Cognition and Neuropathology in Aging: Multidimensional Perspectives from the Rush Religious Orders Study and Rush Memory and Aging Project

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Abstract

It is increasingly recognized that the correlation between neuropathological lesions and cognition is modest and accounts for about a quarter of the variance of cognition among older adults. Some individuals maintain normal cognitive functioning amidst significant brain pathology, while others suffer varying degrees of cognitive and neurological deterioration that render them dependent and frail. We present data from the Religious Orders Study and the Memory and Aging Project pertaining to pathology and cognition, and propose a paradigm shift in consideration of the neurobiology of healthy aging and dementia. Factors that modify or mediate the association between neuropathology and cognition are also discussed. It is hypothesized that the concept of resilient aging can serve as a useful entity in understanding mechanisms that underlie healthy aging amidst disease-related pathology.

INTRODUCTION

The topic of healthy aging becomes increasingly important as the elderly segment of the American population ages. In 2000, there were an estimated 35 million people age 65 or older in the United States, accounting for almost 13% of the population [1]. In 2011, the "baby-boom" generation will begin to turn 65, and by 2030, it is projected that one in five people will be aged 65 or older. The oldest-old population, 85 years and older, is currently the fastest growing segment of the older population.

With the increasing population of older adults, there is a growing interest in optimizing quality of life in old age and in early detection of cognitive decline with aging. Although it is well documented that aging is accompanied by a decline in several domains of cognition, studies have also shown that such decline is not common to all older people, and some older adults can in fact enjoy old age with good memory, concentration, executive function and other cognitive functions. Numerous studies report a link between AD-related pathology and cognitive decline [2–4]; nonetheless, healthy cognition can also occur amidst a spectrum of brain pathology, where some individuals have brains relatively free of pathological lesions, while others show significant accumulations of pathology, despite intact cognition. In community based studies of cognition with autopsy [5–7], it has been found that a third of

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people without dementia can have plaques and tangles that meet criteria for intermediate or even high likelihood of Alzheimer's Disease (AD), as well as infarctions and Lewy bodies [8]. As such, the correlation between neuropathological lesions and cognition is modest and accounts for about a quarter of the variance of cognition among older adults [9–12].

The need and potential impact of research to identify factors that promote resistance to age-associated neurodegeneration is great. The concept of cognitive reserve has emerged to explain individuals' ability to tolerate disease-related pathology in the brain without developing clinical symptoms or signs [13]. A number of factors are thought to contribute to this reserve including education, occupational experience, and leisure activities. For example, individuals with high levels of educational attainment perform better on tests of cognitive function and exhibit less decline over time compared to those with lower education levels [14, 15]. Individuals in occupations involving higher mental demands also show better cognitive performance compared to those engaged in lower mental occupational demands [16]. In addition, individuals who participate in cognitive activities such as reading and playing crosswords, and are engaged in their environment exhibit the least decline in cognitive function compared to those with disengaged lifestyle [17, 18]. Participation in leisure activities is also associated with a reduced risk of dementia [19]. These findings, then, support the cognitive reserve hypothesis and suggest that such factors could be used as indicator of cognitive reserve.

The Rush Alzheimer's Disease Center has two large, community-based, cohort studies of aging and AD that include organ donation: The Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP). The ROS and MAP studies have resulted in more than 200 peer-reviewed publications on a wide variety of issues related to healthy aging, AD and common chronic diseases of aging. These studies have examined a variety of environmental and psychosocial factors contributing to resilience, including socioeconomic status, psychosocial distress, and lifestyle activities in cognitive, physical and social spheres. Below, we will first briefly describe the two cohorts and report findings from these studies as they pertain to neuropathology and cognitive functioning in aging.

THE RUSH RELIGIOUS ORDERS STUDY AND RUSH MEMORY AGING PROJECT

The Rush ROS consists of older Catholic nuns, priests, and brothers without known dementia at the time of study entry who agreed to annual clinical evaluations and signed an informed consent and an Anatomic Gift Act donating their brains to Rush investigators at the time of death [20]. Subjects come from about 40 groups across the USA. More than 1,135 participants have enrolled and are seen annually and have had up to 17 clinical evaluations, which document level of cognition and clinical diagnoses of mild cognitive impairment (MCI), AD, and other causes of dementia. The overall follow-up participation rate exceeds 95% of survivors. Participation in brain autopsy is nearly 95% with over 485 autopsies to date.

