. It has been reported that Mahjong [194–196], Taichi [194, 197], or video games requiring physical activity [198] can preserve functioning or delay the decline in certain cognitive domains, even in people with significant cognitive impairment. Such cognitive activities may thus be effective non-drug treatments for cognitively impaired patients.

The relationship between cognitive leisure activities and neuropathological markers of AD is still controversial. One study of 186 elderly did not find any correlation between cognitive activity and a number of biomarkers such as *in vivo* amyloid load, glucose metabolism, and hippocampal volume [199], while another study of 118 elderly found that lifetime cognitive activity was associated with *in vivo* amyloid load in *APOEε4* carriers [200]. The interaction between leisure physical activity and *APOEε4* in dementia has been studied, more but so far remains controversial [201, 202]. Podewils *et al*. found that leisure physical activity is negatively associated with risk of dementia and the association is more marked in *APOEε4* non-carriers, but is absent in carriers [201]. In contrast, Rovio *et al*. reported a more pronounced association in *APOEε4* carriers [202]. It should also be noted, though, that improving cognition in a trial does not necessarily mean that this procedure will postpone AD.

Conclusions

The interaction between genetic background and environmental factors plays an important role in the risk for AD. As discussed, environmental factors such as bilingualism and multilingualism, education, occupation, playing music, physical exercise, and leisure activities are associated with a negative risk for AD (Fig. 1). However, their causal role in postponing AD is extremely difficult or even impossible to establish in randomized controlled trials.

More studies are needed on the effect of the genetic background of individuals who are exposed to environmental stimulation. The recent 'spontaneous' decrease in the prevalence of AD [203] must also have an environmental basis, although the exact factors involved are not known at present.

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