Published in final edited form as:

J Alzheimers Dis. 2011 ; 25(3): 445–453. doi:10.3233/JAD-2011-101980.

“End-Stage” Neurofibrillary Tangle Pathology in Preclinical Alzheimer's Disease: Fact or Fiction?

Erin L. Abner^a, Richard J. Kryscio^{a,b}, Frederick A. Schmitt^{a,c}, Karen S. SantaCruz^d, Gregory A. Jicha^{a,c}, Yushun Lin^{a,b}, Janna M. Neltner^f, Charles D. Smith^{a,c}, Linda J. Van Eldik^{a,e}, and Peter T. Nelson^{a,f,*}

Julie Schneider

^aSanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA

^bDepartment of Statistics, University of Kentucky, Lexington, KY, USA

^cDepartment of Neurology, University of Kentucky, Lexington, KY, USA

^dDepartment of Laboratory Medicine and Pathology, University of Minnesota, MN, USA

^eDepartment of Anatomy and Neurobiology, University of Kentucky, Lexington, KY, USA

^fDepartment of Pathology, Division of Neuropathology, University of Kentucky, Lexington, KY, USA

Abstract

Among individuals who were cognitively intact before death, autopsies may reveal some Alzheimer's disease-type pathology. The presence of end-stage pathology in cognitively intact persons would support the hypothesis that pathological markers are epiphenomena. We assessed advanced neurofibrillary (Braak stages V and VI) pathology focusing on nondemented individuals. Data from the National Alzheimer's Coordinating Center database ($n = 4,690$ included initially) and from the Nun Study ($n = 526$ included initially) were analyzed, with antemortem information about global cognition and careful postmortem studies available from each case. Global cognition (final Mini-Mental State Examination scores [MMSE] and clinical 'dementia' status) was correlated with neuropathology, including the severity of neurofibrillary pathology (Braak stages and neurofibrillary tangle counts in cerebral neocortex). Analyses support three major findings: 1. Braak stage V cases and Braak VI cases are significantly different from each other in terms of associated antemortem cognition; 2. There is an appreciable range of pathology within the category of Braak stage VI based on tangle counts such that brains with the most neurofibrillary tangles in neocortex always had profound antemortem cognitive impairment; and 3. There was no nondemented case with final MMSE score of 30 within a year of life and Braak stage VI pathology. It may be inappropriate to combine Braak stages V and VI cases, particularly in patients with early cognitive dysfunction, since the two pathological stages appear to differ dramatically in terms of both pathological severity and antemortem cognitive status. There is no documented example of truly end-stage neurofibrillary pathology coexisting with intact cognition.

© 2011 – IOS Press and the authors. All rights reserved

*Correspondence to: Peter T. Nelson, MD PhD, Department of Pathology, Division of Neuropathology and the Sanders-Brown Center on Aging, Rm 311, Sanders-Brown Building, 800 S. Limestone, University of Kentucky, Lexington, KY 40536-0230, USA. Tel.: +1 859 257 1412 x 254; Fax: +1 859 257 6054; pnels2@email.uky.edu..

Authors' disclosures available online (<http://www.jalz.com/disclosures/view.php?id=781>).

Keywords

GRN; miRNA; microRNA; neurofibrillary tangles; neuropathology

INTRODUCTION

Neuropathology, correlated with clinical history, is the gold standard for the diagnosis of Alzheimer's disease (AD). Recent neuropathological guidelines for AD refer exclusively to subjects with documented clinical dementia [1]; no current neuropathological diagnostic criteria exists for the many persons who die with subtle or no cognitive impairment. This is a problem because of an increasing focus on individuals with presumed “preclinical AD” in terms of research into potential therapies and biomarkers.

Two histopathological hallmarks are recognized for postmortem AD diagnosis: neurofibrillary tangles (NFTs), and neuritic amyloid plaques (NPs) [1]. We focus on NFT pathology because NFTs have consistently been found to correlate best with the severity of antemortem cognitive impairment [2–9]. NFT pathology is graded using Braak staging, an ordinal 0–VI scale as defined by Braak and Braak [10, 11]. Braak stages depict the anatomic progression of the pathology: NFTs localize first to medial temporal lobe structures (Braak stages 0–III) and then in other brain areas (stages IV–VI) [12]. The most confident indication that AD pathology underlies antemortem cognitive impairment corresponds to cases with high densities of NPs and Braak stages V or VI.

Due to their shared diagnostic categorization, it is common practice to group together cases with Braak stages V and VI pathology [13–17]. However, Braak staging was not originally developed for clinical-pathological correlation and these assumptions should be carefully evaluated. There are also debates about the biological relevance of pathological markers [18–22]. If truly “end-stage” neurofibrillary pathology could co-exist with intact cognition, it would support the hypothesis that NFTs are epiphenomena. To address these important issues, it is necessary to use quantitative methods since Braak staging masks underlying variation in severity and distribution of AD neurofibrillary pathology [19, 23–26].

