Activation of the Brain to Postpone Dementia:

A Concept Originating from Postmortem Human Brain Studies

Qiong-Bin Zhu[1,2], Ai-Min Bao[2]*, Dick Swaab[2,3]

1Department of Neurology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310020, P.R. China

2Department of Neurobiology; Key Laboratory of Medical Neurobiology of Ministry of Health of China; Zhejiang Province Key Laboratory of Neurobiology, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310058, P.R. China

3Netherlands Institute for Neuroscience, an Institute of the Royal Netherlands Academy of Arts and Sciences, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands

Correspondence to:

Ai-Min Bao, MD, PhD,

Prof. of Neurobiology,

Department of Neurobiology,

Key Laboratory of Medical Neurobiology of Ministry of Health of China

Zhejiang Province Key Laboratory of Neurobiology

Zhejiang University School of Medicine,

Hangzhou, Zhejiang 310058

P.R. China.

Tel.: +86 571 88208789.

E-mail: baoaimin@zju.edu.cn

Running Title

Environmental factors postponing Alzheimer

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Abstract

Alzheimer's disease (AD) is characterized by decreased neuron 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 is that 1) during their functioning, neurons are damaged. 2) accumulation of the damage that is not repaired is the basis for aging, 3) the vulnerability for AD is determined by the genetic background and the balance between the amount of damage and the efficiency of repair, 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, education, occupation, musical experience, physical exercise and leisure activities have been reported to reduce the risk for dementia and decrease the rate of cognitive decline, although methodological problems are present.

Introduction

Dementia and other brain disorders are by far the leading contributors to dependence. Worldwide, approximately 50 million people live with dementia, a figure is thought to rise to 132 million people 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* [4], *PSEN1* [5], and *PSEN2* [6]. *APOEε4* is the most prevalent gene that increases risk in both EOAD and LOAD [7, 8] (reviewed in [9]). GWAS studies have reported some 20 additional genetic risk loci for LOAD (reviewed in [10]). AD is generally based upon interaction between genetic and environmental factors. Environmental factors such as bilingualism, 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 is that neurons sustain damage during their functioning, but that they have systems that repair most of this damage efficiently. The lifetime accumulation of the 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 for AD. Both extra damage due to environmental factors or deficient repair due to polymorphisms may result in an earlier onset of AD. In contrast, by stimulating the brain, the interaction between gene 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 an increased neuronal activity seems to postpone AD changes, observations that paraphrased as ‘use it or lose it’ [13]. Interestingly, as was shown recently in the brains of hibernating animals, hypometabolism can trigger hyperphosphorylation of tau [14]. Moreover, a larger brain size, suggesting increased brain reserve, goes together with a later age of onset of AD [15]. In a study of nuns of 75 to 95 years of age, it was found that those nuns that made more complex sentences in their letters at age 22 and thus had better functioning brains, were better protected against AD [16]. 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 affect the interaction between genes and environment favorably, increase repair and cognitive reserve, thus slow down brain aging and postpone AD. Arguments for this idea will be presented in this review.

Cognitive reserve and neuronal activation

Various observations indicate that extra brain reserve postpones AD. A larger premorbid brain size is correlated to a later start of AD [15, 60]. Furthermore, IQ is positively correlated with premorbid brain size and negatively with brain atrophy in AD patients, where the disease presented with mild to moderate severity [61]. In contrast is a smaller brain size related to an earlier onset, a more rapid progression and longer disease progression of AD [62-64].

A clear example for the small brain size is Down syndrome (DS) [65, 66], which is accompanied by a shorter life expectancy [67] and early cognitive decline [68, 69]. All DS patients show AD related neuropathology at age 40 [70], and develop dementia at a mean age of 55.5 years [71]. Also, the *APOEε4* allele was more frequent in DS individuals than in controls [72]. In contrast, the *APOEε2* allele has a protective effect against AD in adults with DS [73].

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 [74]. Another PET study extended this observation by showing that *APOEε4* carriers showed a more pronounced diminishment of metabolism in AD [75]. In addition, a significant negative relationship was found between brain metabolism as measured by PET and plaque density in AD [76], as well as with the cerebrospinal fluid (CSF) phosphorylated tau protein levels in AD [77].

A decrease of cerebral glucose metabolism may precede cognitive impairment in

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patients with genetic risk factors. Reiman et al. [78] 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, which is in accordance with Herholz's study [74]. Besides, pathological changes (i.e. Aβ) went together with hypometabolism in cognitively normal controls before atrophy occurred [79].

