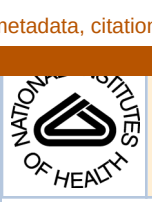

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Cognitive Reserve: Implications for Diagnosis and Prevention of Alzheimer's Disease

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Abstract

Epidemiologic evidence suggests that higher occupational attainment and education, as well as increased participation in intellectual, social, and physical aspects of daily life, are associated with slower cognitive decline in healthy elderly and may reduce the risk of incident Alzheimer's disease (AD). There is also evidence from structural and functional imaging studies that patients with such life experiences can tolerate more AD pathology before showing signs of clinical dementia. It has been hypothesized that such aspects of life experience may result in functionally more efficient cognitive networks and, therefore, provide a cognitive reserve that delays the onset of clinical manifestations of dementia. In this article, we review some of the relevant literature of the noted associations between markers of cognitive reserve and AD and discuss the possible mechanisms that may explain these associations.

Introduction

According to current literature, there is far from perfect correlation between clinical manifestations of Alzheimer's disease (AD) and burden of senile plaques and neurofibrillary tangles. For example, Katzman *et al.* [1,2] described cases of cognitively normal, elderly women who were discovered to have advanced AD pathology in their brains at death. They speculated these women did not express the clinical features of AD because their brains were larger than average. In addition, 25% to 67% of subjects who at autopsy fulfilled pathologic criteria for AD and were assessed and followed in well-characterized cohorts were clinically intact during life [3–6]. Similarly, most clinicians are aware of the fact that a stroke of a given magnitude can produce profound impairment in one patient but have only minimal effect on another. Something must account for the disjunction between the degree of brain damage and its outcome, and the concept of cognitive reserve (CR) has been proposed to serve this purpose. In particular, the CR hypothesis suggests that there are individual differences in the ability to cope with brain pathology [7••].

In this review, we examine some of the environmental factors that affect CR and, therefore, may alter the risk for cognitive decline or clinical AD. These include occupation, education, and physical, mental, and social activities. Because of manuscript size, we do not discuss nonenvironmental factors affecting CR, such as genetics, head size, (although perinatal environment may also affect head size), or other environmental factors such as nutrition.

It should be noted that although some life-experience factors that affect CR are considered environmental, it is possible that they may reflect some genetic effects. In addition, these factors are not independent but interrelated. For example, education is not strictly environmental because subjects with higher intelligence usually complete more years of schooling [8]. Occupational status is related to education and literacy but also represents a

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form of nonformal education. Lifestyle and patterns of intellectual, social, and physical activities are related to educational and occupational attainments and at the same time represent a lifelong type of training. Therefore, although these factors are examined separately for presentation purposes, they represent convergent or divergent constructs to some degree.

There is an extensive literature of retrospective studies on the topic. However, this research design suffers from many limitations including recall bias and misclassification of exposure (*ie*, AD subjects or their family may have a tendency to over-report CR-associated activities that they may consider responsible for the disease). More importantly, it provides less confidence in dementia diagnosis, because documentation of cognitive change can be only of historic nature. The association between factors that may affect CR (such as educational background) and dementia diagnosis provides an additional potential confounder. Because low education is associated with poorer performance on the neuropsychologic tests that are used to diagnose dementia, the association between education and dementia is better explored by way of prospective studies where decline from a previous level of cognitive performance is documented. Also, the lack of temporal depth of cross-sectional studies raises concerns with issues of causal directionality. Does participation in stimulating activities promote cognitive performance or is it that better-performing, cognitively capable subjects tend to participate in more intellectual, social, and physical activities? There are also plenty of examples of associations (*eg*, between dementia diagnosis and occupation) noted in cross-sectional studies that were refuted when the data were inspected longitudinally [9–11]. Because of these factors and the size limitations of this article, we consider only prospective longitudinal studies.

Occupation

Neuronal plasticity and development is by no means confined to early life and may be affected by professional experiences that occupy such a large percentage of our time, energy, and effort during adulthood.

No association between occupation and incident AD was present in two population-based longitudinal studies [10,11]. The associations between occupation and incident dementia have been equivocal or negative in some other prospective studies [12]. Although sedentary occupations (office, service, or intellectual work) as opposed to physical ones (farming, construction, or factory work) were associated with decreased risk for dementia, the associations were not significant when a no-occupation group (students, housewives, pensioners) were included in the analyses. In two other prospective studies, occupational position did not predict incident dementia [13], and a protective effect for higher occupational attainment seemed to be partly mediated by educational status [14].