The Rush MAP is a companion study that is more diverse in life experience make-up than ROS. Participants are older community-dwelling persons who are recruited and followed with nearly identical annual evaluations to ROS and all agree to donate brain, spinal cord, nerve and muscle to Rush investigator's at the time of death. More than 1,350 participants have enrolled and are seen annually and have had up to 13 clinical evaluations. The overall follow-up participation rate exceeds 90% of survivors. Participation in brain autopsy is more than 80% with more than 340 autopsies to date.

The annual clinical evaluations in ROS and MAP include a uniform structured interview and examination that consists of a self-report medical history, neurological examination and cognitive testing by trained nursing and neuropsychological testing personnel who are blind to previous evaluations, as previously described [21, 22]. Data on education, occupation, early life history, history of memory or other cognitive difficulties, stroke, Parkinson disease, depression, head trauma, and other conditions with the potential to cause cognitive impairment are collected by structured questionnaire, as are medications and other personality traits.

Cognition is measured using a battery of 21 tests, 19 of which are used to assess five domains of cognitive function. These include 7 tests of episodic memory, 4 tests of semantic memory, 4 tests of working memory, 2 tests of perceptual speed, and 2 tests of visuospatial ability [23–25]. A composite measure of global cognition is made by averaging the z-scores of all tests as previously described [26].

Clinical diagnoses in ROS and MAP are established in a three-step process combining mechanical decision rules and clinical judgment as previously described and in accord with current established criteria [21, 22]. At the time of death, all available clinical data are reviewed by a neurologist and a summary diagnostic opinion is rendered regarding the most likely clinical diagnosis. Difficult cases are subjected to case conferencing with a second neurologist and a neuropsychologist.

Brain autopsies are conducted in a standardized fashion [27, 28]. The location, age, and volume of all macroscopic infarctions are recorded. Bielschowsky silver staining is used to visualize neuritic plaques, diffuse plaques, and neurofibrillary tangles in the frontal, temporal, parietal, entorhinal cortex, and the hippocampus. Neuropathologic diagnoses are established by a board-certified neuropathologist blinded to age and all clinical data. NIA-Reagan, [29] Braak, [30] and CERAD [31] classifications are scored. Infarctions are documented along with their age, volume (in mm3), side, and location. Lewy bodies were identified with antibodies to α-synuclein and recorded as nigral predominant, limbic type, or neocortical type as recommended by the Report of the Consortium on DLB International Workshop [32].

NEUROPATHOLOGY OF AGING AND DEMENTIA

Analyses of neuropathological data in the ROS and MAP cohorts have yielded several findings. Studies that investigated the spectrum of pathologies in probable AD and MCI have shown that mixed pathologies are common in most of these cases [33, 34]. In persons diagnosed with probable AD, nearly 90% had pathologically confirmed AD, and almost half had mixed pathologies [34]. In MCI, more than half had pathologically diagnosed AD (58.7% amnestic; 49.2% nonamnestic) and about 20% had mixed pathologies (22.7% amnestic; 15.3% nonamnestic), suggesting that clinically diagnosed probable AD and MCI are pathologically heterogeneous disorders. Persons with MCI have intermediate level of AD pathology and cerebral infarctions from those without cognitive impairment and those with dementia, suggesting that MCI may be the earliest clinical manifestation of common age-related neurologic disorders [20].

A recent study that compared community-based and clinic-based cohorts has found that spectrum of pathologies underlying cognitive impairment in clinic-based cohorts differs from community-based cohorts [35]. Community-based persons with clinical AD had less severe AD pathology and more often had infarcts and mixed pathologies compared to clinic-based persons. Cerebral infarcts and mixed pathologies were also more common in community-based persons with MCI compared to clinic-based persons.

NEUROBIOLOGY OF HEALTHY COGNITION AND DEMENTIA IN AGING: A PARADIGM SHIFT

Evidence from ROS and MAP cohorts suggests a paradigm shift in the consideration of the neurobiology of healthy aging and dementia. The standard paradigm for the study of cognition is to identify the presence of cognitive and/or functional decline and to attribute this to one of several common brain disease states, such as AD, vascular disease, Lewy body disease or any number of rare conditions, e.g., fronto-temporal dementia, progressive aphasia. Some findings support this traditional paradigm, at least in part. For instance, analyses of ROS and MAP cohorts confirm that persons identified as having clinical AD meet neuropathologic criteria for AD, where approximately 90% of persons with NINCDS probable AD and nearly 65% of those with NINCDS possible AD meet NIA-Reagan criteria for high or intermediate likelihood AD [36]. This is comparable to what is reported in clinic-based studies. Cerebral infarctions also contribute to dementia in many of these persons, increasing the odds of dementia by nearly threefold.