In the current study we assessed the range of cognitive impairments, and quantitative neurofibrillary changes, associated with Braak stages V and VI pathology. Data were analyzed from two large autopsy series: the National Alzheimer's Coordinating Center (NACC) [27] database and the Nun Study [28]. These analyses incorporated many individuals who died without evidence of antemortem cognitive impairment.

METHODS

Database with initial inclusion and exclusion criteria

Data from two large autopsy series were included in the present study. All procedures were performed with approval by local Institutional Review Boards. The Nun Study is a longitudinal study of participants from seven regions in the United States [28, 29]. Cases initially included in the current study ($n = 526$) had available neuropathological data and no clinical history of prion disease, trinucleotide repeat diseases, or pathologically-confirmed frontotemporal dementia that might explain a dementia syndrome with early death. Exclusion criteria for the Nun Study were missing Braak stage ($n = 10$) or any patient with documented (and pathologically-verified) non-AD dementia disorder ($n = 21$, which does not include some “mixed” cases with DLB and/or VaD). Thus, 495 cases were included as the initial basis of study.

The NACC registry represents data obtained from 29 different ADCs [27]. The following groups were initially included from the NACC data: death after 1999, and, available neuropathological data. There were no inclusion or exclusion criteria with regard to cognitive decline during life. Using these criteria, 4,690 cases were included from the NACC registry. The average number of included subjects per ADC was 147.5, median 127, and range 4–425 cases per ADC. Additional criteria for the NACC registry cohort were applied to exclude cases where the Braak stage was missing ($n = 191$), without Mini-Mental Status Examination (MMSE) test scores ($n = 102$), age less than 60 at death ($n = 113$), or any patient with documented non-AD dementia(s) that included prion disease, Parkinson's disease dementia, multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, documented “vascular dementia”, any other known subtype of frontotemporal lobar degeneration, or a primary pathological diagnosis of “Other” ($n = 974$). In comparison to the Nun Study, there were greater numbers of these cases in the NACC registry, as expected. 3,310 NACC registry cases were included as the initial basis of study.

Additional inclusion and exclusion criteria

Additional exclusion criteria were applied to the NACC dataset to improve the validity of correlations between Braak stage and documented antemortem cognitive status and to include only cases that would be considered at least “possible AD” on the CERAD continuum (Table 1). The final dataset included only cases where the final evaluations were performed within 3 years of death and where there was some evidence of neuritic plaques (CERAD “possible AD”, “probable AD”, or “definite AD”), providing a sample of 1,856 cases using NACC data, of which 568 cases were Braak V and 651 cases were Braak VI. Additional cases were not excluded from the Nun Study based on these criteria because all patients died within 3 years of the final evaluations, and there were no Braak V or VI cases without neuritic amyloid plaques.

Definition of “dementia” and MCI

Antemortem diagnosis of “dementia” is of interest because the current pathological criteria for AD only apply to subjects with dementia, while the current study is concerned with non-demented individuals. Cases from NACC span two distinct data collection protocols: Minimum Data Set (MDS) [1999–2005] and Uniform Data Set (UDS) [2005 to present]. All patients with a reported diagnosis of dementia at the last clinical evaluation (CLINDEM = 1 for MDS subjects and DEMENTED = 1 for UDS subjects) were considered to have antemortem “dementia”. For MDS subjects, a clinical diagnosis of dementia is determined by DSM-IV criteria. For UDS subjects, clinical dementia is defined as meeting “the criteria for dementia (in accordance with standard criteria for dementia of the Alzheimer's type or for other non-Alzheimer's dementing disorders)”. Additionally, if a patient did not have a clinical diagnosis of dementia but had a final MMSE score of 20 or lower ($n = 17$ in the Nun Study), he or she was also considered to have dementia.

Designation of mild cognitive impairment (MCI) was also according to the NACC coding scheme. For MDS subjects, an MCI diagnosis is defined as no clinical diagnosis of dementia combined with evidence of questionable dementia (e.g., Clinical Dementia Rating = 0.5). For UDS subjects, MCI is defined as not normal for age, no clinical diagnosis of dementia, evidence of cognitive decline, and essentially normal functional activities [30]. By definition, these patients did not carry a diagnosis of dementia. Another subset of non-demented patients was indicated to have had “normal cognition” prior to death (no MCI, dementia, or other neurological condition resulting in cognitive impairment). Clinical MCI diagnosis was not available for the Nun Study cohort.

Pathological criteria and methods

Cases with Braak stage V or VI were included from the NACC registry where there were enough NPs (according to CERAD criteria [31]) so that the brain pathology would be considered to be on the AD spectrum. Concomitant pathology was operationalized from the NACC registry data in relationship to neocortical Lewy bodies and hippocampal sclerosis. Cerebrovascular pathology was not evaluated because there is currently no solid rubric for clinical-pathological correlation for the NACC registry. Neocortical LBs were determined by indication of “diffuse” or “intermediate” cortical LB pathology using the NACC registry NPLEWY variable, based on consensus diagnostic features. The “brainstem-predominant” variant of DLB was not included initially because this pathology has a low probability of correlating with a DLB syndrome clinically [32]. Hippocampal sclerosis is operationalized from the NACC database using the NPSCL, NPPHIPP, and NPCHIPP variables.