Nevertheless, in a cohort of nondemented middle-aged individuals, occupational status (assessed 10 years before the cognitive assessment and rated in five categories of increasing cognitive complexity and demands) was associated with general cognitive skills, verbal memory, and visual search (although not as strongly as childhood cognition and education) [8]. A large prospective study indicated that higher lifetime occupational attainment (manager business/government, professional/technical), as opposed to lower attainment (unskilled/semiskilled, skilled trade or craft, clerical/office worker) was associated with decreased risk for incident dementia [15]. Former professional, skilled employment was reported as a protective factor for incident dementia in another cohort [16]. In another longitudinal study, non–blue-collar job and employment status (as opposed to being unemployed) were associated with lower risk of incident dementia [17]. In another report, manual occupations involving goods production (tailors, dressmakers, house constructers,

carpenters, mechanical technicians, formers, typographers, welders, and metal workers), but not manual jobs (including service production), carried a higher risk for incident dementia [18]. Being in charge of personnel had a protective effect for incident dementia in another cohort [19]. Finally, there was a significant association between occupation and incident dementia in three additional epidemiologic longitudinal studies [20].

Education

There are studies from China [21], India [22], England [13], and the United States [23–25] that reported no association between education and incident dementia. However, lower incidence of dementia in subjects with higher education has been reported by at least eight cohorts from France [26], Sweden [27], Finland [12], China [28], and the United States [14,15,20,29]. Similar associations emerged in a pooled analysis of four European population-based prospective studies of individuals 65 years and older [30].

An association between education and risk for clinical dementia, but not between education and neuropathologic findings of AD at autopsy, was reported from a study, suggesting that education modifies the clinical expression in subjects with underlying neuropathology [6]. In another prospective study with neuropathologic confirmation, education was found to modify the association between AD pathology and levels of cognitive function (for the same degree of brain pathology there was better cognitive function with each year of education) [31••].

In a cohort of nondemented middle-aged individuals, independent paths from educational attainment to general cognitive skills, verbal memory, and visual-motor search were demonstrated [8]. There is also evidence for a role of education in age-related cognitive decline, with several studies of normal aging reporting slower cognitive and functional decline in individuals with higher educational attainment [32–39]. These studies suggest that the same education-related factors that delay the onset of dementia also allow individuals to cope more effectively with brain changes encountered in normal aging.

Physical Activities

Although it makes intuitive sense that only cognitively challenging activities might be related to risk for dementia, there is also evidence for protection even for noncognitive activities. There is basic research evidence that environmental enrichment in the form of voluntary wheel running is associated with enhanced neurogenesis in the adult mouse dentate gyrus [40]. It has also been shown that physical activity sustains cerebral blood flow [41], may improve aerobic capacity and cerebral nutrient supply [42,43], may enhance cortical high-affinity choline uptake and dopamine receptor density [44], may stimulate trophic factors and neuronal growth [45], and can upregulate brain-derived neurotrophic factor gene expression [46,47]. Therefore, although it is conceivable that physical activity may merely be a nonspecific marker of good health indirectly related to dementia (or even not related to dementia at all), it is also possible that it has a direct physiologic association with brain disease.

In terms of clinical data, some prospective studies have reported no effect of exercise on risk for dementia and cognitive impairment [48,49•,50,51]. Nevertheless, many other cohorts have reported that physical activities provide protection for future cognitive decline [8,32,52–56]. In addition, high levels of physical activity were associated with reduced risk of dementia in at least four prospective studies [21,57–59]. Decreased risk for cognitive decline has been reported not only for strenuous [32] but also moderate physical activities [55,57].

Some intervention studies examining the role of exercise have found improvements in cognitive function with physical fitness training [60,61••]. In a meta-analysis of such trials, exercise had the greatest effects for executive function, but other cognitive domains also improved [61••]. Other physical intervention characteristics that provided maximum benefit included combined strength and aerobic training, sessions of moderate duration (no shorter than 30 minutes), overall training program of long duration (6 months or more), higher percentage of female participants, and "mid-old" participants (between 65 and 70 years of age) [61••].

Social and Intellectual Activities

It has been theorized that changes in everyday experiences and activity patterns may result in disuse and consequent atrophy of cognitive processes and skills (a view captured in the adage "use it or lose it") [62••,63]. Taking into account the considerable plasticity of cognitive abilities of older adults, one might predict that deliberate practice of such skills would at least result in stable performance or may even reverse age-related changes. Does the stimulation provided by typical everyday activities facilitate the maintenance and improvement of general cognitive skills by way of exposure to cognitive training [64]? In other words, could everyday experience affect cognition in a manner that is analogous to physical exercise for musculoskeletal and cardiovascular functions?