However, abundant neuropathology in persons *without* dementia is observed as well: 62.2% of persons with MCI meet NIA-Reagan criteria for AD (intermediate or high likelihood) and 32.4% have cerebral infarctions. These numbers are similar for persons with amnestic as well as non-amnestic MCI. Even more surprisingly, 37.3% of persons without cognitive impairment (*no dementia and no MCI*) meet NIA Reagan criteria for AD, 21.6% have cerebral infarctions, and 13.4% have Lewy bodies [8]. Similar findings have been reported from other cohort studies going back more than two decades [37, 38]. This indicates that these individuals had reserve, repair or resilience factors that protected them against the deleterious effects of brain pathology.

Conversely, in a preliminary analysis of 100 persons without identifiable pathology (no or low likelihood of AD, no infarctions, no Lewy bodies, no other identifiable pathology), 11% met NINCDS criteria for probable or possible AD and 29% had MCI, while (only) 60% had normal cognition. This indicates unidentified causes of cognitive decline and/or excessive functional brain failure with aging.

Based on clinical/psychometric and neuropathological data from ROS and MAP projects, we propose a paradigm in which we describe aging along intersecting spectra of cognition and pathology Fig. (1).

This classification can further be illustrated using neuropsychological and pathological data from ROS and MAP cohorts. The analyses were performed using 812 subjects who have died with autopsy data to date. A composite measure of global pathology was quantified using a modified Bielschowsky silver stain as previously described [39]. A global measure of cognition was generated by averaging the z-scores of all tests as described above. Using the mean values of these composite measures to indicate normal cognition and pathology, subjects were then classified into four quadrants, as shown in the scatterplot Fig. (2).

FACTORS ASSOCIATED WITH PATHOLOGY AND COGNITION

The major neuropathologic indices of AD, cerebrovascular disease, and Lewy body disease all together only account for about 25–30% of the variance of a global measure of cognitive function assessed proximate to death [8]. This leaves as much as 80% of the variation of cognition in old age to factors other than these common diseases. While some of the variation likely represents pre-morbid differences in cognition and structural and functional changes in neurons, synapses, and dendrites downstream from these neuropathologic

indices, it is likely that neurobiologic changes separate from these neuropathologies (e.g., neurochemical or inflammatory responses) are also related to resilience.

Analysis of ROS and MAP data has identified a number of environmental and psychosocial factors that are associated with resilience. Education modifies the association of amyloid to cognitive function such that the relation between pathology, particularly amyloid, and level of cognitive function differs by years of education [40, 41]. The relation of AD pathology to the clinical manifestations of the disease also differs by gender such that the pathology is more likely to be clinically expressed as dementia in women than in men [42]. Social networks modify the association between pathology and cognitive function [43]; participation in cognitively stimulating activities is associated with reduced incidence of dementia, MCI, and less rapid decline in cognitive function [44]. The personality trait of conscientiousness is also shown to modify the association of neurofibrillary pathologic changes and cerebral infarction with cognition proximate to death [45]. In addition, processing resources, specifically perceptual speed and working memory, modify the association of AD pathology with other cognitive systems, suggesting that recruiting such additional brain networks helps maintain cognitive function despite the accumulation of pathology [46].

Another major focus of the ROS and MAP studies is to examine the association of pathology to psychological distress and depressive symptoms; such studies have yielded several provocative findings. Chronic psychological distress and depressive symptoms are associated with increased risk of MCI and AD, double the rate of cognitive decline in late life. However, distress is not associated with neurodegenerative or other recognized brain pathology, suggesting that other neurobiologic mechanisms may underlie the association between distress and cognition [47, 48].

It is important to note that these other demographic and psychosocial factors account for nearly another 20% of the variance in the global measure of cognition. As such, indicators of life experiences account for as much of the variance of global cognition as did measures of the neuropathology of the three most common conditions that cause age-related cognitive decline and dementia.

SUMMARY

Clinical-pathological studies such as those discussed in this overview, as well as other population-based epidemiological studies [5–8, 49–52] provide evidence that the relationship between pathology and cognition is complex and that while plaques and tangles may be highly correlated with AD-type dementia, these lesions are neither necessary nor sufficient for cognitive decline. Even though the traditional paradigm has focused on identifying disease-related pathology, clinicopathologic correlations account for only about a quarter of the variance in cognition. There are, in fact, individuals who maintain normal cognitive functioning amidst significant brain pathology. It has been hypothesized that such individuals have cognitive reserve that helps them tolerate the disease-related pathology and function without developing clear clinical symptoms or signs. As such, the concept of resilient aging promotes plastic response to the disease process, and can serve as a useful entity in understanding mechanisms that underlie neurodegenerative diseases and thereby develop interventions that target resilience. Consequently, interventions that likely increase cognitive reserve, such as physical activity and cognitive stimulation have recently gained attention; remarkably, these modalities share biological mechanisms, particularly in the promotion of neurotrophic factors and reduction of inflammation and oxidative stress. More work is needed in this area in future research.

