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EXPERT REVIEWS

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Non-pharmacological interventions have the potential to reduce cognitive decline and to improve psychosocial aspects in mild cognitive impairment and Alzheimer's dementia, and the absence of side effects makes them a favorable option also for preventive strategies. We provide an overview on recent studies involving cognitive training and reminiscence, stimulating and challenging experiences such as visual art and music, physical activities, and electromagnetic stimulation. We review findings on neuroplasticity in the aging brain and their relevance for cognitive improvement in patients with neurodegenerative diseases. We discuss cognitive reserve and possible mechanisms that drive neuroplasticity and new learning. Finally, we identify promising avenues for future intervention strategies and research, such as combinations of cognitive and pharmaceutical interventions, and individual strategies adapted to the disease stage and tailored to the needs, predispositions and preferences of patients.

KEYWORDS: Alzheimer's disease • dementia • mild cognitive impairment • neuroplasticity • non-pharmacological intervention

For many years, pharmacological treatment of Alzheimer's disease (AD) has been aiming at the improvement of cognitive and behavioral symptoms in patients with moderate to severe dementia. These include antipsychotic and anxiolytic drugs, and a limited number of drugs approved specifically for dementia, mostly cholinesterase inhibitors and memantine. However, treatment effects are generally modest at best, and none of these drugs can reverse dementia. Thus, there has been considerable emphasis in recent years on developing drugs to reduce dementia progression or, even better, to prevent progression to dementia when applied to patients who suffer from mild cognitive impairment (MCI) and are at high risk for developing dementia. Many of these investigational drugs target amyloid deposition as a key process in the pathophysiology of AD but, unfortunately, none of them have demonstrated clinical efficacy yet in a Phase III trial [1,2].

There is also a large variety of non-pharmacological interventions that have been explored for treatment of psychological and behavioral symptoms in MCI and AD [3–14]. Interventions may also include social and cultural activities [15] as well as art therapy. These often aim broadly at improving quality of life (QoL) by promoting active engagement, enjoyment, empowerment and creativity [16]. Furthermore, interventions targeting patients' and caregivers' wellbeing and quality of life by improving behavioral disturbance, mood and disease management were shown effective as well [10]. A comprehensive assessment of studies aiming at these qualitative outcomes, which are of obvious relevance for patients' wellbeing, would exceed the scope of our review and we will focus on studies describing outcomes that are related to the biomedical aspects of neurodegeneration and its cognitive and psychological manifestations.

Non-pharmacological interventions have few if any unfavorable side effects. They can therefore be applied without concern also at early stages of the disease, including primary and secondary prevention programs. The paucity of side effects is in contrast to many pharmacological interventions that are currently under

investigation, which may cause severe side effects such as intracranial hemorrhage [17] or inflammatory reactions [18] and which therefore may have an unfavorable benefit to risk relation when used for prevention. There is also evidence for efficacy of non-pharmacological interventions in manifest dementia from controlled studies, especially for reduction of disturbing emotional and behavioral symptoms even at severe stages of dementia, complementing and sometimes exceeding the effects of pharmacotherapy.

Many non-pharmacological interventions are aiming to induce neuroplastic changes in the brain. Current research into the effects and mechanisms of neuroplasticity has demonstrated that training and exercise in normal subjects can induce synaptic plasticity and, in the long term, even macroscopic structural alterations [19]. It is therefore intriguing to investigate whether this type of intervention could also be beneficial at an early stage of AD. Three main concepts for intervention at that stage have been emerging: i) maintaining and improving the cognitive abilities that are declining in AD by targeted cognitive training, ii) enhancing cognitive reserve [20], which appears to be a mechanism that explains the relative resilience of subjects with a high level of education and cognitive activity against AD and iii) facilitating neurogenesis, mainly by physical exercise.

