Pathological and Resilient Brain Aging: Lessons Learned Under the Neuropathology Microscope

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Neuropathology Core: Goals

- Characterize pathological processes at the tissue and cellular level
- Provide diagnostic information aligned with latest guidelines
- Build a highly accessible, appropriately safeguarded biorepository
- Understand the biological substrate of behavior (cognitive, motor, psychological) in an individual and a population
- Contribute to development of diagnostic and therapeutic strategies
UW NP Core Case Example

- 87 yo man
- ACT Research Participant for 22 years
- PMHx: Hypertension, polio (1933), migraines
- Social History: Navy veteran
- Family History: No dementia
- Clinical Dx: Control (not demented)
Parietal Lobe
PHF-tau 40X
Neuropathological Diagnosis

BRAIN (1,120 GRAMS), ADULT AUTOPSY:

• Alzheimer's Disease Neuropathologic Change: HIGH (A3, B3, C3)
  – A3: Thal Aβ Phase 4 of 5
  – B3: Braak and Braak Stage V of VI for neurofibrillary tangle distribution
  – C3: CERAD frequent neuritic plaques

• Vascular brain injury: PRESENT
  – Chronic microvascular (arteriolar) brain injury: NONE
  – Chronic macrovascular (arterial) brain injury: PRESENT
    • Right globus pallidus infarct (1.6 x 1.0 x 0.6 cm)
    • Left caudate nucleus infarct (0.3 x 0.1 cm)
    • Left hippocampus infarct (0.2 cm)
  – Acute vascular brain injury: NONE

• Cerebral amyloid angiopathy: MODERATE

• Hippocampal sclerosis: PRESENT (left side only)

• pTDP-43 pathology: PRESENT (left side only)

• Age-related changes:
  – Arteriolosclerosis: MODERATE
  – Atherosclerosis: MODERATE
Resilience (two forms)

• Resistance to development of neurodegeneration with advanced age
  – Advanced age
  – Low pathology
  – No Dementia

• Resilience to cognitive effects of neurodegeneration
  – High pathology
  – No dementia
Alzheimer’s disease neuropathologic change, Lewy body disease, and vascular brain injury in clinic- and community-based samples


Featured Article

Mixed neuropathologies and estimated rates of clinical progression in a large autopsy sample

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Fig. 1. Co-occurrence of Alzheimer’s disease neuropathologic change (ADNC), Lewy body disease (LBD), and vascular brain injury (VBI) stratified by age. ADNC = moderate/frequent neuritic plaques and Braak stage III–VI; LBD = Lewy bodies in any brain region examined; VBI = gross infarcts and cortical microinfarcts. 191 NACC participants with age of death less than 65 years were excluded. Abbreviations: ACT, Adult Changes in Thought study; NACC, National Alzheimer’s Coordinating Center.
Summary of NACC-ACT Studies

• Multiple co-morbidities are common with advanced age

• Dementia prevalence increases with multiple co-morbidities

• Rate of cognitive decline associated with co-morbid pathologic processes
Neuropathologic comorbidity and cognitive impairment in the Nun and Honolulu-Asia Aging Studies

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ABSTRACT

Objective: To examine frequencies and relationships of 5 common neuropathologic abnormalities identified at autopsy with late-life cognitive impairment and dementia in 2 different autopsy panels.

Methods: The Nun Study (NS) and the Honolulu-Asia Aging Study (HAAS) are population-based investigations of brain aging that included repeated cognitive assessments and comprehensive brain autopsies. The neuropathologic abnormalities assessed were Alzheimer disease (AD) neuropathologic changes, neocortical Lewy bodies (LBs), hippocampal sclerosis, microinfarcts, and low brain weight. Associations with screening tests for cognitive impairment were examined.

Results: Neuropathologic abnormalities occurred at levels ranging from 9.7% to 43%, and were independently associated with cognitive impairment in both studies. Neocortical LBs and AD changes were more frequent among the predominantly Caucasian NS women, while microinfarcts were more common in the Japanese American HAAS men. Comorbidity was usual and very strongly associated with cognitive impairment. Apparent cognitive resilience (no cognitive impairment despite Braak stage V) was strongly associated with minimal or no comorbid abnormalities, with fewer neocortical AD lesions, and weakly with longer interval between final testing and autopsy.

Conclusions: Total burden of comorbid neuropathologic abnormalities, rather than any single lesion type, was the most relevant determinant of cognitive impairment in both cohorts, often despite clinical diagnosis of only AD. These findings emphasize challenges to dementia pathogenesis and intervention research and to accurate diagnoses during life. Neurology® 2016;86:1000-1008
Percent of Honolulu-Asia Aging Study (HAAS) (top) and Nun Study (NS) (bottom) autopsied participants with moderate (+, light blue) or severe (+++, dark blue) cognitive impairment in each strata based on the lesion comorbidity index. No or mild cognitive impairment makes up the balance of cases to reach 100%. The bottom rows indicate the number of participants in each stratum.
Summary from Nun-HAAS

- Prevalence of different pathologies varies by cohort
- Cognitive resilience strongly associated with minimal or no comorbid abnormalities
- Proportion of individuals displaying cognitive resilience was virtually identical between studies
- Proportion of individuals resistant to all four diseases was virtually identical between studies
- Sex, ethnicity, and/or lifestyle choices may significantly influence resistance to developing different types of brain injury
• Much more work is needed
  – Larger and more diverse/representative study populations
  – Correlational analyses with clinical, radiographic, exposure, genetic data
  – Quantitative and molecular approaches to understand biological underpinnings
Neuropathology Core for WHI

- Pathological basis of aging and neurodegeneration in WHI participants
  - Unique from other cohorts with brain autopsy because of combination of
    - Size of cohort
    - Exclusive focus on women
    - Extremely deep, longitudinal clinical data
Neuropathology Core for WHI

• Research resource
  – Bank of brain regions optimized for future research
  – Bank of digitized images from neuropathologic evaluations
  – Legacy of WHI participants to understanding aging and disease on human brain
Brain Donation

The Ultimate Gift to Science