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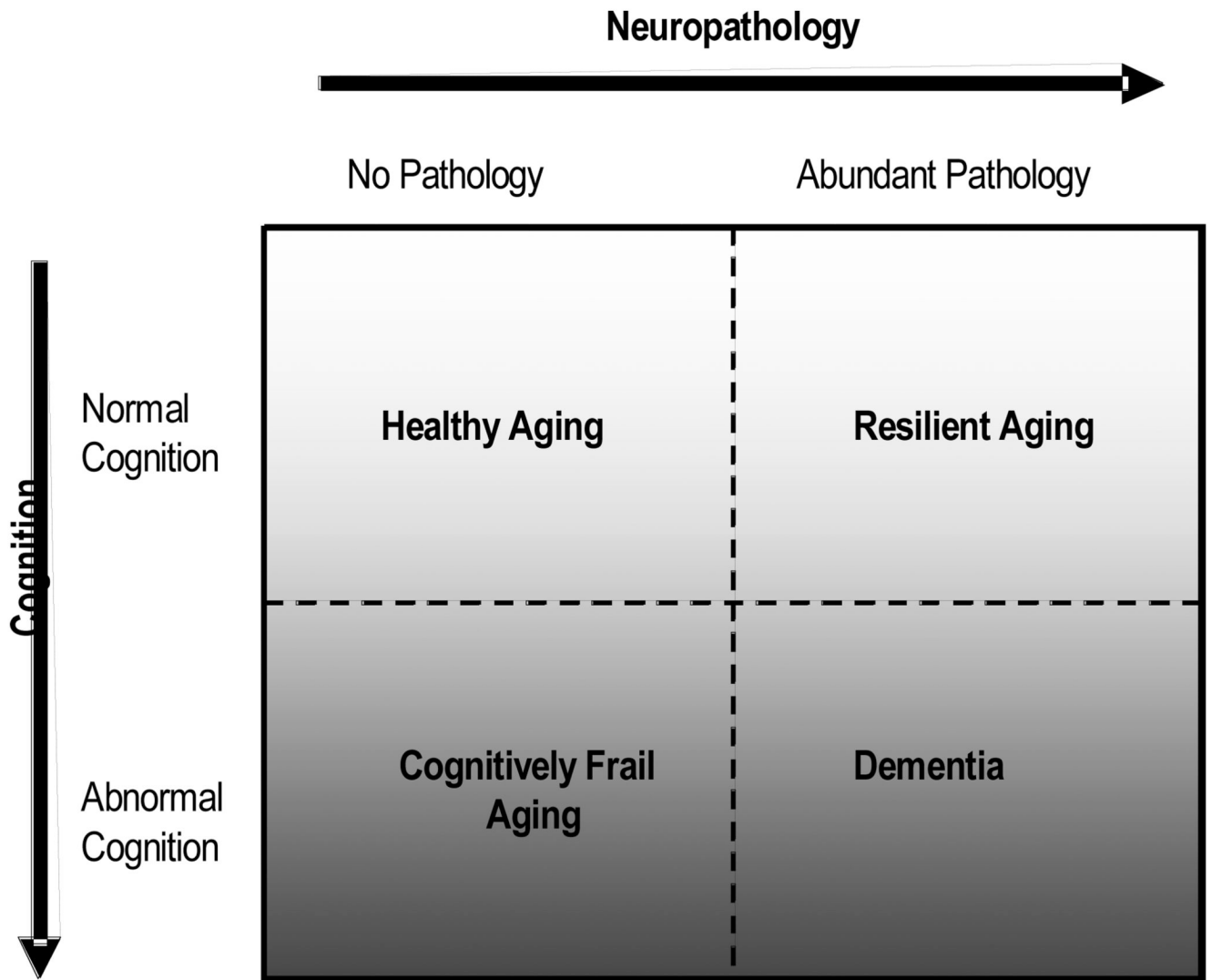
Fig. (1).
Healthy Aging indicates normal cognitive functioning with little or no AD or other pathologies. Such individuals do not meet accepted pathologic criteria for AD, nor do show cerebral infarctions or Lewy bodies. *Resilient aging* indicates normal cognition amidst moderate or high densities of AD and/or other pathologies. *Cognitive Frailty* is used to indicate abnormal cognitive function despite little to no pathology. *Dementia* indicates abnormal cognition and moderate to high densities of AD or other pathologies.