Interestingly, increased activity was observed in early/ preclinical AD stages in various brain areas. Increased metabolism was found in the nucleus basalis of Meynert in MCI patients as compared to controls and late stage AD patients [80]. Increased basal forebrain metabolism was also found in MCI patients (Aβ positive or negative), while it decreased in patients with further cognitive decline [81]. In addition, cortical hypermetabolism was observed in mostly Aβ-negative MCI subjects [82]. Hypermetabolism in the hippocampus was found in Aβ positive MCI patients [83]. Our micro-array study also showed neuronal hyperactivity in the prefrontal cortex in preclinical AD patients, as demonstrated by an increased expression of a large number of genes [84, 85]. 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 early AD stages [86]. Indeed, in an AD mouse model deficiency of this microRNA increased Aβ deposition, tau expression, phosphorylation and aggregation [87-90].

There is also an increasing amount of literature indicating that metabolically very active neurons are less vulnerable for aging and AD, a phenomenon that we have paraphrased as 'use it or lose it' [13, 91]. We found various examples of such a relationship in the hypothalamus. Increased plasma vasopressin (AVP) levels were found in elderly subjects [92]. During aging there is an activation of AVP neurons in the supraoptic nucleus (SON) in women [93, 94]. These neurons remained intact in AD [95, 96]. The corticotropin releasing hormone (CRH) neurons in the hypothalamic PVN are activated during aging in males and even more activated in AD (reviewed in [97]).

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 could be restored by increasing the intensity of environmental light. In addition, was the increased light-input counteracting the age-related decrease in the number of AVP expressing neurons in the SCN [98, 99]. In humans, We found by actigraphy that additional bright light improved the day-night rhythm in patients with intact vision, but not in patients with compromised sight [100]. 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 [101]. 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 was found in different brain areas. Increased metabolic activity was observed in the nucleus basalis of Meynert using the size of the Golgi apparatus as a measure of metabolic activity [80]. This spontaneous activation was observed in the phase of mild cognitive impairment patients, i.e. Braak stages III and IV, an observation that was confirmed later by in vivo PET [81]. In addition, we found activation of the expression of 865 genes taking place in the prefrontal cortex (PFC) in early, preclinical, AD (i.e. between Braak stages II-III), just before the accumulation of plaques and tangles. These genes were involved in synaptic activity, plasticity and energy metabolism[84]. These studies suggest that a phase of spontaneous early activation occurs during preclinical/ early AD stages that may compensate temporarily for the neuropathological AD changes and that seems to prevent for some time cognitive impairment.

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 [102]. Another study [103] 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 [104]. Although these experiments are presumed to lead to 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 FTD-like tau-pathology by autophagic-lysosomal degradation [105], indicating that neuronal activity may diminish AD pathology.

Environmental stimulation of cognitive reserve

Bilingualism and multilingualism as a stimulus for cognitive reserve

Several retrospective studies present evidence that bilingualism delayed the onset of dementia by around four years. Bialystok et al. firstly reported that bilingual patients with cognitive complaints showed symptoms of dementia 4 years later than monolingual people, without a change in rate of progression [107]. Later retrospective studies carefully controlled for multiple confounding variables, i.e. education, gender, cognitive and occupational levels, immigration status, and they reported positive effects for bilingualism as well [108, 109]. Wilson et al. reported that a higher level of mastery of a foreign language was associated with a reduced risk of MCI [110]. However, the idea that bilingualism reduces the risk for dementia is still controversial, since other studies did not support such a protective effect of bilingualism on age-related cognitive decline, nor on developing dementia [111-113] or onset delay of dementia [114-116]. However, the definition of bilingualism, design and statistical structure of the studies varied [114, 115, 117]. Thus, well-controlled prospective studies are still lacking. Support comes, however, from the study of Klein et al. [118], 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 symptoms of dementia.

Recent data seems to show an even stronger protection of cognition by multilingualism than bilingualism. In a retrospective nested case-control study consisting of subjects with cognitive impairment without dementia and normal controls

aged 65 and over, multilingualism presented a lower risk of cognitive impairment without dementia when compared to bilinguals, after adjustment for education and age [119]. In another study [120], in which the observed 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. [107]. In a study consisting of patients with dementia, Alladi et al. confirmed that bilingual patients developed dementia 4.5 years later than monolingual patients, while no additional benefit of speaking more than 2 languages was found [109]. It is at present thus not clear under what circumstances multilingualism may provide more protection than bilingualism on the diminishment 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 is also studied with imaging techniques. A computed tomography (CT) study showed that bilingual patients with AD had more brain atrophy than monolingual patients [121]. Another study reported that multilingual MCI and AD patients had a thicker cortex than the monolinguals [122]. Besides, bilingualism protected the brain also against pathological changes. Early bilingualism was associated with lower CSF-tau [123]. 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. Until now, no systematic study about the association between bilingualism or multilingualism and AD related genetic background has been done.