Based on the existing literature, we suggest two possible approaches for training that are based on considerations regarding the target of training, and the predisposition of the patient: first, one might want to train the brain areas affected by neurodegeneration. For instance, in the case of amnestic MCI a prime target would be the hippocampus and relevant outcomes are memory function with hippocampal volumetry and connectivity as physiological measures. This approach is straightforward but might only work in early stages of neurodegeneration. Several types of training are known to affect the hippocampus including aerobic exercise, navigation and musical training. While exercise could be a feasible intervention up until later stages of dementia, training of complex musical or navigation tasks would likely be frustrating and unsuccessful if the hippocampus is already affected by degeneration.

Second, one could aim to develop a training that relies on functions and structures that are relatively spared or preserved, and that also shows effects in these areas, thereby strengthening remaining networks. In the case of amnestic MCI, frontal and cortical association areas are likely candidates as they have important roles in executive functions, memory and attention. Here, relevant outcome measures would be volumetric measurements of cortical structure and a variety of cognitive tests assessing memory, attention and executive functions. Better understanding of both, specificity of training effects and predisposition toward different types of training in individuals, would be required to design successful training interventions.

Most non-pharmacological interventions have been addressed in recent reviews and meta-analyses, and another comprehensive review is beyond the scope of this paper. Thus, we will briefly summarize the state of knowledge, and we then turn to suggestions for new promising intervention approaches. We discuss possible underlying mechanisms for different types of trainings, open issues and future directions for research.

Selection of papers & presentation

For this focussed review, PubMed searches were conducted using the keywords 'dementia', 'mild cognitive impairment' and 'aging' in combination with 'plasticity', 'psychosocial treatment', 'cognitive intervention', 'exercise', 'electrophysiological stimulation' and 'art therapy'. From the large number of items retrieved, comprehensive reviews and recent original papers not yet covered in these reviews were selected preferentially. The final selection was based on our judgment of relevance with a particular focus on possible links between the interventions and neuroplasticity, also including papers on relevant physiological mechanisms. Interventions primarily related to patient care or nutrition were not targeted in our review.

We also included papers using non-pharmacological interventions to study brain plasticity in normal control subjects when related to the effects seen in MCI and AD. An overview on interventions and subject groups covered in our review is provided in Table 1.

Effects of cognitive interventions in healthy aging & MCI

A wide range of different cognitive interventions have been investigated, ranging from computer-based trainings to group interventions using games and social activities. Overall outcome measures that have been used to assess training effects have been just as variable, ranging from behavioral tests to questionnaires and test of activities of daily living and quality of life as well as subjective cognitive impairments. This variability in trainings and outcome variables and in other design dimensions, such as the intensity and duration of training or the target group, has rendered systematic comparisons across studies challenging. Furthermore, the quality of studies according to methodological criteria is variable, and high-quality randomized controlled trials are still sparse [9,10,13]. Some criteria, such as double-blinding of interventions, are difficult to achieve with most non-pharmacological interventions, but many studies also lack an adequate control group. Interestingly, when attention from caregivers or trainers was controlled for differences of intervention to control group were smaller, indicating that social aspects of interventions are an important mediator that should be accounted for in the study design [10]. Overall, most reviews and meta-analyses conclude that cognitive interventions can delay the onset of dementia and improve cognition in healthy adults, MCI patients and AD patients [7–9,11,13,14].

In a recent meta-analysis, Li et al. evaluated the effects of various types of cognitive training interventions in MCI [11]. Cognitive interventions were shown to yield moderate improvements in language abilities, self-rated anxiety and self-rated functional ability, and small effects for Mini Mental State Examination (MMSE) score, episodic memory, semantic memory, executive function and working memory, visuo-spatial ability, attention and processing speed and other domains of self-ratings, such as memory, QoL, activities of daily living (ADL) and depression.

Table 1. References by intervention type and subject group.