In a German population survey, only poor living accommodations were associated with increased risk of incident dementia, whereas indicators of social isolation such as low frequency of social contacts within and outside the family circle, low standard of social support, and living in single-person household did not prove to be significant [16]. Another study that evaluated social and leisure activity data in elderly community residents from France reported that traveling, doing odd jobs, and knitting were associated with lower risk of incident dementia [65,66]. Community activities and gardening were also protective for incident dementia in China [17]. A longitudinal study in Sweden reported that having an extensive social network was protective for development of incident dementia [67]. The same group also reported that both social interaction and intellectual stimulation may help in preserving mental function in the elderly, because engagement in mental, social, and productive activities was associated with decreased risk for incident dementia [50].

Participation in a variety of leisure activities of an intellectual (*eg*, reading magazines, newspapers, or books; playing cards, games, or bingo; going to classes) or social (*eg*, visiting or being visited by friends or relatives) nature was assessed in another population of nondemented elderly in New York [59]. During follow-up, subjects with high leisure activity had 38% less risk of developing dementia. The risk of incident dementia was reduced by approximately 12% for each additional leisure activity adopted. In another prospective study, frequency of participation in common cognitive activities (*eg*, reading newspapers, magazines, or books) was assessed at baseline for 801 elderly Catholic nuns, priests, and brothers without dementia [49•]. During follow-up, a 1-point increase in the cognitive activity score was associated with a 33% reduction in the risk for AD. Additionally engagement in cognitive activities was also associated with slower rates of cognitive decline. Finally, in another prospective cohort from New York, participation in leisure activities (in particular reading, playing board games, playing musical instruments, and dancing) was associated with a reduced risk for incident dementia [51]. Increased participation in cognitive activities was also associated with reduced rates of decline in memory in this study.

The hypothesis of lifestyle modifications affecting brain disease outcome becomes even more exciting in the face of increasing animal research about neuronal plasticity and its

association with learning and a physically and socially enriched environment. Exposure to an enriched environment, defined as a combination of more opportunities for learning and social interaction, produces not only a host of structural and functional changes in the brain, but also influences the rate of neurogenesis in adult and senescent animal models [68,69]. Intellectually and socially engaged lifestyle may increase synaptic density in neocortical association cortex (on the basis of stimulation [70]), which may result in more efficient cognitive function of unaffected neurons that might be able to compensate for loss of function of affected brain areas.

Imaging Studies

Physiologic data from imaging studies have served as an indirect affirmation of the CR hypothesis and have provided the first attempts to investigate the neural correlate of CR.

Structural imaging

According to the CR hypothesis, among subjects with similar degrees of pathology, those with higher CR would be expected to demonstrate less cognitive impairment. Stated differently, among patients of similar cognitive status, those with more CR would have (or be able to tolerate) more severe degrees of pathology. In order to test this hypothesis, some imaging studies have used brain atrophy as a surrogate for pathology. In healthy patients, some studies have failed to demonstrate an association between education and cerebral hemisphere volume [71–73], but this may be due to low power because of statistical measurement error for parenchymal volume [71]. On the contrary higher education was associated with increased cerebrospinal fluid volume, and, therefore, more atrophy (*ie*, subjects with higher CR remained cognitively normal despite more brain changes) in another study [71]. Among patients with AD and controlling for degree of clinical decline, higher levels of education have been associated with more severe parietal atrophy (higher parietal region peripheral CSF volume) [74].

Taxi drivers in London, who are required to undertake intensive navigational study of the city as part of their training, manifest significantly larger posterior hippocampi than control subjects, and the size of the hippocampus correlates with the amount of their occupational experience [75]. Finally, aerobic fitness training is associated with reduced brain tissue loss in healthy older adults [76•].

Functional imaging

Functional imaging studies at rest have also been used to investigate the CR hypothesis. There is good regional correlation between cerebral blood flow or metabolism (assessed by positron emission tomography [PET]) and histologically confirmed postmortem dementia changes. Therefore, cerebral blood flow or metabolism can be considered an indirect, surrogate measure of disease pathology in vivo, with lower flow or metabolism indicating more advanced pathology. Patients with higher occupational attainment [77], higher education [78], higher premorbid IQ [79], or more engagement in intellectual, social, and physical activities [80•] manifested more prominent cerebral blood flow or metabolism deficits (and hence more pathology) when controlling for clinical severity. In other words, as compared with low CR individuals, subjects with higher CR can manifest milder clinical deficits despite comparable burden of pathologic involvement. These observations support the prediction that individuals with more CR can tolerate more pathology.

