

Healthy Brain Aging: Role of Cognitive Reserve, Cognitive Stimulation, and Cognitive Exercises

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The final decade of the 1900s was called the Decade of the Brain, in recognition of advances in science and technology that provided unprecedented views of the human brain in action and enhanced appreciation of the complexity and resilience of the normally functioning brain. The coming decade may well become the Decade of Brain Fitness, as scientists, clinicians, and entrepreneurs test the limits of current knowledge for improving and sustaining human cognitive function to the end of life.

Americans believe that they can improve their brain health through their lifestyle choices. In a recent poll [1] of middle-aged and older adults, 88% endorsed the idea that brain health can be improved (35% said “a little” and 53% said “a lot”). Eighty-four percent reported that they were doing things to improve their brain health, including arts, crafts, and hobbies; games and puzzles; and exercising physically.

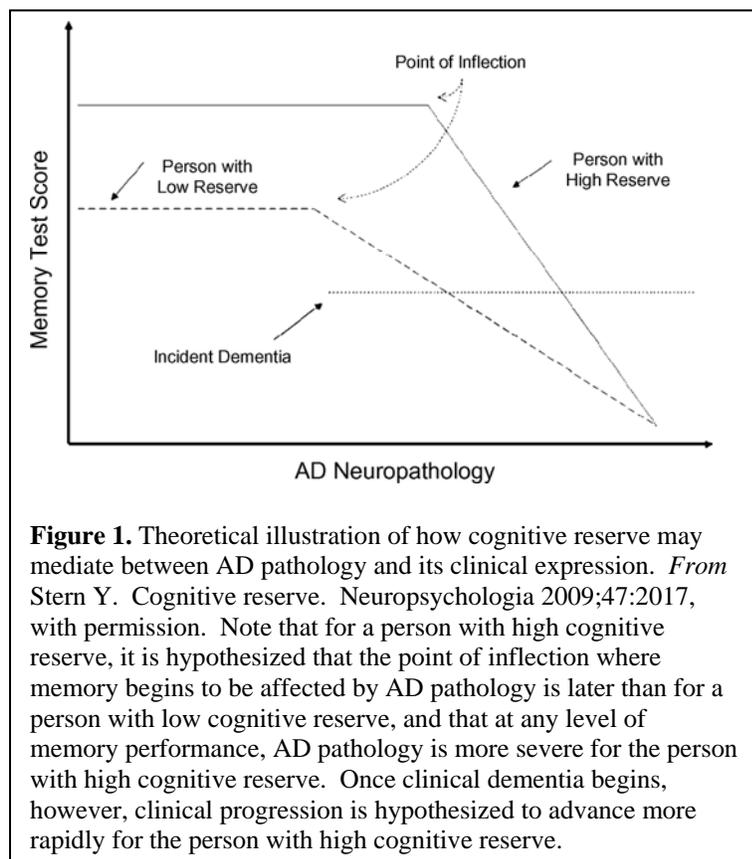
This chapter will critically examine current knowledge about the role of cognitively stimulating lifestyles and cognitive training interventions in preserving cognitive performance in later life. The emphasis will be on optimizing cognitive well-being in normally aging older persons, and to a lesser extent, on the question of delaying or preventing dementing disorders such as Alzheimer’s disease (AD). Suggestions for advising patients about brain-healthy lifestyles will be provided, cautioned by the recognition that major gaps exist in our knowledge of how best to “engineer” a cognitively healthy old age.

Key Terms, Concepts, and Hypotheses

Terms such as brain health and brain fitness are popular but seldom defined. Paralleling current definitions for physical fitness [2], **brain fitness** could be defined as attributes that people have or achieve that relate to the ability to perform cognitive activity. The emphasis in this definition is on function -- i.e., cognition in action in the everyday world -- rather than on brain structure, and in this regard, it is important to recognize that there are multiple, partially distinct components of cognitive function, including attention, learning and memory, language, visuospatial processing, reasoning, and executive skills. Individuals may be very “fit” in terms of language and communication, but less fit in memory or attention, and different interventions may be needed to improve fitness in each area. Optimal brain fitness would require the absence of brain disease or systemic illness that critically impacts the brain, but persons with brain injury, or those experiencing early stages of a degenerative brain disease, may be more or less fit depending up their genetic predispositions, endowments garnered from early life experiences, and current lifestyle choices.