Intervention types	Subject groups			
	Adults, young and middle age	*Normal elderly*	*Mild cognitive impairment*	*Dementia*
Active lifestyle and sensory stimulation		[54,101,123]		[3–6,10,15]
Art therapy				[16,113,114]
Reminiscence and validation		[37,38]	[36]	[4–6,10,35,38]
Physical exercise and motor training	[65,66,77]	[45,49]	[26,46,99,100]	[4–6,10,12,15,45,62,73, 75,76,99,100]
Music	[64,67,68,77–80,82, 110,111,115–117]	[19,22,54,69,74, 105–107,110,118]		[3–6,10,15,72,73,75,76]
Cognitive training	[63,77]	[8,9,13,22,23,39, 41–43,54]	[7,9,11,13,26, 28,31,44]	[7,10,14,29,30,32–44,55]
Memeory	[83]	[21,40,108]	[21,27]	[72]
Electrophysiological stimulation	[84,85]	[84,85]	[85,88]	[10,87,89–94,96–98]

Not all studies investigated long-term effects of the trainings, but those that did found only small to moderate effects on objective measures of cognition, but moderate to large effects on functional ability and self-rated QoL, indicating relatively more subjective long-term effects of cognitive interventions. Reijnders *et al.* performed the most recent comprehensive review of cognitive training studies in healthy seniors and in MCI patients [9], building on earlier meta-analyses [21,22]. Reijnders *et al.* took the quality of the studies as assessed by the Consort score into account in their evaluation of study outcomes and concluded that the overall quality of cognitive intervention studies was only medium. Benefits of cognitive interventions for both MCI and healthy elderly individuals were observed in several domains of cognition, including memory, executive functions and attention in several studies, along with subjective measures of cognition and quality of life.

How efficient are non-pharmacological approaches compared with pharmacological interventions? A recent systematic review and meta-analysis [10] concluded that non-pharmacological treatments can be as effective as drugs (in the domains of cognition, ADLs, behavior, mood) and even more effective for more general measures of quality of life, and supported a clear recommendation for non-pharmacological interventions for patients with dementia. non-pharmacological interventions were effective in delaying institutionalization, an important factor with regards to costs of disease and quality of life. The interventions that crucially contributed to this effect were characterized by inclusion or focus on caregivers, in particular skill training in management of the disease, counseling and support, rather than cognitive interventions. However, approaches targeted at improving patients' cognition and at improving activities of daily living were demonstrated as effective as well, especially when combined with pharmacological treatment.

An important question is whether the effects of the training intervention generalize to other tasks and abilities. Across several reviews and meta-analyses clear near transfer effects of cognitive interventions emerged, while far transfer effects, for example, to daily activities, if measured at all, were difficult to establish. Even in healthy adults, transfer effects of cognitive interventions can be absent. For example, no transfer effects of a computerized cognitive training were found in a large study with healthy seniors [23]. Furthermore, effectiveness of interventions seems to differ by disease stage: while MCI patients benefit from cognitive interventions targeted at improving specific cognitive skills, such as memory strategies, AD patients gain more from global cognitive stimulation and restorative rather than compensatory approaches [7,9,14]. The heterogeneity of MCI [24] and cognitive impairment profiles in AD [25] creates challenges for the development of effective interventions at early stages and for understanding the underlying mechanisms of training-related changes. Spared functionalities and target areas of training would ideally be identified in each patient in the context of an individualized therapeutic decision. In this context, developments of more sensitive screening measures that can detect and differentiate different types of dementias early on and facilitate staging of disease will be extremely helpful.

How specific are training effects? Conclusions about task specificity of trainings are difficult to establish across studies due to differences in study design characteristics and variability of interventions and outcome measures. Systematic comparison of different training protocols within one study is required in order to differentiate global effects from training-specific effects, and only few such studies exist so far. Talassi *et al.* compared two different training programs for MCI patients that differed regarding the focus of the training, that is cognitive versus

physical training, and found significant cognitive and affective improvements only for the cognitive training [26]. However, the physical training control group was small. Olchik *et al.* compared memory training to an educational intervention or no training for MCI patients, with modest effects for the memory training [27]. In a direct comparison of an active computer-based training targeting auditory processing speed and more passive computer-based activities for MCI patients, Barnes *et al.* did not find significant effects of either training on overall cognition, but directions of changes for specific sub-categories of outcome measures in the domains of memory, learning, language and visuospatial processing seemed to indicate possible training-specific effects [28].