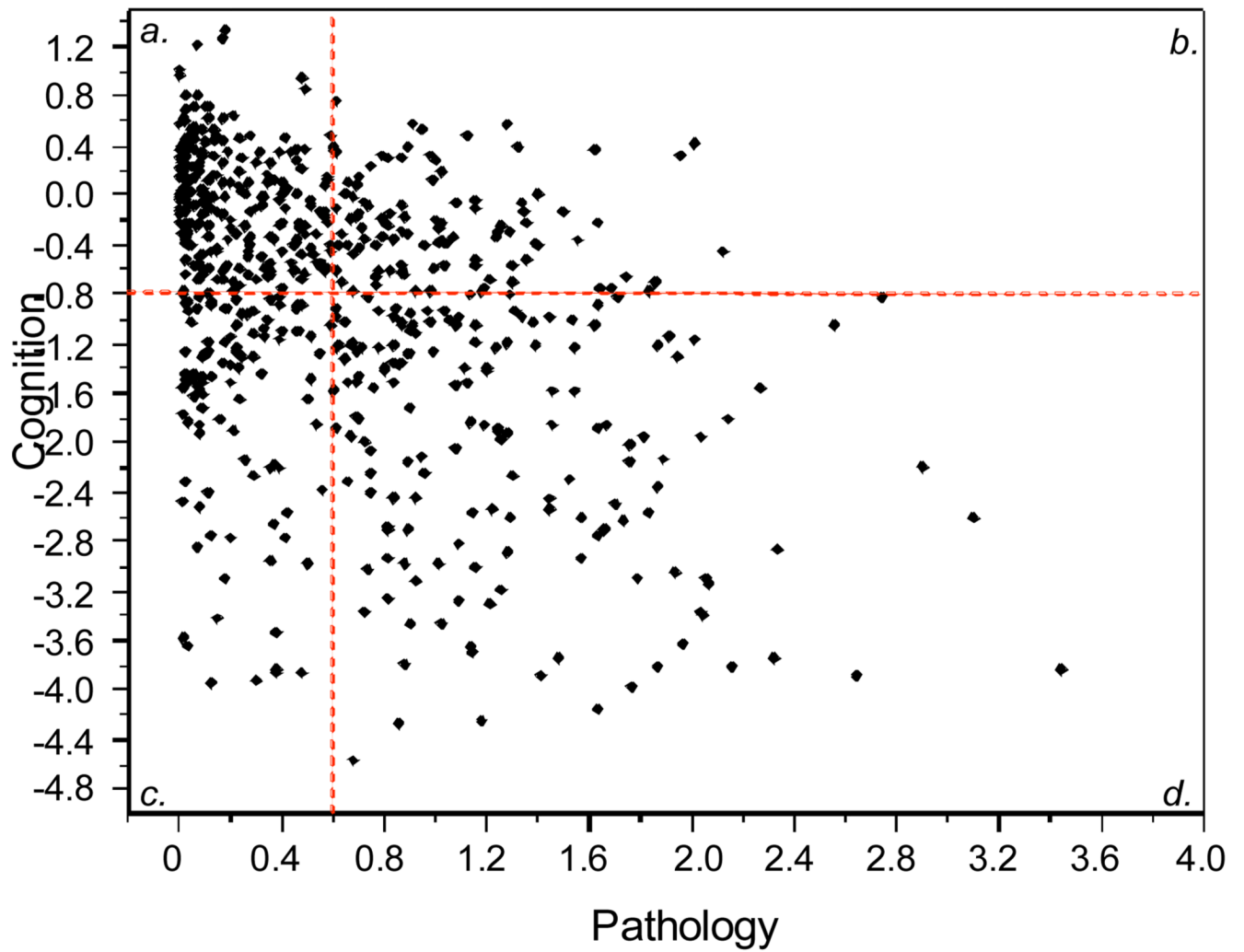
Fig. (2).
That is, individuals with high cognition and low pathology were considered *healthy* (Quadrant *a*), whereas those with high cognition but also high pathology were considered *resilient* (Quadrant *b*). Conversely, individuals with low cognition but low pathology were considered *cognitively frail* (Quadrant *c*), where as those with low cognition and high pathology were considered to have *dementia* (Quadrant *d*).