Concepts such as **brain reserve** and **cognitive reserve** have gained prominence in discussions of the differential attributes that individuals have for coping with the challenges of brain injury or brain disease. **Brain reserve** generally refers to the structural neural substrate (e.g., brain size or neuronal count) that supports cognitive function. Given the same degree of AD brain pathology, for example, individuals with larger brains are less likely to exhibit clinical symptoms of dementia than those with smaller brains [3]. Similarly, healthy older adults with high executive function have increased cortical thickness in certain key brain regions compared to those with average executive function [4]. **Cognitive reserve** refers to the brain’s capacity to actively cope with brain damage through the implementation of cognitive processes. Two individuals with the

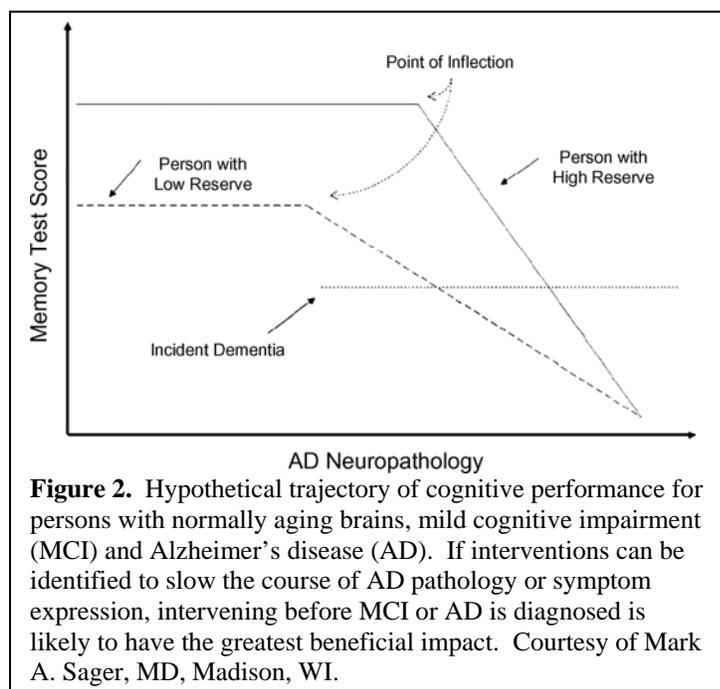
same degree of structural brain reserve might adapt to brain injury more or less successfully if one has more cognitive reserve, i.e., more cognitive processes to enlist or to employ in compensation. Epidemiologic studies have shown that the risk of AD is lower for persons with higher levels of education, higher occupational attainment, or higher premorbid IQ [5,6], and because of such observations, education and occupation are often used as proxies in predicting who is likely to have more or less cognitive reserve. Functional neuroimaging studies have begun to document associations relevant to cognitive reserve [5]. For example, in one recent study [7], cognitively healthy older adults with higher cognitive reserve (as estimated by IQ,



education /occupation, and activities), had larger MRI-derived whole brain volumes and *reduced* brain activity during cognitive processing, presumably because they were making more efficient use of cognitive networks. In patients with mild AD, by contrast, those with higher cognitive reserve had smaller brain volumes, but *increased* brain activity, suggesting active attempts at cognitive compensation, despite more advanced neuropathology. **Figure 1** shows how cognitive reserve might mediate between AD pathology and its clinical expression. The concepts of brain reserve and cognitive reserve may be relevant to understanding individual differences in coping with a wide range of dementing disorders (e.g., frontotemporal dementia [8]; dementia with Lewy bodies [9].