Pharmacological and non-pharmacological interventions are not mutually exclusive, rather, evidence seems to indicate that combinations therapies are beneficial. Combination of antidementia drugs with cognitive interventions [29–32] consistently showed stronger improvements of combined therapy on cognition of MCI or AD patients than pharmaceutical intervention alone or than combination with a control training intervention. Follow-up examinations showed that effects are most likely to endure if the cognitive intervention program is kept up, for example, with the help of the caregiver [29,33].

Reminiscence therapy, as defined by the American Psychological Association [34] as the use of life histories, written, oral, or both, to improve psychological wellbeing, originates from work with healthy people who wanted to review their life but has become a popular intervention for elderly people or dementia patients in care homes or geriatric health facilities [35,36]. Reminiscence therapy may include cues, such as songs or pictures, for memory retrieval [37]. It does not require memory encoding and does not provide substantial cognitive training. While simple reminiscence can be understood as unstructured autobiographical storytelling, life-review covers the entire life span, is performed in a one-to-one format, focuses on the (re-)evaluation of life events and on the integration of positive and negative life events in a coherent life story. Life-review therapy focuses on reducing bitterness revival and boredom to promote a positive view on one's past often explicitly applying therapeutic techniques that have been developed in other therapeutic frameworks, such as cognitive therapy [38]. In a recent meta-analysis of 128 studies comparing reminiscence with non-specific changes in control-group members, Pinquart and Forstmeier found, among others, moderate effect sizes for ego-integrity, depression, small effect sizes for purpose in life, death preparation, mastery, mental health symptoms, positive wellbeing, social integration and cognitive performance [38]. The authors also report larger improvements of depressive symptoms in those receiving life-review therapy rather than life-review or simple reminiscence.

Neuroimaging studies of cognitive training interventions

Suo and Valenzuela reviewed functional and structural brain alterations after training trials and found that functional changes in frontal cortices have been described in virtually all studies [39]. This provides evidence for persistent plasticity in the frontal association cortex, which is also the main anatomical substrate supporting cognitive brain reserve. In addition, functional and structural changes are also frequently seen in hippocampus, parietal cortex and the corpus callosum, which are all structures that are preferentially impaired in dementia.

While to our knowledge no studies have yet investigated training effects in MCI patients using neuroimaging techniques, some recent studies investigated the effects of cognitive training interventions on functional and structural brain characteristics in healthy elderly adults. These studies show that behavioral changes can be related to changes in brain areas related to higher-order functions, demonstrating neuroplasticity in the aging brain. Improvements in memory performance due to memory training in healthy seniors were related to increases in cortical thickness in right insula, bilateral orbitofrontal cortex and fusiform cortex, while cortex thinned in similar areas in a non-training control group [40]. Furthermore, training on a set of different cognitive tasks (working and episodic memory and perceptual speed) changed white matter structure in the anterior corpus callosum, likely moderating improved interhemispheric connectivity of frontal areas [41].

Are training effects also reflected in changes in brain function? Using fMRI, Erickson *et al.* demonstrated training-related reductions in hemispheric asymmetry of task-related activations in prefrontal cortex, indicating stronger compensatory activity across the two hemispheres related to training. However, training focused on the same tasks that were tested in fMRI, limiting conclusions about training-related gains in general brain function [42]. A cognitive training intervention in a recent study by Mozolic *et al.* succeeded in reducing distractibility of seniors during attention tasks, and furthermore resulted in changes in resting state brain perfusion in right inferior frontal cortex [43]. Cognitive training in MCI and mild AD also improved brain metabolism as assessed with FDG PET [44]. Six months of weekly group sessions with cognitive exercises targeted at improving cognitive reserve, compared with a control group who merely performed self-administered attention training, resulted in significantly slower decline of brain metabolism, especially in left anterior temporal pole and anterior cingulate cortex. Both imaging and behavioral data indicated that MCI patients particularly benefited from the cognitive intervention.