In order to further investigate the neural basis of CR, some investigators have started using brain imaging not only during rest but also during cognitive activation. Most of these studies were performed for healthy participants [81–83]. However, one PET activation study that noted associations between an index of CR (comprised of education and literacy measures)

and brain activation during a nonverbal memory task was performed in AD patients [84]. The directionality of the association between CR and cerebral activation was noted to change with the advent of AD in that study.

Possible Mechanisms

Overall, the accumulated data seem to make a case for a protective effect of occupation, education, and physical, intellectual, and social activities for cognitive decline and dementia. But how is this protection imparted?

What could be the biologic nature of the final common pathway of CR's protection against cognitive decline? The neural correlate of CR can be conceived in at least two ways [7••]. First, bigger brains may tolerate more loss before exhibiting impaired function because of higher number of healthy synapses or neurons, resulting in increased number of remaining available ones when a certain percentage of them are affected by a pathologic process [1]. This can be seen as a passive role of CR, which focuses on the “hardware” of the brain.

A second possible model focuses more on the mode in which cognitive tasks are processed (*ie*, more efficient use of brain networks) as opposed to underlying anatomic differences. Even though the number of neurons or synapses might be the same, enhanced synaptic activity or more efficient circuits of synaptic connectivity might exist in those with higher CR. In addition, more efficient use of alternative brain networks (*ie*, more efficient ability to shift operations to alternate circuits) may occur. This model focuses on the potential active aspects of CR and the “software” of the brain that controls this activity.

A third possibility is that environmental factors may even hinder the development of the disease pathology. Involvement in challenging avocations during life may even decrease neurodegeneration. According to this model, factors that affect CR may enhance brain repair and recovery mechanisms, thus slowing the rate of progression.

What are the possible mechanisms by way of which life experiences may affect the brain? First, this may be mediated by increased training. Increased “brain exercise” may result in alteration of a variety of underlying neurobiologic processes such as enhanced chronic neuronal activation, increased regional cerebral blood flow, and increased glucose and oxygen metabolism [85], or even by way of higher ability for generation of new neurons into adulthood [68,86–88].

Second, life experiences may affect the brain via differential exposure to neurotoxins. It is possible that the connection between lower socioeconomic status (such as suggested by lower education, occupation, or less engaged lifestyle) and dementia is through exposure to more environmental insults (such as pollutants and industrial and nonindustrial toxins), habits such as heavy drinking, or other factors associated with low income and poverty (such as malnutrition, healthcare quality and access, and higher rates of cerebrovascular disease) that may result in incipient neurologic damage and lower the threshold for clinical manifestation of dementia [89–91]. According to this model, higher cognitive capacities in high-education occupation subjects may be mediated through avoidance of potentially neurotoxic factors and behaviors.

Third, life experiences and brain function may not be directly linked at all. According to this model, the examined factors may not reflect true environmental influences but may be just markers of innate capacities. Innate might refer to either genetic or early-life developmental factors or a combination of these. The innate capacities might in turn lead to higher levels of educational and occupational attainment and increased engagement in stimulating vocational activities. These, in turn, may have no association, but just coexist with a genetically

predetermined lower risk for cognitive decline and dementia. For example, it may be that subjects genetically predetermined to become demented have early subclinical cognitive dysfunction since their birth, which in turn leads them to fewer years of schooling, lower performance in literacy tests, lower occupational attainments, and more sedentary lifestyle.

Finally, it is likely that a combination of the different scenarios exists. We consider this as the most likely scenario. It is known that education, occupation, literacy, and intellectual, social, and physical aspects of lifestyle are affected by both genetic and environmental factors [8,92–100]. Also, although clear autosomal dominant genetic contributions have been identified for familial AD, more than 95% of AD is of the sporadic form. Therefore, lower education, literacy, occupation, and activities on one hand and dementia on the other may be genetically predetermined to a certain degree, but aspects of environmental experience may also exacerbate risk or accelerate dementia onset. This may in turn take effect via a combination of both increased cognitive training and healthier behaviors (that lead to lower neurotoxic exposure). These mechanisms may actually be interactive in many possible combinations. For example, life experiences may have a differential effect on subjects with different innate capacities, or different genetic predispositions for dementia and cognitive training may have a differential effect on subjects with varying levels of exposure to neurotoxins.

Conclusions

Accumulated results from clinical research suggest that inter-individual differences in life experiences may partially mediate the relationship between brain pathology and its clinical manifestation. However, we are currently lacking sufficient scientific data informing the mechanisms of underlying physiologic effect of life experiences. Investigations of the nature and specifics of the neural instantiation of CR may lead to the exciting prospect of suggestions of particular life-experience modifications that could affect the risk for dementia.

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