Education and cognitive reserve

The risk of developing clinical cognitive AD changes was found to be reduced in subjects with higher education in most cohort studies [124-128], but not all [129, 130]. Some found that the association between education and AD is gender dependent [131], while various others found that the education effect is mainly present in the lowest education group [132-134].

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 was associated with a lower Clinical Dementia Rating Scale [135]. Some prospective studies found a significantly steeper rate of decline over time in cognitive performance among those with more education [136-140]. Higher educated patients showed faster disease progression not only in LOAD, but also in EOAD [141]. The idea is that when AD clinically manifests in better educated patients, brain pathology is already quite advanced due to the higher brain reserve. This has indeed been confirmed in some imaging studies [142-144]. In contrast, one study in 482 patients with possible or probable AD, found a significantly slower rate of cognitive decline among those with more education [145].

Opinions differ when it comes to the association between AD typical neuropathological changes and education. While education has been reported to reduce the risk of dementia associated with a lower amyloid load [146], bigger head circumference [147], fewer neuritic plaques [148, 149] and a lower Braak stage [148], there are conflicting reports on an educational effect on brain atrophy [150], and on diffuse plaques [149] and tangles [146, 149, 151]. Moreover, education was found to diminish the cognitive consequences of severe but not of mild white matter pathology [152], while the opposite pattern was found for tangles and neuritic plaques [148, 149, 151]. In addition, education was negatively associated with plasma tau levels in MCI and early AD [153].

One study showed that education cancels out the genetic liability of *APOEε4* for cognitive decline, probably by enhanced reserve [154]. This is in accordance with a study that was based upon pooled data from three major population-based studies [155]. 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 [156]. 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 [157]. In addition, some cross sectional studies associate the risk of developing dementia with lower occupational achievements [158-163], but this is not the case for all studies [164-166]. The differences may be caused by the interaction between the level of education and risk of dementia [167]. Recurrent novelty at work seems to be a major stimulus for the brain [168]. Less complicated, e.g. manual work, is associated with earlier development of AD [162, 169] and complicated, intellectual work is associated with a reduced risk of AD [170]. Besides, occupational exposure to deleterious environments and substances, e.g. metals, chlorinated solvents and extremely low frequency magnetic fields (ELF-MF) increase the risk of AD [171].

Occupational complexity is correlated with a 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 was associated with greater speed, better memory, and better mental status at baseline in older individuals but there were no associations of occupational complexity with rates of cognitive decline over time [172]. Finkels et al. even reported that a previous high level of complexity of a job that involved working with people was associated with faster decline after retirement [173], in accordance with the results of the Glostrup 1914 Cohort [174]. 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 [175]. Also, a later retirement age is associated with a later age at diagnosis of AD [176]. These studies illustrate that 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 in AD patients. Multiple studies have indeed shown that occupational therapy could delay functional decline in

AD patients (reviewed in [177]).

Measurements of hippocampal volume and brain atrophy suggest that occupational complexity may enhance the cognitive reserve and reduce the adverse effects of neuropathology on cognition [178]. Occupation may protect cognition in *APOEε4* carriers as well. The onset of cognitive impairment in carriers with high lifetime intellectual enrichment, was approximately 8.7 years later than in carriers with low intellectual enrichment [179]. However, no significant difference was found between *APOEε4*-carriers and no *ε4*-carriers in terms of the effect of occupation in another study [180]. Again, self-selection is confounding studies on occupation. The effect of occupation on *APOEε4* carriers is thus far from settled. Until now, there appears to be no systematic study about the association between occupation and AD-related pathological changes.