Pathological assessments in the Nun Study were as described in detail previously [29, 33]. Briefly, NFTs, diffuse amyloid- β (A β) plaques (DP; plaques without surrounding dystrophic neurites), and neuritic A β plaques (NP; A β plaques surrounded or invested by argyrophilic dystrophic neurites) were counted as described previously [33]. An arithmetic mean was calculated from the count of the 5 most involved fields for DPs (number of DPs per 2.35 mm²; 100 $\times$ fields), NPs (number of NPs per 2.35 mm²; 100 $\times$ fields), and NFTs (number of NFTs per 0.586 mm²; 400 $\times$ fields) for each region using silver-stained sections of middle frontal gyrus, middle temporal gyrus, inferior parietal lobule, and occipital lobe including primary visual area. Mean neocortical counts represent an average derived from the four cortical areas. Post-hoc auditing of tangle counts was performed by a neuropathologist and tau immunohistochemistry performed as required for challenging cases.

Statistical methods

Descriptive statistics (means and proportions) were compared using *t* tests and chi-square tests of association. Final MMSE scores were compared using Kolmogorov-Smirnov tests, multiple linear regressions, fitting age at death, years of education, and Braak stage as predictors. Logistic regression was used to assess the prevalence of concomitant pathologies given Braak stage and antemortem dementia status. All analyses were performed using SAS 9.2®.

RESULTS

Overall, 71.4% of cases from the NACC registry (evaluated within 3 years of death) had documented dementia. Also from the NACC registry, 378 patients were “normal cognition” controls (17.3%; data not shown). From the Nun Study, 47.3% had documented dementia whereas 34.2% if cases had final MMSE scores over 25 (34.2%; data not shown). Thus, the current study included patients who spanned the spectrum of cognitive performance in the elderly.

Among patients with the final evaluation within 3 years of death, and with enough neuritic plaques to merit a diagnosis of “possible”, “probable”, or “definite” AD according to the CERAD definition [31] (hereafter “CERAD-positive”), there were 1,219 patients in the NACC registry data with Braak V or VI pathology (Table 1). Note that the ages of most of the included subjects were older than 80 at death, so the CERAD-based registration according to differing ages would not greatly affect this analysis. Of these patients, 568 had Braak stage V pathology, and 651 had Braak stage VI pathology. Individuals with no antemortem diagnosis of dementia were more common for Braak stage V (6.3%) than Braak stage VI (0.8%) ($\chi^2 = 29.0$, 1 d.f., $p < 0.0001$). In the Nun Study, individuals with no

antemortem diagnosis of dementia were also more common for Braak stage V (42.2%) than Braak stage VI (9.2%) ($\chi^2 = 22.5$, 1 d.f., $p < 0.0001$).

Table 2 provides additional comparisons between CERAD-positive cases with Braak V and Braak VI pathology. In the NACC cohort, Braak stage VI cases tended to be younger (79.5 versus 83.8 years at death) and had lower average final MMSE scores ($p < 0.0001$). Cases with antemortem documented “normal” cognition were 7.5 times more likely to be Braak stage V than stage VI (15% versus 2%), and MCI cases were 6 times more likely to be stage Braak V than Braak VI (18% versus 3%). In the Nun Study, Braak stage VI cases were again younger (89.3 versus 91.4 years at death) and had considerably lower average final MMSE scores ($p < 0.0001$) than Braak stage V cases.

Data from the NACC registry were analyzed to determine the sampled cohort's antemortem global cognitive outcomes (final MMSE test scores) comparing Braak stages V and VI in CERAD-positive cases. We used the same inclusion criteria as in Tables 1 and 2 (final $n = 1,219$ with 568 Braak V and 651 Braak VI). In Fig. 1, the distribution of MMSE score outcomes from the NACC registry dataset is shown, using an empirical cumulative distribution function, to enable comparison between Braak V and VI cases. Note that the median MMSE is shifted 5 points between Braak V and Braak VI ($p < 0.0001$, Kolmogorov-Smirnov test). A greater proportion of low-MMSE cases (MMSE < 5) were Braak VI and high-MMSE (MMSE > 25) cases being Braak V ($\chi^2 = 53.6$, 6 d.f., $p < 0.0001$; data not shown).

Because significant cognitive deterioration may occur within three years, and even slight worsening of MMSE scores can indicate cognitive impairment, we sought to test a select cohort of individuals with final MMSE scores of 30 attained within a year of death (Fig. 2). There was no case with Braak stage VI and final MMSE score of 30 among nondemented persons tested within a year of death in either the NACC registry or Nun Study datasets (combined $n = 89$).