Effects of aerobic exercise on cognition & brain plasticity in aging

Aerobic exercise in elderly individuals induces structural brain changes and improvements in cognition [45,46]. The most robust effects are observed in hippocampus and prefrontal brain areas, and for memory and executive function tasks [47–51]. For example, 1 year of aerobic exercise training resulted in volume increase of anterior hippocampus that effectively reversed typical age-related losses in a comparable time frame. Exercise-related hippocampal effects were furthermore associated with higher serum changes of brain-derived neurotrophic factor over the training period and

with improvements in spatial memory. Stretching exercises did not have such a protective effect, but pre-training fitness levels predicted the amount of age-related losses, further supporting the protective effect of overall physical fitness [50]. Several recent reviews have addressed possible underlying mechanisms. Protective effects of physical exercise and fitness on brain volume and cognition have been related to a neurogenic reserve hypothesis [52], and it has been suggested that exercise-induced hippocampal neurogenesis followed by integration of surviving neurons into existing networks through brain activity in cognitive tasks might result in the best outcomes [47,48]. Indirect beneficial effects of exercise are also likely to be mediated by improvement of microvascular status, which is a significant cofactor in the pathophysiology of AD [53].

A promising approach seems to be the combination of cognitive and physical exercises. In healthy elderly adults, 6 months of 'combination training' comprising cognitive and aerobic exercises, music listening and group recreational activities resulted in increases in cortical thickness in right angular cortex, precuneus and posterior cingulate cortex, and increases in functional connectivity involving frontal eye fields, important for attentional control. While no clear training-specific effects were shown on MMSE and memory scores, attention and task switching, training effects were obtained for performance on everyday tasks. Furthermore, the results indicated that the training effect was modulated by dopamine-related genes [54]. Coelho *et al.* studied the effects of a 16-week training paradigm combining physical and cognitive exercises on gait and cognitive functions ('frontal battery') in AD patients in early stages [55]. The exercise group compared with a no training control group improved on stride length and some cognitive tests related to abstraction, organization, motor sequencing, behavior self-control and attention. However, the non-random group assignment in the study poses an important limitation [55].

Further support for potential positive effects of a cognitively and physically active lifestyle comes from animal studies. Studies on the effects of environmental enrichment (EE) that involves housing with enhanced opportunities for cognitive and physical activity have been conducted in different transgenic mouse models of AD that yield partly inconsistent, but predominantly positive results on neural pathology and behavior [56]. EE seems to influence AD-like pathology via multiple mechanistic pathways, including (but not limited to) effects on amyloid plaques [57], hippocampal neurogenesis and neurotrophic factors [58,59] and glial pathology [60]. Interestingly, exposure to EE early in life seems to be more effective in reducing AD-related cognitive deficits than late exposure after onset of amyloidogenesis, indicating long-lasting protective effects [61]. EE effects might also be dependent on the severity and trajectory of the disease. In a mouse model of AD that shows fast deterioration (APP/PS1KI), EE did not improve most behavioral and physiological markers of the pathology [62]. Further research will be required to understand the diverse effects of EE on neuronal pathology and on behavioral indices of cognitive performance and learning in AD mouse models, and to transfer these findings to potential preventive strategies against dementia in humans.

Complex learning challenges as a driving force for plasticity

A growing number of successful demonstrations of training-related functional and structural plasticity in the adult human brain suggest that complex tasks that are cognitively challenging and involve a new motor learning component might be especially effective in inducing brain plasticity [63,64] including activities such as juggling, golfing or playing a musical instrument [65–68]. Interestingly, such training protocols are also likely to show effects not only in the unimodal sensory or motor areas, but also in association areas. This makes them interesting candidates for strategies against cognitive decline. While most of this research is performed in young adults, some studies have systematically addressed the question of training-related plasticity in healthy aging participants using neuroimaging and behavioral methods in combination with complex training paradigms like golfing, juggling and dancing [65,69,70]. Healthy elderly seniors who learned to juggle showed training-related grey matter changes in temporal visual areas, left hippocampus and bilateral nucleus accumbens [70]. Golf practice resulted in grey matter increases in sensorimotor and parietal regions in middle-aged adults [65]. Furthermore, interventions that involve active music-making are increasingly being recognized as a valuable tool for neurological and psychiatric rehabilitation and to promote healthy cognitive aging [19,71–73]. One experimental study showed promising increases in higher-order cognition after 6 months of music training [74]. Music has also recently been demonstrated an efficient tool to enhance mnemonic abilities in AD patients [72] and musically accompanied exercise for dementia patients has been shown to improve cognition compared with a control group [73].