There is increasing recognition that the neuropathological substrates of AD begin years or even decades prior to clinical diagnosis [10], raising the possibility of intervening at preclinical stages to prevent the disease, or at least delay the onset of clinically significant symptoms. At present, there are no known treatments or lifestyle modifications that can prevent the progression of AD pathology. However, the hypothesis that onset of clinical symptoms may be delayed by interventions is attracting great attention, and several prospective studies are underway to identify risk and protective factors and to pinpoint when in the lifespan each factor may have the most pronounced impact on AD pathology and symptom progression. This view of AD, as one among many chronic diseases that are not currently curable, but may be preventable to some degree, reflects an important shift in mindset among researchers and clinicians in the field. This view is referred in this chapter as the **prevention hypothesis**, although it might be more realistic to call it the forestalling hypothesis. **Figure 2** shows hypothetical impacts of earlier interventions on slowing the rate of cognitive decline. By the time clinical dementia emerges,

affected individuals have already experienced extensive brain impairment, lessening the odds that cognitive symptoms can be effectively ameliorated. The same may be true of Mild Cognitive Impairment (MCI), which is often a precursor of AD.



Cognitively Stimulating Lifestyles: What is Known?

A majority of epidemiologic studies that have examined cognitive stimulation as a lifestyle variable have found slower rates of cognitive decline among those who routinely engage in more cognitively demanding tasks compared to those with a more mentally sedentary lifestyles [6, 11]. Many of these same studies have also shown a reduced risk for AD and other dementias among more cognitively active persons.

One recent population-based study [12] of cognitively healthy adults 65 years and older found that a 1-point

increase in frequency of engagement across seven cognitive activities (reading books; reading magazines; reading newspapers; playing cards, checkers, crosswords, or other puzzles; going to a museum; viewing television; and listening to the radio) was associated with a 64% reduction in odds of developing dementia over a 4-year period; on average, individuals with cognitive activity scores at the 10th percentile were twice as likely to develop dementia as those with cognitive activity scores at the 90th percentile. On the scale used by Wilson et al., a 1-point increase in the cognitive activity scale would correspond, for example, to engaging in a cognitive activity daily rather than several times per week, or several times a week rather than several times a month. The most pronounced difference in AD risk was between cognitively inactive lifestyles compared to an average level of cognitive activity, with smaller additional benefit seen from the average to highly-active range.

Another prospective study of nondemented persons 75 and older [13] found that those in the highest one-third of cognitive activity (corresponding to 11 activity days/week from set of six activities consisting of reading books or newspapers, writing for pleasure, doing cross-word puzzles, playing board games or cards, participating in organized group discussions, and playing musical instruments) had a 63% lower risk of developing dementia in the next five years than those in the lowest third of cognitive activity. Reading, playing board games, and playing musical instruments were the activities most closely linked to dementia odds.

While each of these investigations came to similar conclusions regarding the potentially protective role of cognitively stimulating lifestyles, the specific activities that they found to be beneficial varied. An earlier epidemiologic study conducted in France reported lower AD risk

with traveling, doing odd jobs, knitting, gardening [14]. None of the epidemiologic studies of leisure-time cognitive activities have attempted to validate engagement through direct observation or informant report, and most do not assess duration or intensity of engagement in cognitively stimulating activities. The overall conclusion from these observational studies is encouraging and lends some support to the general idea that “more is better” when it comes to cognitive stimulation, but it is clear that the field lacks a metric (i.e., a cognitive “yardstick”) for measuring the types or amount of activities that would be most beneficial.

Questions of cause and effect are unanswered in this area of research [15]. Is lowered engagement in cognitive leisure activities prior to the onset of dementia due to prodromal disease that makes the performance of these activities more difficult and less appealing? Is engagement in cognitively demanding leisure activities simply a marker for generally higher intellectual ability or a byproduct of higher education? A few studies have used statistical modeling and long-term follow-up to try to shed light on these questions. Schooler and Mulato [16] followed a representative sample of more than 600 employed men (average age = 64 at baseline) and their spouses over a period of 20 years. The focus of their study was on the preservation of intellectual flexibility in relation to the cognitive complexity of leisure activities. Across this lengthy follow-up, they found evidence for reciprocal (i.e., bi-directional) associations; that is, initial high levels of intellectual functioning led to high levels of cognitive complexity in activities, which, in turn, resulted in higher levels of intellectual functioning. These researchers concluded that: “...our findings strongly suggest that...doing substantively complex tasks...is an ‘analog of aerobic exercise,’” but again, these conclusions are based on observational research. Studies relating work histories to cognitive preservation are relevant to Schooler’s substantive complexity hypothesis [17]. Individuals whose main occupations require engagement with data or people in complex ways are more likely to maintain cognitive skills as they age [17,18] than those with less intellectually or socially demanding jobs. Retirement may reduce some of the cognitive benefits of stimulating work, at least in the short term [19].