The overall proportion of Braak stage VI cases in nondemented patients was low, but a quantitative analysis was required to determine the distribution of neocortical NFTs in Braak stages V and VI cases. Only Nun Study data were used for this analysis because the NACC data are limited to semi-quantitative Braak stage information to grade the severity of NFT pathology. Figure 3A incorporates textured data about summed NFT counts from neocortical regions – frontal, inferior parietal lobule, superior and mid-temporal gyri, and occipital cortex. Assessing the Braak V and Braak VI cases (3B), the correlation between neocortical NFTs counted postmortem and antemortem global cognitive status as defined by MMSE scores is highly significant ($p < 10^{-42}$ by Pearson correlation). The results are in line with expectations given that we are only studying patients at one end of the pathological spectrum. In addition to “floor effects”, it is not appropriate to perform additional regression-based statistics in this sample because of the known impact of comorbid pathologies; these particular topics are more fully explored elsewhere [33].

Among Braak V and VI cases, patients with high cognitive status as manifested by MMSE scores correspond to the cases with the lowest number of neocortical NFTs, and, above a particular threshold (orange line in Fig. 3B), every case without exception had been profoundly impaired (MMSE score < 15). For example, there is a single Braak VI case that had final MMSE score of 29, but this case actually had relatively low neocortical NFTs counted. Whereas only 7.7% of Braak stage V cases met the threshold of neocortical NFTs indicated in Fig. 3B, 60.4% of Braak stage VI cases were above this threshold in terms of counted neocortical NFTs, with profound cognitive impairment.

DISCUSSION

Using large autopsy series with robust clinical and pathological data from each case, we found that Braak stage VI pathology was quite rare in individuals without documented antemortem dementia. Braak stages are ordinal variables, not continuous variables, which can mask both individual variations in pathological severity and also the overall heterogeneity of the disease itself. All individuals in the Nun Study with neurofibrillary tangle counts above a particular threshold had severe antemortem cognitive impairment. In persons with eventual Braak stage V pathology, the antemortem global cognition was substantially more intact than for Braak VI cases. These findings accentuate the differences between Braak stages V and VI, particularly in the context of early clinical symptoms which is mostly Braak stage V.

One possible limitation to the current study is that neuropathologists may become aware of patients' clinical information, and a pathologist may be reluctant to diagnose an advanced Braak stage for a patient with intact antemortem cognition. The behaviors of individual neuropathologists cannot be completely ruled out as a systematic bias, because the NFT counts from research centers outside of the University of Kentucky were not available to us in the current study. However, if neuropathologists changing their diagnoses due to clinical information was a systematic bias, then one would expect that there would be a group of high-status individuals denoted as Braak stage IV despite having high neocortical tangle counts, and we see no evidence of this in either the Nun Study data or the database of the University of Kentucky ADC (together $n > 1,000$ autopsy cases with detailed NFT counts and close clinical correlation) [19].

It is also a potential limitation that inter-rater reliability of Braak staging between neuropathologists is imperfect [34] which results in apparently contradictory final MMSE scores for given Braak stages among different research cohorts (Table 2) and among published studies from reputable research centers [35, 36]. However, the current study design is intended to reflect the overall state of clinical-pathological correlation in Braak stage V and VI cases and in this sense having results from multiple neuropathologists is preferable. It may not be currently feasible or practical to perform quantitative assessment of neurofibrillary pathology in all AD cases, yet our results may help to shape the thresholds for neuropathologists for optimal clinicalpathological relevance.

Another note of caution relates to the fact that autopsy cohorts are samples of convenience rather than epidemiological cohorts. There are biases in terms of research volunteers, and autopsy rates are never perfect. Dementia research clinics have recruitment biases that are reflected in clinical and pathological parameters [37, 38] and this phenomenon is clearly illustrated by the high percentage of NACC registry patients with dementia (71.4%). It is not known what would occur in a truly representative, unbiased sample. However, the biases intrinsic to our sampled datasets would not be predicted to alter our conclusions in Braak V and VI cases that were based on data from state-of-the-art clinical research centers. Further, we include data from the Nun Study, a more population-based cohort, which had dementia rate more in-line with expectations (47.3%), near 100% autopsy rate, and average autopsy less than 10 months from the final MMSE assessment.

The current study is in agreement with prior published work showing that advanced Braak stages are rare in individuals without documented dementia, whereas amyloid plaque density can be high in cognitively intact people [2, 20, 33, 39]. The severity of amyloid plaque pathology can be correlated with some cognitive loss in early stages of the disease [4, 6, 39] and indeed one does not see generally Braak V or Braak VI pathology without appreciable neuritic amyloid plaques (see Table 1). This seems to underscore the biological co-

dependencies and synergies of these two lesion types. Yet it is the involvement of the cerebral neocortex with NFTs that correlates best with the severity of global antemortem cognitive impairment [2–4, 7, 9, 40–42]. Most of these prior studies do not specifically address those cases with at least moderate neurofibrillary pathology, but without dementia.