Dancing represents an excellent combination of cognitive challenge (memorizing the steps), musical stimulation, social interaction and aerobic exercise. Behaviorally, contemporary dance practice improved attentional control in healthy seniors [69]. Dancing interventions are even possible in patients with moderate AD, who demonstrate procedural learning in Waltz lessons, indicating remaining potential for new learning and neuroplasticity. However, depressive comorbidity seems to limit the effects of dance practice [75]. So far, evaluation of dance interventions for seniors has focused on the psychosocial effects while neurological effects remain to be investigated in future studies [76]. Overall, it is yet unclear if effects of complex activities on behavior reflect different strategies, compensation mechanisms or measurable neuroplastic changes.

Several lines of evidence suggest an enhancement of neuroplastic effects mediated through multimodal interactions. In healthy adults, multimodal auditory-sensorimotor piano training compared with purely auditory training results in stronger plastic changes within auditory cortex [67,68] and auditory-visual-motor training results in stronger functional gains during auditory-visual processing in multisensory association cortex than auditory-visual training [77]. These results suggest that training on complex skills that involve the integration of multiple sensory modalities is more likely to elicit neural plasticity in

both sensory and association areas than unimodal training. Musical training is an ideal model to study these interactions. During musical practice the auditory and motor systems are in close interaction, and direct mapping of motor actions to auditory and tactile feedback is crucial to playing an instrument [78–81]. To what extent similar beneficial effects of multisensory training can be found for other domains (e.g., visuo-motor trainings) and in elderly individuals or patients with dementia remains to be investigated.

The locations of training effects in studies with healthy adults seem to be to some extent training-specific, although this is difficult to establish across studies without direct comparisons of different types of trainings. Musical training most consistently modulates processing and structure of auditory and motor areas and their connectivity [64]. In the visual-spatial-motor domain, training on a complex visual-motor task such as juggling or golfing leads to grey and white matter changes in motor tracts as well as in frontal and parietal association areas related to complex spatial processing [65,66]. Other types of complex cognitive and motor training tasks specifically affect medial temporal lobe structure and function in healthy adults, including musical training [82] and navigation training [83]. More precise knowledge about task-specificity and location of neuroplastic effects will be helpful to develop training and rehabilitation approaches that can target affected cognitive domains and brain areas.

Electrophysiological stimulation

Electrical or magnetic stimulation of the brain can induce neuroplastic changes and thus also have therapeutic potential. Repetitive transcranial magnetic stimulation (TMS) can enhance long-term potentiation (LTP) as well as long-term depression, depending on stimulation frequency [84]. Changes of cerebral activity and cognition induced by TMS have been demonstrated in normal subjects and psychiatric patients [85]. When treatment is applied repeatedly, long-term effects on cerebral glucose metabolism as an indicator of synaptic activity have been observed [86]. There have been a few studies indicating beneficial effects in elderly subjects and patients with AD [87]. Studies described transitory improvement in a face-name association memory task in elderly subjects [88], and in object and action naming even in severe stages of AD [89]. Persistent improvement of sentence comprehension for at least 8 weeks after 10 sessions over 2 weeks with stimulation of the dorsolateral prefrontal cortex was observed in a placebo-controlled study [90]. Improvements by 4 points on the Alzheimer Disease Assessment Scale-Cognitive (ADAS-cog) and also on the Clinical Global Impression of Change (CGIC) were observed in a pilot study of 6 AD patients up to 4.5 months after 6 weeks of combined treatment with rTMS and a cognitive training scheme [91]. Another study found significant improvements on the MMSE, Instrumental Daily Living Activity (IADL) scale and the Geriatric Depression Scale (GDS) for up to 3 months in AD patients treated with high-frequency rTMS, while changes were not significant in patients

treated with low-frequency rTMS or sham stimulation [92]. An alternative technique is stimulation by transcranial direct current (tDCS), which led to short-term improvement of memory in two pilot studies in patients with AD [93,94].