Crowe and colleagues [20], reporting on a long-term follow-up of twin pairs discordant for development of AD, found that higher levels of intellectual-cultural activities in *middle age* were associated with reduced risk of AD 20 years later. Similar associations have been reported between cognitively complex work in middle age and dementia risk in late life [21]. With such lengthy follow-up intervals, the possibility that cognitively inactive lifestyles might be due to prodromal dementia becomes less plausible, but other possible confounds cannot be ruled out.

Older adults with higher levels of education or higher estimated IQ tend to engage more often in cognitively demanding leisure activities than persons with lesser education or lower IQ. It is not clear yet whether individuals’ choices of leisure activities influence cognitive trajectories above and beyond what might be expected based on their education and general ability level. Several studies suggest at least partially independent effects of these different factors [22, 23], and at least one major epidemiologic study found that frequency of recent cognitive leisure activity had a *stronger* link to AD risk than either education or occupational level [24].

Lifestyles that combine cognitively stimulating activities with physical activities and rich social networks may provide the best odds of preserving cognitive function in old age. In a 9-year follow-up of a healthy aging sample in Sweden, individuals who were active on any of these key

dimensions (cognitive, physical, and social) had lowered dementia risk, but those who were active on two or all three dimensions had the lowest risk of all [25].

Cognitive Training Interventions: What is Known?

The fact that older adults benefit from direct training programs that focus on specific cognitive skills is well known and well documented. A meta-analytic review of memory training concluded that there are reliable gains in memory performance from participation in memory training classes, and that the effect is relatively robust (average gain with training = 0.73 SD vs. 0.38 SD for controls) across many different studies and samples [26, 27]. Still, several important questions have been raised about this research. Many early studies were based on relatively small and select samples, and in some cases, benefits were short-lived once training was discontinued. More recent studies continue to report positive outcomes from training specific cognitive skills, but the strength and significance of training effects are open to differing interpretations [for contrasting reviews, see 28, 29].

The Advanced Cognitive Training for Independent and Vital Elderly (“ACTIVE”) study was the first large-scale randomized controlled trial of the effects of cognitive training for nondemented older adults [30]. The sample consisted of 2,832 community-residing volunteers aged 65 to 94 years (mean = 73 years) recruited from six sites across the United States. All had MMSE scores of 23 or higher and were free of significant functional deficits at the start of the study. The design was randomized, single blind with four groups: memory training, reasoning training, speed of processing training, and no-contact control. Participants were trained in small groups for 10 1-hour sessions over a 5 to 6 week period. Each training program produced an immediate positive effect on its corresponding cognitive ability (as measured on similar tasks). Gains were especially noticeable for speed of processing and reasoning training, with a more modest benefit from memory training. Subsequent follows-up have shown that modest benefits persist from training for at least 5 years [31]. The ACTIVE study provides good evidence that even a relatively small amount of training can benefit specific cognitive skills and that the benefits persist to some degree for extended periods of time. An important limitation in outcomes, however, is that training benefits were task-specific and usually did not extend to apparently similar, more naturalistic cognitive tasks (e.g., remembering a shopping list rather than a list of unrelated words of the type used in training). Despite this, at 5 years post training, participants in the ACTIVE training program were less likely than controls to have declines in health-related quality of life [32], suggesting that well designed cognitive training interventions could have benefits for important aspects of everyday life..

Cognitive researchers have begun to explore other types of training programs in the hope of finding more generalized benefits. One commercially available program, Brain Fitness marketed by Posit Science, consists of an on-line program of graduated cognitive exercises designed to enhance “brain plasticity”[33]. In the largest outcome study to date [34], 487 cognitively healthy and well educated older adults (mean age = 75) were randomly assigned to experimental training with the Brain Fitness program or an active control condition where they spent an equivalent number of hours on content-oriented coursework. The experimental program emphasized procedural learning (i.e., learning “how” rather than “what”) that involved practice with auditory language processing (tracking and comparing sounds of increasing complexity) for 60 minutes

per day, 5 days per week for 8 to 10 weeks. Testing at the end of training indicated large benefits on auditory processing speed, moderate benefits on self-reported everyday cognitive skills, and small but statistically significant benefits on memory performance. In this study, too, training primarily benefited skills most closely related to those used in training, but there was some evidence for more generalized benefits. Other studies with the Brain Fitness program have shown that benefits persist to some degree for at least three months [35], but longer-term results are not available.