Musical experience and cognition reserve

Musical experience has the capacity to engage auditory, cognitive, motor, and emotional functions and remains relatively preserved with aging. Elderly people who did long-term musical training earlier in life, do better in a wide range of auditory processing tasks [181-184]. They have also a faster performance and timing in language tasks [185], enhanced auditory attention [186], music-related motor abilities [187] and executive functions [188]. Moreover, early life music training seems also to have a beneficial effect that stays into late adulthood [189, 190]. Music training in elderly people seems to be beneficial for cognition as well. Piano lessons for older adults resulted in enhanced cognitive flexibility, general processing speed, and working memory [191], as well as executive functions, attention, visual scanning and motor ability [192]. It should be noted, however, that these observations were not based upon formal randomized well controlled tests. It can, therefore, not be excluded that those persons who have chosen voluntarily to follow a music training are different from the 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 years follow-up [193]. Another study showed that music

lessons in childhood and adolescence were associated in old age with lower risk of developing MCI, but not with a lower rate of cognitive decline [194].

Possibly because of the relative neuropathological preservation of medial frontal and limbic areas in AD [195], are music-induced emotions and memories preserved even in more advanced stages of AD [196, 197]. This enables the application of music therapy in all stages of dementia. Stimulating background music was reported to temporarily enhance awareness [198] and episodic memory [199-201] and verbal fluency [202]. The "Index music" method, by which the subjects has to tell a memory of their choice related to the music presented to them, has been found to increase autobiographical memory quality scores of AD patients [203]. Both singing and listening to music may help to maintain general cognition and executive function and alleviate depression [204]. 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 psychological stress and burden as experienced by caregivers [205]. In addition, singing in a choir improved cognition and visuospatial processing in AD patients [206] and 6-month karaoke-singing improved psychomotor speed and mood were in AD patients [207]. However, another study reported a lack of improvement of 12 weeks singing on verbal memory in AD patients [208]. Moreover, playing a musical instrument enhances cognition as measured by the Mini-Mental State Examination scores in MCI patients [209]. Until now, there is, however, no study trying to explain the differences in observations by the association between musical experience and genetic background.

Physical activity and cognition reserve

A large number of studies have consistently shown a relationship between more physical activity and a reduced risk for 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 [210]. In a meta-analysis of 16 prospective, epidemiological studies, people engaged in a more baseline level of physical activity had a reduced risk

of developing any type of dementia of 28% and a reduced risk of developing AD of 45%, even after controlling for confounding variables [211]. Leisure-time physical activity clearly reduced the risk of AD. However, the risk reduction was 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 relation to AD risk [212], suggesting that work-related physical activity may not be enough to protect against AD.

It has been suggested that physical activities at any time in life protect against cognitive impairment [213], while early/mid-life physical activity showed a stronger protection than late-life exercises. Mid-life physical activity appeared to protect against dementia in late life [214]. A population-based case-control study [215] showed that those who took moderate exercise during mid-life had a lower risk for MCI than those who took it at late-life. While teenage physical activity was most strongly associated with lower odds of late-life cognitive impairment among all four stages of life [213], 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 of cognition impairment. A recent prospective cohort study derived from the population-based study [216] found that moderate intensity mid-life physical activity among MCI participants decreased the risk of incident dementia. In a meta-analysis based upon 15 prospective studies, Sofi et al. [217] reported a consistent protection for 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 65 years or older individuals and showed after 5 years that higher levels of physical activity were associated with a reduced risk of cognitive impairment, AD and other dementias [218]. A recent study quantified the intensity of physical activity and identified that physical activity over a specific range (0–2000 kcal/week or 0–45 metabolic equivalent of task hours /week) was 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 hours/week or 500 kcal/week was associated with a ~13% decrease in the risk for AD [219]. Physical activity was found to protect against cognitive decline, while the protection level was different in different types of physical exercises. Many programs including physical exercise were 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 improvements compared to non-impaired controls [220]. In addition, a combination of fun-recreational activities as well as cognitive, aerobic and sensorial stimuli counteracted aging-related cognitive decline [221]. However, a meta-analysis on walking for non-demented sedentary elderly revealed that walking improved set-shifting (Task switching) and inhibition (Stroop Color Word Test) without improving cognitive impairment. Specifically no improvements were found in executive functioning [222].