In a prior review [19] of 11 different studies, comprising 555 nondemented cases, 12 were by pathology Braak stage V (2.2%) and three Braak stage VI (0.5%). Similar observations were made using smaller numbers of nondemented cases with Braak V or VI pathology [20, 39, 43] although the distribution of neurofibrillary tangle pathology in Braak VI cases was not assessed. A published case report described a nondemented individual with Braak stage VI pathology – a woman with a final MMSE score of 28 [44]. Although this person did not have dementia diagnosed at death, she did score at or below the 20th percentile on three cognitive tests [44] which suggested cognitive deterioration. Another prior study evaluated nondemented individuals with Braak stages V ($n = 11$) and VI ($n = 1$) to assess parameters that impact “preserved cognitive function” [20], a fascinating concept outside the scope of the current study. Here we found that there was not a single case with Braak stage VI and final MMSE score of 30 among nondemented persons tested within a year of death in either the NACC or Nun Study datasets. Further, using counts of neocortical neurofibrillary tangles, we find that every brain with tangle pathology above a particular threshold in the cerebral neocortex had been profoundly impaired. Preclinical AD lasts for ten years or more [19, 45–49], and it seems most sensible to target individuals for therapeutic interventions before many neocortical NFTs are present.

Clinical-pathological correlation in large autopsy series with hundreds of non-demented individuals and 1,370 Braak V/VI cases can provide insights into biological mechanisms. There has been debate about the biological impact of AD pathological hallmarks [18, 19, 22]. Although unable to provide a definitive test of mechanism, our data seem most compatible with the hypothesis that neocortical NFTs contribute to the mechanism (s) involved in cognitive deterioration. We found that the highest amounts of neocortical NFT pathology (assessed with NFT counts) were never observed in the brains of individuals who were cognitively intact before death. Future studies or case reports germane to “end-stage NFTs in nondemented individuals” should include pathological assessments augmented with quantitative counts of neocortical NFTs, because Braak staging can mask significant variations in pathological severity.

Acknowledgments

We are deeply grateful to all of the participants in the Nun Study and ADCs. We thank Paula Thomason, Ela Patel, Dr. Huaichen Liu, and Sonya Anderson, for technical support and Sarah E. Monsell, MS for help with NACC data. We also thank Dr. Stephen Scheff for help with pathological evaluations.

Supported by NIH (R01 NS061933, P30 AG028383, and U01 AG016976)

REFERENCES

1. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. *Neurobiol Aging*. 1997; 18:S1–S2. [PubMed: 9330978]
2. Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology*. 1992; 42:631–639. [PubMed: 1549228]
3. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, Craft S, Leverenz JB, Montine TJ. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Ann Neurol*. 2007; 62:406–413. [PubMed: 17879383]

4. Nelson PT, Abner EL, Schmitt FA, Kryscio RJ, Jicha GA, Smith CD, Davis DG, Poduska JW, Patel E, Mendiola MS, Markesbery WR. Modeling the association between 43 different clinical and pathological variables and the severity of cognitive impairment in a large autopsy cohort of elderly persons. *Brain Pathol.* 2010; 20:66–79. [PubMed: 19021630]
5. Berg L, McKeel DW Jr, Miller JP, Storandt M, Rubin EH, Morris JC, Baty J, Coats M, Norton J, Goate AM, Price JL, Gearing M, Mirra SS, Saunders AM. Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. *Arch Neurol.* 1998; 55:326–335. [PubMed: 9520006]
6. Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J. The importance of neuritic plaques and tangles to the development and evolution of AD. *Neurology.* 2004; 62:1984–1989. [PubMed: 15184601]
7. Bierer LM, Hof PR, Purohit DP, Carlin L, Schmeidler J, Davis KL, Perl DP. Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. *Arch Neurol.* 1995; 52:81–88. [PubMed: 7826280]
8. Wilson RS, Leurgans SE, Boyle PA, Schneider JA, Bennett DA. Neurodegenerative basis of age-related cognitive decline. *Neurology.* 2010; 75:1070–1078. [PubMed: 20844243]
9. Dolan D, Troncoso J, Resnick SM, Crain BJ, Zonderman AB, O'Brien RJ. Age, Alzheimer's disease and dementia in the Baltimore Longitudinal Study of Ageing. *Brain.* 2010; 133:2225–2231. [PubMed: 20647264]
10. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 1991; 82:239–259. [PubMed: 1759558]
11. Braak H, Braak E, Bohl J. Staging of Alzheimer-related cortical destruction. *Eur Neurol.* 1993; 33:403–408. [PubMed: 8307060]
12. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging.* 1995; 16:271–278. discussion 278–284. [PubMed: 7566337]
13. Nelson PT, Schmitt FA, Jicha GA, Kryscio RJ, Abner EL, Smith CD, van Eldik LJ, Markesbery WR. Association between male gender and cortical Lewy body pathology in large autopsy series. *J Neurol.* 2010; 257:1875–1881. [PubMed: 20563821]
14. Sonnen JA, Larson EB, Walker RL, Haneuse S, Crane PK, Gray SL, Breitner JC, Montine TJ. Nonsteroidal anti-inflammatory drugs are associated with increased neuritic plaques. *Neurology.* 2010; 75:1203–1210. [PubMed: 20811000]
15. Iwakiri M, Mizukami K, Ikonovic MD, Ishikawa M, Hidaka S, Abrahamson EE, DeKosky ST, Asada T. Changes in hippocampal GABABR1 subunit expression in Alzheimer's patients: association with Braak staging. *Acta Neuropathol.* 2005; 109:467–474. [PubMed: 15759131]
16. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londo E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology.* 2005; 65:1863–1872. [PubMed: 16237129]
17. Horiguchi T, Uryu K, Giasson BI, Ischiropoulos H, Lightfoot R, Bellmann C, Richter-Landsberg C, Lee VM, Trojanowski JQ. Nitration of tau protein is linked to neurodegeneration in tauopathies. *Am J Pathol.* 2003; 163:1021–1031. [PubMed: 12937143]
18. Castellani RJ, Lee HG, Zhu X, Perry G, Smith MA. Alzheimer disease pathology as a host response. *J Neuropathol Exp Neurol.* 2008; 67:523–531. [PubMed: 18520771]
19. Nelson PT, Braak H, Markesbery WR. Neuropathology and cognitive impairment in Alzheimer disease: a complex but coherent relationship. *J Neuropathol Exp Neurol.* 2009; 68:1–14. [PubMed: 19104448]
20. Erten-Lyons D, Woltjer RL, Dodge H, Nixon R, Vorobik R, Calvert JF, Leahy M, Montine T, Kaye J. Factors associated with resistance to dementia despite high Alzheimer disease pathology. *Neurology.* 2009; 72:354–360. [PubMed: 19171833]
21. Smith MA, Casadesus G, Joseph JA, Perry G. Amyloid-beta and tau serve antioxidant functions in the aging and Alzheimer brain. *Free Radic Biol Med.* 2002; 33:1194–1199. [PubMed: 12398927]