Could standard, commercial video games help to sustain older adults' cognitive skills? There is some preliminary positive evidence. In a recent small-scale study [36], 40 cognitively healthy older adults were randomly assigned to either a video game practice group or a no-contact control group. The experimental group engaged in approximately 24 hours of practice with a strategy-based real-time video game over a 7 to 8 week period. Participants improved their speed of completion and game scores over time, but more importantly, scores on unrelated, standardized tests of executive function also improved for the experimental group relative to controls. The authors speculated that the greater transfer of training observed with the video game practice may have been due to the constantly shifting task priorities necessitated by these games, which required flexibility and rapid response. It is not known yet how long benefits from playing such games might persist or if skills besides executive function might be enhanced.

In their review of recent training studies, Green and Bavelier [37] conclude that lasting, generalized cognitive benefits are unlikely to come from brain-training regimes that focus on one type of task, and that more durable, generalized benefits may come from tasks that are complex and tap many systems in parallel. If this is the case, natural training regimes (e.g., video games) may prove more beneficial for sustaining older adults' cognition than current programs that have been specifically designed for the purpose of brain training. Other novel training approaches designed to increase the breadth and persistence of training benefits [for a review, see 38] include collaborative training models, where older adults engage in cooperative problem solving [39]; wellness programs that combine cognitive training with physical exercise [40]; and programs designed to enhance cognitive skills through engagement in volunteer activities such as literacy training with children [41].

Will any cognitive training program prove useful in delaying the onset of clinical dementia? There are no data available on this question. The obstacles to a clinical trial that could address this question are significant. Long-term follow-up would be needed, and it is likely that only a sustained and varied training program could hope to produce this important benefit. In the literature at present, the paucity of follow-up results, small sample sizes, and heterogeneous methods of training and measuring outcomes suggest that caution is needed in promoting the potential of structured cognitive interventions for healthy older adults [28].

We do know that cognitive training can produce modest, specific benefits for persons with preclinical cognitive conditions such as MCI or with varying degrees of dementia. Belleville and colleagues [42] observed relatively strong gains in face-name memory for a small group of MCI patients given practice and memory-strategy training compared to a no-intervention control. By contrast, the ACTIVE study reported that participants who had lower memory scores but no dementia at baseline (possible MCI cases) benefited significantly from reasoning and speed-of-

processing training, but not from memory training [43]. There have also been several case examples and small-sample studies illustrating that specialized interventions such as spaced-retrieval training can improve recall of names and other practical skills among patients with AD [44, 45], and improvement on standard memory measures has been reported from a program that combined computerized attention and sensory processing activities with pencil-and-paper exercises such as mazes, crossword puzzles, and anagrams in a small group of persons with mild to moderate dementia [46]. However, larger-scale trials of these types of interventions are needed in persons with MCI and AD to establish clinical efficacy [47]. Research to date has been limited by lack of adequate controls, small sample sizes, and interventions that combine multiple training techniques and approaches, making it difficult to assess the contributions of any individual strategy [48].

Potential Mechanisms for Neuroprotective Effects of Cognitive Stimulation and Training

The mechanisms by which cognitively stimulating activities might promote brain and cognitive reserve are unknown, but there are multiple hypothesized modes of effect.

