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RESISTANCE, RESERVE, AND RESILIENCE: SYSTEMS THAT DEFEND AGAINST AGE-RELATED COGNITIVE DECLINE—OBSERVATIONS FROM THE HONOLULU-ASIA AGING STUDY (HAAS)

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Background: Dementia is usually attributable to one or a combination of neuropathologic abnormalities, including Alzheimer amyloid plaques and neurofibrillary tangles. Most demented individuals have at least two types of dementia-related abnormality. Older decedents without abnormalities may be viewed as showing resistance to the relevant pathogenic processes. Others with brain or cognitive reserves may maintain normal cognitive performance even when 1 or 2 types of histopathologic abnormality have developed. We hypothesize essential resilience as a third defense against established neuropathology. **Methods:** Analyses involved 572 autopsied HAAS participants (Japanese-American men) dying at age 80 or older whose baseline Cognitive Assessment and Screening Instrument (CASI) score had been normal (>=74). End-of-life severe impairment was based on a final CASI score <60. Four overlapping reserve elements were each dichotomized as 0 or 1: (i) negligible brain atrophy, (ii) higher education, (iii) higher occupational complexity, (iv) higher adult life cognitive test scores. A neuropathologic burden index (Neurology, March 2016) was the sum of four histopathologic abnormalities, each scored 0.4 (moderate) or 1.0 (severe) for Alzheimer lesions, microinfarcts, Lewy bodies, and hippocampal sclerosis. **Results:** Among 159 participants with a neuropathologic burden index of zero, 145 (91%) maintained normal cognition. Among 387 with burden indices 0.4 - 1.8 (most with two moderate or severe lesion types), the proportions developing severe impairment fell from 49%, to 35%, to 29%, to 25%, to 13% respectively in decedents with zero, 1, 2, 3, or all 4 reserve elements. Of 26 decedents with neuropathologic burden indices >=2, 22 (85%) developed severe cognitive impairment. We continue to search for factors determining essential resilience. **Conclusions:** In this autopsied cohort, brain and/or cognitive reserves provided a powerful attenuation of cognitive impairment attributable to a panel of neuropathological abnormalities. A hypothesized additional contribution by essential resilience remains to be demonstrated.