22. Jellinger KA. Criteria for the neuropathological diagnosis of dementing disorders: routes out of the swamp? *Acta Neuropathol.* 2009; 117:101–110. [PubMed: 19052757]
23. Mizuno Y, Ikeda K, Tsuchiya K, Ishihara R, Shibayama H. Two distinct subgroups of senile dementia of Alzheimer type: quantitative study of neurofibrillary tangles. *Neuropathology.* 2003; 23:282–289. [PubMed: 14719543]
24. Gertz HJ, Xuereb J, Huppert F, Brayne C, McGee MA, Paykel E, Harrington C, Mukaetova-Ladinska E, Arendt T, Wischik CM. Examination of the validity of the hierarchical model of neuropathological staging in normal aging and Alzheimer's disease. *Acta Neuropathol.* 1998; 95:154–158. [PubMed: 9498050]
25. von Gunten A, Bouras C, Kovari E, Giannakopoulos P, Hof PR. Neural substrates of cognitive and behavioral deficits in atypical Alzheimer's disease. *Brain Res Rev.* 2006; 51:176–211. [PubMed: 16413610]
26. Delacourte A, David JP, Sergeant N, Buee L, Wattez A, Vermersch P, Ghazali F, Fallet-Bianco C, Pasquier F, Lebert F, Petit H, Di Menza C. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. *Neurology.* 1999; 52:1158–1165. [PubMed: 10214737]
27. Beekly DL, Ramos EM, van Belle G, Deitrich W, Clark AD, Jacka ME, Kukull WA. The National Alzheimer's Coordinating Center (NACC) Database: an Alzheimer disease database. *Alzheimer Dis Assoc Disord.* 2004; 18:270–277. [PubMed: 15592144]
28. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. *JAMA.* 1996; 275:528–532. [PubMed: 8606473]
29. Riley KP, Snowdon DA, Markesbery WR. Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun Study. *Ann Neurol.* 2002; 51:567–577. [PubMed: 12112102]
30. Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol.* 2005; 62:1160–1163. discussion 1167. [PubMed: 16009779]
31. Mirra SS. The CERAD neuropathology protocol and consensus recommendations for the postmortem diagnosis of Alzheimer's disease: a commentary. *Neurobiol Aging.* 1997; 18:S91–94. [PubMed: 9330994]
32. Jellinger KA. A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders. *Biochim Biophys Acta.* 2008; 1792:730–740. [PubMed: 18718530]
33. Nelson PT, Jicha GA, Schmitt FA, Liu H, Davis DG, Mendiondo MS, Abner EL, Markesbery WR. Clinicopathologic correlations in a large Alzheimer disease center autopsy cohort: neuritic plaques and neurofibrillary tangles “do count” when staging disease severity. *J Neuropathol Exp Neurol.* 2007; 66:1136–1146. [PubMed: 18090922]
34. Alafuzoff I, Arzberger T, Al-Sarraj S, Bodi I, Bogdanovic N, Braak H, Bugiani O, Del-Tredici K, Ferrer I, Gelpi E, Giaccone G, Graeber MB, Ince P, Kamphorst W, King A, Korkolopoulou P, Kovacs GG, Larionov S, Meyronet D, Monoranu C, Parchi P, Patsouris E, Roggendorf W, Seilhean D, Tagliavini F, Stadelmann C, Streichenberger N, Thal DR, Wharton SB, Kretschmar H. Staging of neurofibrillary pathology in Alzheimer's disease: a study of the BrainNet Europe Consortium. *Brain Pathol.* 2008; 18:484–496. [PubMed: 18371174]
35. Jellinger KA, Attems J. Neuropathological evaluation of mixed dementia. *J Neurol Sci.* 2007; 257:80–87. [PubMed: 17324442]
36. Whitwell JL, Josephs KA, Murray ME, Kantarci K, Przybelski SA, Weigand SD, Vemuri P, Senjem ML, Parisi JE, Knopman DS, Boeve BF, Petersen RC, Dickson DW, Jack CR Jr. MRI correlates of neurofibrillary tangle pathology at autopsy: a voxel-based morphometry study. *Neurology.* 2008; 71:743–749. [PubMed: 18765650]
37. Schneider JA, Aggarwal NT, Barnes L, Boyle P, Bennett DA. The neuropathology of older persons with and without dementia from community versus clinic cohorts. *J Alzheimers Dis.* 2009; 18:691–701. [PubMed: 19749406]
38. Jicha GA, Abner E, Schmitt FA, Cooper GE, Stiles N, Hamon R, Carr S, Smith CD, Markesbery WR. Clinical features of mild cognitive impairment differ in the research and tertiary clinic settings. *Dement Geriatr Cogn Disord.* 2008; 26:187–192. [PubMed: 18724049]