A more direct but invasive approach is provided by deep brain stimulation (DBS), which has proven therapeutic efficacy in Parkinson's disease [95]. In a pilot study, six AD patients received DBS of the fornix and hypothalamus [96]. Evaluation of the ADAS-cog and MMSE scores suggested possible improvements at 6 and 12 months, and PET scans showed a reversal of the impaired glucose utilization in the temporal and parietal lobes that was associated with cognitive improvement [97]. However, due to the invasiveness of the procedure, costs are very high and acceptability by patients may be low [98].

Cognitive reserve & modulating factors for learning across the life span

While now a lot of efforts are being made to diagnose dementias at an early stage to maximize potential treatment options, researchers are also increasingly looking for protective factors that will prevent neural degeneration in the first place. Longitudinal and cross-sectional studies suggest that an active lifestyle including physical exercise [99,100] and education in combination with stimulatory experiences in late life [101] might be protective against mild cognitive impairment and several forms of dementia and neurodegenerative diseases [102].

Education and life-long learning seem to provide a cognitive reserve and to protect to some extent against cognitive decline. Individuals with higher education typically show greater brain pathology when dementia is diagnosed, indicating that neurodegeneration was successfully compensated for a longer period of time [103]. A recent study showed the protective effect of learning and practicing multiple languages throughout life [104]. Music also seems to serve as a protective factor against age-related cognitive decline: For example, musicians' long-term experience seems to delay the onset of age-related losses regarding neural encoding during speech perception at the brainstem level [105], as well as regarding the auditory working memory capacity and the ability to understand speech in noisy environments [106]. Long-term musical practice also seems to prevent age-related decline in higher-order cognition such as nonverbal memory, naming and executive processes [107]. Higher levels of remaining cognitive capacities also moderate training effects in response to cognitive intervention: The existing potential for learning as measured by a short cognitive test at the outset of a 7-week memory and cognitive training program predicted subsequent training-related improvements in cognition [108].

It is largely unknown to what extent cognitive reserve modulates the trajectory of decline in dementia. Clinical observations indicate that while it might delay onset or slow progression in early stages of disease, after breakdown of reserves and onset of dementia decline may be more rapid [109]. It is also yet unclear if protection based on previous learning experience and cognitive reserve is dependent on early education or if it can be built up later in life. Some answers can be found in studies within

the framework of musical training that compared effects of training that occurred early or later in life while keeping total training years constant. Early training results in larger benefits than late training in behavioral tasks that are related to musical performance, such as demanding motor and auditory synchronization tasks, but even late trained musical experts still show benefits compared with nonmusician controls [110]. Early compared with late musical training also results in more pronounced structural correlates of musical expertise in the corpus callosum [111]. However, recent studies have shown that the aging brain remains plastic, as described above [65,69,70]. Thus, while the potential for learning and reorganization and the benefits of training seems to decline across the life span, there is a remaining potential for learning and neuroplasticity later in life that should be exploited.

The quickly evolving field of art gallery programs for dementia patients and their scientific evaluation can be understood as an approach to strengthen preserved abilities of Alzheimer's patients. Aspects of patients' aesthetic perception are spared in the face of cognitive decline, as reflected in participants' art preference stability in early and late stages of AD despite the absence of explicit memory [112,113]. An investigation of an art gallery program's effect on participants' cognition demonstrated ambiguous results regarding episodic memory enhancement and increased verbal fluency through aesthetic responses to visual art [114].