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 would be 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 [223]. This is in accordance with an earlier meta-analysis of 30 trials with 2,020 participants [224], 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 less than 4 months. As reviewed by Rolland [210] physical activity brought 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 including 16 trials with 937 participants provided evidence that exercise programs can significantly improve the ability to perform activity of daily life and possibly also improve cognition in people with dementia, although some caution was advised in

interpreting these findings [225]. This result was in accordance with a meta-analysis which focused on cognitive-physical interventions [226]. However, there are also studies that showed no effects of physical activity on cognition in a cognitively impaired population [227], except for depression [228]. Although this field is in its infancy, it appears that physical activity may be 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 dose-response relationship is needed in order 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 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 midlife leisure time physical activity were related to a lower risk of dementia. More benefits of midlife leisure time physical activity were shown in *APOEε4* non-carriers [229]. This conclusion was the opposite of that of another study, which suggested stronger protective effects of physical activity on the risk of dementia in *APOEε4* carriers compared to non-carriers [230]. A third study demonstrated that carriers of dopamine-related genotypes, like DRD3 ser9gly and COMT Val158Met polymorphisms had the greatest benefits from exposure to a combination training of sensorial stimuli and fun-recreational activities [231]. 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 AD pathological change (Aβ/tau) burden has been the topic of a few cross-sectional studies. When measured in vivo either by PET or by CSF analysis [232], a negative association between physical activity level and beta-amyloid load was found in cognitively intact elderly. A similar relationship was found between physical activity and CSF tau in another study, that disappeared ,however, after controlling for cardiovascular risk factors, *APOEε4* status and depressive symptoms [233]. In healthy late-middle-aged adults, engagement in

moderate physical activity was associated with higher CSF Aβ42, lower total tau/Aβ42, and lower phosphorylated tau/Aβ42. In contrast, neither light nor vigorous physical activity was associated with any of the biomarkers [234]. In addition, a relationship was found between high levels of physical activity and reduced amyloid determined by PET in vivo in *APOEε4*-positive, individuals [235]. However, such a relationship is difficult to interpret because the brain changes may cause a 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 cognition reserve

Various studies have reported effects of leisure activity on the risk of cognitive decline/impairment and on the risk AD (for reviews see [236] and [237]). The results from these studies are, however, inconsistent. Some studies reported a protective effect of social activities on the risk of cognitive decline/impairment [238-241], while others did not find a significant effect [240, 242, 243]. However, a recent meta-analysis showed significant associations between cognitive leisure activities and diminished risk of cognitive impairment and dementia [244]. Prospective studies showed a protective role of leisure activity against dementia as well. A recent study, which examined a sample of 1,475 elderly (≥ 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" were associated with decreased risk of dementia [245], in accordance with a prospective study of Swedish twins [246], as well as with another 20-year cohort study [247]. Some studies reported not only that life-long leisure activity had a protective effect, but also that late-life leisure activity reduced the risk of dementia [193, 248, 249]. One longitudinal study showed that stimulating activity, either mentally or socially oriented, may protect against dementia [250]. This is in accordance with a recent longitudinal study which showed that late-life leisure activities protect against cognitive impairment among elderly Chinese, while the protective effect was more profound for educated elderly [251]. Another study found significant differences on the level of social activity at baseline between those with stable MCI and those who had progressed

to dementia, indicating that social activity may affect further prognosis in MCI in a positive way [252]. However, two other studies did not find a significant protective effect of late life social support activities [253] or of midlife social engagement [254] 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 reduce the risk of dementia.

The effect of leisure activities on cognitive function appeared to be domain specific. One study reported that participation in political activities was related to better cognition. This appeared, however, not to be the case for but social-cultural or organizational activities [255]. Another study reported that reading, watching TV and listening to radio, may diminish 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 [242]. 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 [256].

The potential impact of leisure activity/cognitive training in late life on 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 had an average effect size of 0.6 on neuropsychological performance, which is consistent with the findings from observational studies [257]. The effect size for RCTs did not depend on duration of the follow-up periods. However, the quality of reports was 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 [258]. The effect of mental activity/cognitive training is preserved in cognitively impaired elderly according to a cross-sectional study [259].

There are, however, few RCTs that have focused on the effects of social and other types of activity in 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 were just focused on one leisure activity. It has been reported that Mahjong [260-262], Taichi [260, 263] or video games requiring physical activity [264] can preserve functioning or delay 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 AD neuropathological markers 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 [265], while another study of 118 elderly found that lifetime cognitive activity was associated with in vivo amyloid load in *APOEε4* carriers [266]. The interaction between leisure physical activity and *APOEε4* on dementia was studied more but so far remains controversial [267, 268]. Podewils et al. found that leisure physical activity was negatively associated with risk of dementia and the association was more marked in *APOEε4* non-carriers, but was absent in carriers [267]. In contrast, Rovio reported a more pronounced association in *APOEε4* carriers [268]. 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. However, t 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 genetic background of the subjects that are tested on the results of environmental stimulation. The recent ‘spontaneous’ decrease in prevalence of AD [271] must also have an environmental basis, although

the exact factors involved are not known at present.

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