A growing number of animal studies suggest that cognitive stimulation may have direct effects on the brain substrates that support cognition. Stimulating environments and physical exercise promote neurogenesis in the dentate gyrus in mice [49] and increase neuronal plasticity and resistance to cell death [50]. Exposure to such environments may also slow or prevent accumulation of key indicators of AD pathology, abeta levels and amyloid pathology, in transgenic mice [51]. It is not known yet how extensively similar brain changes occur in response to cognitively stimulating environments in humans, or if processes such as hippocampal neurogenesis are causally related to preserved brain function [50]. In a recent human study focusing on physical exercise [52], an aerobic exercise program was found to increase cerebral blood flow in the dentate gyrus, and blood flow, in turn, correlated with performance on a memory task, suggesting to the researchers that dentate gyrus cerebral blood flow may provide an imaging correlate of exercise-induced neurogenesis. This same technique might be valuable in studying effects of cognitive training programs. A host of mechanisms for brain plasticity and compensation other than neurogenesis are being investigated, including dendritic length and branching, synaptic modulations, neuronal morphology, neural network redundancies, and neurochemical effects [53-57].

Functional neuroimaging studies are being employed to identify brain regions and cognitive processes that mediate cognitive reserve [5]. Much of the work to date has focused on understanding the brain regions involved in performance of specific memory tasks and on whether there are age differences in the extent or pattern of brain activation during task performance. Two major findings have emerged. On some tasks, young and old persons activate the same or similar brain regions; as task difficulty increases, the magnitude of activation is often higher among older individuals, suggesting that greater effort is required among the old to achieve a comparable level of performance. On other tasks, older subjects sometimes recruit (i.e., activate) additional brain regions, not used by the young, while performing a memory task. The first finding may be an example of age-related differences in neural network efficiency, while the latter may be an example of active neural compensation. Heightened activation or recruitment of additional brain regions sometimes correlates with

estimates of brain reserve (e.g., IQ or years of education), and sometimes not, and the pattern of correlations can differ for younger and older adults.

Recently, neuroimaging researchers have begun to search for substrates of a more general cognitive reserve network that might support performance across a broader range of tasks. It is this type of reserve that could provide the basis for sustaining everyday cognitive performance in the face of advancing brain change due to age or incipient AD. Only very preliminary results are available. Stern and colleagues [58] identified a network of brain regions in younger adults that was activated during performance on two different memory tasks and was positively correlated with estimates of cognitive reserve. The activated regions (bilateral superior frontal gyrus, bilateral medial frontal gyrus, and left middle frontal gyrus) support cognitive control processes (e.g., working memory or attentional switching), suggesting that individuals with greater cognitive reserve may have generally enhanced control over their cognitive processing. In this study, however, the pattern of brain activation was less consistent across tasks for older subjects, so the role of a more general cognitive reserve network is unclear at this point.

Implications for Clinical Practice and Public Health Policy

There is a great deal of evidence that older adults retain the ability to learn new things, and observational studies show that cognitively active older persons are more likely to retain their cognitive abilities than those who are cognitively inactive. What we do not know is whether a cognitively active lifestyle, or participation in specific cognitive training programs, can prevent or delay the onset of clinical dementia. Given limitations in current knowledge, it can be difficult to answer patients' questions about the "best" things to do to increase the odds of healthy cognitive aging. However, the risks of harm from recommending a cognitively active lifestyle, or enrollment in a memory training class, are small.

Table 1 lists recommendations that the author currently uses in discussions with clients who are interested in mental activities that might promote brain fitness. As the literature on mental exercise and cognition grows, more specific recommendations may become possible.

Table 1. Recommendations for a Cognitively Active Lifestyle

Recommendation	Rationale
Make time for cognitively stimulating activities that you've always enjoyed.	Continuing favorite activities can ensure sustainability of cognitive stimulation. Long-term exposure to cognitive stimulation may be needed for practical functional benefits.
Add some new cognitive challenges, as your time and enjoyment permit.	Trying new activities may enhance brain plasticity by requiring new learning or development of new cognitive strategies.
Aim to engage in cognitively stimulating activities several times a week or more...generate some "mental sweat."	Current knowledge does not permit a prescription for how often or how long individuals should engage in cognitively stimulating activities. However, epidemiologic studies suggest that more is better, within clinically reasonable limits.

Be aware that there is no one cognitive activity, or combination of activities, that is uniquely good for reducing AD risk.	Many different types of cognitively stimulating activities have been associated with preserved cognitive skill. There are no data yet to show that cognitive activities prevent or delay AD.
Social interactions can be a great way to stimulate the mind.	Group training of cognitive skills has been shown to be effective in sharpening specific cognitive skills, and broader social networks have been associated with reduced AD risk.