Another open question is whether previous learning experience might not only enhance cognitive performance, but also new learning in old age. In younger adults, modulation of new learning by previous experience has been demonstrated in the auditory [115] and in the tactile domain [116], and modulates responsiveness to neuroplasticity induced by TMS [117]. Data from older adults are still sparse, but one study showed that structural brain characteristics can modulate subsequent training effects: pre-training characteristics in structural hemispheric connectivity predicted gains in fluid intelligence in response to a logical reasoning training in healthy seniors [118].

Motivation and experience of self-efficacy might be additional important factors for training outcomes. On the one hand, lack of random assignment of participants to trainings is a major methodological shortcoming that limits the interpretation of results [55], but on the other hand self-selection of training could positively influence commitment and compliance. Therefore, subjective preferences for certain kinds of interventions could be an important factor in individual treatment choices. Furthermore, the importance of the intervention's reward value should not be underestimated. Work in animal studies has shown that learning and plasticity are modulated by aminergic reward-related neurotransmitters [119,120]. In this context, training programs that contain a reward scheme (e.g., computer games) or that contain material or activities that are inherently rewarding, such as music [121], might be especially promising approaches. The role of the reward networks in training effects remains to be established in future studies.

Expert commentary & five-year view

Non-pharmacological interventions provide tools to improve cognitive impairment and quality of life without little if any side effects. Several studies indicate that the magnitude of their effect can even exceed current symptomatic pharmacological interventions. The broad range of possible interventions and flexibility of practical implementation is a practical strength, but lack of standardization also impedes the systematic assessment of effects. There are very few randomized controlled trials, and even then many only report significant effects in the active group and absence of significant effects in the control group but fail to do a direct comparison between the two groups, which is required standard in drug trials. In addition to improvement in cognitive and physiological measures, more general outcome measures such as quality of life and subjective wellbeing are also of obvious relevance to elderly subjects.

For the future, it seems particularly attractive to conduct studies of combined intervention approaches, such as combining physical exercise with cognitive training, because they may use complementary physiological and mutually enhancing routes to maximize the therapeutic effect. Combinations of multimodal sensory and motor training, as well combinations with electrophysiological stimulation or pharmacological intervention also seem promising. non-pharmacological interventions do not imply a choice against pharmacological interventions, but should be seen as complementary, and future studies on potential additional beneficial effects of combinations of both types of treatments would be highly informative. Future research on training specificity of behavioral effects and of brain plasticity by directly comparing different training approaches within one study or by harmonizing study design characteristics and outcome measures across studies will help to design trainings that more efficiently target specific cognitive domains, brain functions and structures relevant to neurodegenerative processes. Advanced imaging techniques and biomarkers as well as improved statistical techniques currently developed mainly for pharmacological studies [122] could also be applied to non-pharmacological interventions to better understand the mechanisms of action and to corroborate clinical results.

Social inclusion programs should provide better access for disadvantaged parts of the population to avoid that training programs are taken up only by people who already have a high cognitive reserve due to their education [123]. Activities involving arts and social activities with their positive effects on quality of life might also increase the motivation to engage in targeted cognitive and combined training programs and thus also improve their outcomes.

Key issues

- Various types of non-pharmacological interventions are effective in improving cognitive and psychosocial aspects of neurodegenerativ e diseases.
- While early stage mild cognitive impairment seem to benefit most from targeted cognitive training (e.g., memory training), Alzheimer's disease patients benefit from stimulating interventions (including arts and music) with social interaction and involvement of caregivers, especially with regard to psychosocial aspects and management of the disease.
- Neuroplasticity in healthy elderly individuals has been demonstrated in functional and structural imaging studies, but neural correlates of training in patients are yet unknown.
- Cognitively and physically challenging activities provide the most efficient stimuli to induce neuroplastic changes, and complex activities like making music, juggling and dancing provide promising avenues for effective intervention.
- Strategies combining complex cognitive training with physical activity, electrophysiological stimulation or pharmacological treatment might be the most promising avenue for slowing neurodegeneration. They should be investigated in future studies, ideally with monitoring of functional and structural brain plasticity by brain imaging.

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