39. Price JL, McKeel DW Jr, Buckles VD, Roe CM, Xiong C, Grundman M, Hansen LA, Petersen RC, Parisi JE, Dickson DW, Smith CD, Davis DG, Schmitt FA, Markesbery WR, Kaye J, Kurlan R, Hulette C, Kurland BF, Higdon R, Kukull W, Morris JC. Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. *Neurobiol Aging*. 2009; 30:1026–1036. [PubMed: 19376612]
40. Haroutunian V, Hoffman LB, Beeri MS. Is there a neuropathology difference between mild cognitive impairment and dementia? *Dialogues Clin Neurosci*. 2009; 11:171–179. [PubMed: 19585952]
41. Baner C, Jellinger K, Lassmann H, Fischer P, Leblhuber F. Correlations between mental state and quantitative neuropathology in the Vienna Longitudinal Study on Dementia. *Eur Arch Psychiatry Clin Neurosci*. 1996; 246:137–146. [PubMed: 8739399]
42. Duyckaerts C, Bannecib M, Grignon Y, Uchihara T, He Y, Piette F, Hauw JJ. Modeling the relation between neurofibrillary tangles and intellectual status. *Neurobiol Aging*. 1997; 18:267–273. [PubMed: 9263190]
43. Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, Wilson RS. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology*. 2006; 66:1837–1844. [PubMed: 16801647]
44. Berlau DJ, Kahle-Wroblewski K, Head E, Goodus M, Kim R, Kawas C. Dissociation of neuropathologic findings and cognition: case report of an apolipoprotein E epsilon2/epsilon2 genotype. *Arch Neurol*. 2007; 64:1193–1196. [PubMed: 17698712]
45. Small BJ, Mobly JL, Laukka EJ, Jones S, Backman L. Cognitive deficits in preclinical Alzheimer's disease. *Acta Neurol Scand Suppl*. 2003; 179:29–33. [PubMed: 12603248]
46. Jicha GA, Carr SA. Conceptual evolution in Alzheimer's disease: implications for understanding the clinical phenotype of progressive neurodegenerative disease. *J Alzheimers Dis*. 2010; 19:253–272. [PubMed: 20061643]
47. Schmitt FA, Davis DG, Wekstein DR, Smith CD, Ashford JW, Markesbery WR. "Preclinical" AD revisited: neuropathology of cognitively normal older adults. *Neurology*. 2000; 55:370–376. [PubMed: 10932270]
48. Caselli RJ, Osborne D, Reiman EM, Hentz JG, Barbieri CJ, Saunders AM, Hardy J, Graff-Radford NR, Hall GR, Alexander GE. Preclinical cognitive decline in late middle-aged asymptomatic apolipoprotein E-e4/4 homozygotes: a replication study. *J Neurol Sci*. 2001; 189:93–98. [PubMed: 11535238]
49. Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, Thibodeau SN, Osborne D. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med*. 1996; 334:752–758. [PubMed: 8592548]

Fig. 1.

NACC registry data: empirical distribution of final MMSE scores by Braak stage V and stage VI. Only cases with final MMSE tests administered within 3 years of death and with enough neuritic plaques in the brain to satisfy CERAD criteria of “possible”, “probable”, or “definite” Alzheimer's disease, were included (total $n = 1,219$). Note that the median MMSE is shifted 5 points between Braak V and Braak VI ($p < 0.0001$, Kolmogorov-Smirnov test).

Fig. 2.