The possibility of improving and sustaining brain fitness is beginning to impact public policy. In 2007, the Centers for Disease Control and Prevention issued a “National Public Health Road Map to Maintaining Cognitive Health,” in partnership with the Alzheimer’s Association, the American Association of Retired Persons, the Administration on Aging, and others [59]. The emphasis is on preserving cognitive function, rather than on preventing dementia, and the goals are largely aspirational (e.g., to “help people understand the connection between risk and protective factors and cognitive health”). The emphasis on primary prevention for large and diverse communities is ambitious, and it may set in motion a natural experiment, which over time, may inform us of the success and limitations of a public health approach.

Funding is needed to study potential benefits of nonpharmacologic interventions on brain fitness, including cognitive stimulation and training. Only a small fraction of federal dollars for research are devoted to interventions other than drugs, and private funds are hard to attract outside of the commercial product realm. If this continues, we are likely to see many more products marketed for brain health, including more “brain games,” with little or no evidence of efficacy.

Key Gaps in Research and Suggestions on How to Fill These Gaps

To better understand the roles of cognitive stimulation and cognitive training in sustaining cognitive function in healthy older people, and in possibly preventing or delaying the onset of AD, conceptual and methodological advances are needed, in addition to more research.

A few of the key gaps in research and suggestions for addressing these gaps are outlined below.

- **There is currently no metric for measuring cognitive stimulation or comparing the relative stimulating properties of different cognitive activities.** Each study in this area has measured cognitive activity in unique ways, and in most cases, relatively little effort has been made to establish the reliability and validity of cognitive activity measures. In contrast to the realm of physical activity, where classification systems have been developed that permit the comparison of total energy expenditure across diverse physical tasks, there is no such common metric for cognitive stimulation or cognitive effort. At a minimum, it would be helpful for researchers who are studying cognitive leisure activities to adopt a standard tool for measuring these activities, to fast-track the development of more specific guidelines regarding the intensity, duration, and types of activities that are most beneficial.
- **Concepts such as brain reserve and cognitive reserve are heuristically useful, but as currently used, they do not explain how increased coping comes about.** More basic

research is needed to increase understanding of how factors such as higher initial education, or more cognitively stimulating leisure activities, may be impacting the brain, structurally and functionally.

- **The practical impact of cognitive training programs remains to be demonstrated.** Although cognitive training clearly benefits specifically trained skills, more research is needed to address questions of practical importance and to design training programs which cross-train multiple skills of the types that might enhance transfer of training to everyday situations. More randomized controlled trials of the type used in ACTIVE are needed, using broader and more ambitious training regimes. Programs that promote activities and lifestyles which embody what Schooler calls “substantive complexity” [16, 60] warrant further study [39].
- **There is no evidence yet that cognitively stimulating activities or cognitive training programs delay or prevent dementia.** Longer term follow-up studies are needed to assess whether or not participation in cognitive training programs and/or adoption of cognitively stimulating lifestyles forestalls the expression of clinical dementia or impacts neurobiology in disease-modifying ways. We also need to learn when in the lifespan such experiences would be most beneficial. Fratiglioni and colleagues [11] have provided a useful image for depicting when various risk and protective factors might be of benefit in preventing AD, but at this point, it is uncertain whether cognitive stimulation and training should be added to the list of protective factors or when in the course of life their effects may be the greatest. Environmental stimulation and education in childhood and youth are probably critical in setting the stage for brain reserve, but from a public health perspective, we also need to know if choices made in midlife and later can reliably sustain or add to cognitive reserve.

Synopsis

Current knowledge about the roles of cognitively stimulating lifestyles and cognitive training interventions in preserving cognitive function in later life was reviewed. Potential mechanisms for beneficial effects of cognitive stimulation and training were discussed, and key gaps in research were identified. Suggestions were provided for advising patients about brain-healthy lifestyles, acknowledging that much remains to be learned in this area of research. More randomized controlled trials, using challenging regimes of training and stimulation and long-term follow-up, are needed, measuring cognitive trajectories in normal aging and relative risk of Alzheimer’s disease as outcomes.

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