Combining Nun Study and NACC registry data to assess non-demented cases with final MMSE score of 30 within the last year of life ($n = 89$ cases). These cases were evaluated to assess the range of neurofibrillary pathologies seen in those individuals with the most rigorously documented intact cognition based on MMSE scores near death. There are no brains with Braak stage VI pathology in this group. Note that there are many cases in this category with Braak stages I–III. This clearly indicates that Braak stage III, in the context of preclinical disease, should not be considered “Intermediate likelihood” for AD.

Fig. 3.

Nun Study data: Assessing the variation of neocortical neurofibrillary tangle (NFT) pathology at different disease stages. A) Final MMSE scores ($\pm$ SEM) across Braak stages from the Nun Study autopsy cohort. Note that average final MMSE scores for Braak stage VI are dramatically lower than Braak stage V. B) Final MMSE scores are shown in correlation with NFTs counted in the cerebral neocortex stratified by Braak stage V or VI. Each data point represents one individual. Summed counts were used from inferior parietal lobule, superior and mid-temporal gyri, frontal (Brodmann Area 46), and occipital cortex (Brodmann Areas 17/18) as described in the Methods section. There is, as expected, a shift with increased counted neocortical NFTs in Braak VI cases. The correlation between NFTs counted postmortem, versus antemortem global cognitive status as defined by MMSE scores, is highly significant ($p < 0.0001$) but there is substantial variance ($R^2 = 0.25$). Above a particular threshold of counted neocortical NFTs (80 NFTs; see dashed orange vertical line), every patient had a final MMSE score under 15. 0% (0/44) of Braak stage IV cases (data not shown), 7.8% (5/64) of Braak stage V cases, and 60.4% (55/91) of Braak stage VI cases had neocortical NFT counts above this threshold.

Table 1

Included cases from NACC registry and the Nun Study

	Braak stage 0–IV		Braak stage V		Braak stage VI	
	N	No dementia n (%)	N	No dementia n (%)	N	No dementia n (%)
NACC dataset, total included cases	1336	799 (59.8)	834	52 (6.2)	1140	23 (2.0)
Cases with final evaluation < 3 y before death	1142	651 (57.0)	623	47 (7.5)	717	11 (1.5)
CERAD “possible”, “probable”, or “definite” for AD and final evaluation < 3 y before death	637	430 (67.5)	568	36 (6.3)	651	5 (0.8)
Nun Study dataset, total included cases*	335	221 (66.0)	64	27 (42.2)	87	8 (9.2)

* All cases with Braak stages V or VI had final evaluation < 3 years prior to death and at least CERAD[31] “possible” neuritic plaque pathology.

Table 2

Demographics, pathological, and clinical information about ‘CERAD[31]-positive’ cases with Braak stages V and VI pathology (evaluated within 3 years of death) in the NACC registry and the Nun Study

	Braak V	Braak VI	<i>p</i> value
NACC cases, <i>n</i>	568	651	–
Adjusted* Final MMSE score, Mean ± SEM	11.0 ± 0.4	8.0 ± 0.3	<0.0001
Male gender, <i>n</i> (%)	282 (49.7)	335 (51.5)	0.53
Age at death, Mean ± SEM	83.8 ± 0.3	79.5 ± 0.3	<0.0001
Maximum education level in years, Mean ± SEM	14.6 ± 0.1	14.2 ± 0.1	0.046
Neocortical Lewy bodies, <i>n</i> (%)	66 (11.6)	51 (7.8)	0.025
Hippocampal sclerosis, <i>n</i> (%)	58 (10.2)	56 (8.6)	0.36
Non-demented, <i>n</i> (%)	36 (6.3)	5 (0.8)	<0.0001
“Normal cognition” cases, <i>n</i> (%)	15 (2.7)	2 (0.3)	0.0005
MCI cases, <i>n</i> (%)	18 (3.2)	3 (0.5)	0.0003
Months between final evaluation and death, Mean ± SEM	12.4 ± 0.4	14.8 ± 0.4	<0.0001
Nun Study cases, <i>n</i>	64	87	–
Adjusted* Final MMSE score, Mean ± SEM	14.9 ± 1.1	5.8 ± 1.0	<0.0001
Male gender, <i>n</i> (%)	0.0	0.0	–
Age at death, Mean ± SEM	91.4 ± 0.6	89.3 ± 0.5	0.0083
Maximum education level in years, Mean ± SEM	15.6 ± 0.4	15.0 ± 0.4	0.26
Neocortical Lewy bodies, <i>n</i> (%)	2 (3.1)	5 (5.7)	0.45
Hippocampal sclerosis, <i>n</i> (%)	8 (12.5)	15 (17.2)	0.42
Non-demented, <i>n</i> (%)	27 (42.2)	8 (9.2)	<0.0001
“Normal cognition” cases not assessed	–	–	–
MCI cases not assessed	–	–	–
Months between final evaluation and death, Mean ± SEM	9.4 ± 0.8	9.8 ± 0.7	0.68

* Adjusted for age at death and education.