
Notes: OBJECTIVES: We compared the ability of molecular biomarkers for Alzheimer disease (AD), including amyloid imaging and CSF biomarkers (Abeta42, tau, ptau181, tau/Abeta42, ptau181/Abeta42), to predict time to incident cognitive impairment among cognitively normal adults aged 45 to 88 years and followed for up to 7.5 years. METHODS: Longitudinal data from Knight Alzheimer's Disease Research Center participants (N = 201) followed for a mean of 3.70 years (SD = 1.46 years) were used. Participants with amyloid imaging and CSF collection within 1 year of a clinical assessment indicating normal cognition were eligible. Cox proportional hazards models tested whether the individual biomarkers were related to time to incident cognitive impairment. "Expanded" models were developed using the biomarkers and participant demographic variables. The predictive values of the models were compared. RESULTS: Abnormal levels of all biomarkers were associated with faster time to cognitive impairment, and some participants with abnormal biomarker levels remained cognitively normal for up to 6.6 years. No differences in predictive value were found between the individual biomarkers (p > 0.074), nor did we find differences between the expanded biomarker models (p > 0.312). Each expanded model better predicted incident cognitive impairment than the model containing the biomarker alone (p < 0.005).

CONCLUSIONS: Our results indicate that all AD biomarkers studied here predicted incident cognitive impairment, and support the hypothesis that biomarkers signal underlying AD pathology at least several years before the appearance of dementia symptoms.


Notes: Although both normal aging and Alzheimer's disease (AD) are associated with regional cortical atrophy, few studies have directly compared the spatial patterns and magnitude of effects of these two processes. The extant literature has not addressed two important questions: 1) Is the pattern of age-related cortical atrophy different if cognitively intact elderly individuals with silent AD pathology are excluded? and 2) Does the age- or AD-related atrophy relate to cognitive function? Here we studied 142 young controls, 87 older controls, and 28 mild AD patients. In addition, we studied 35 older controls with neuroimaging data indicating the absence of brain amyloid. Whole-cortex analyses identified regions of interest (ROIs) of cortical atrophy in aging and in AD. Results showed that some regions are predominantly affected by age with relatively little additional atrophy in patients with AD, e.g., calcarine cortex; other regions are predominantly affected by AD with much less of an effect of age, e.g., medial temporal cortex. Finally, other regions are affected by both aging and AD, e.g., dorsolateral prefrontal cortex and inferior parietal lobule. Thus, the processes of aging and AD have both differential and partially overlapping effects on specific regions of the cerebral cortex. In particular, some frontoparietal regions are affected by both processes, most temporal lobe regions are affected much more prominently by AD than aging, while sensorimotor and some prefrontal regions are affected specifically by aging and minimally more by AD. Within normal older adults, atrophy in aging-specific cortical regions relates to cognitive performance, while in AD patients atrophy in AD-specific regions relates to cognitive performance. Further work is warranted to investigate the behavioral and clinical relevance of these findings in additional detail, as well as their histological basis; ROIs generated from the present study could be used strategically in such investigations.


Notes: BACKGROUND: Cross-sectional studies suggest that the cognitive impact of Alzheimer disease pathology varies depending on education and brain size. OBJECTIVE: To
evaluate the combination of cerebrospinal fluid biomarkers of beta-amyloid(42) (Abeta(42)), tau, and phosphorylated tau (p-tau(181)) with education and normalized whole-brain volume (nWBV) to predict incident cognitive impairment. DESIGN: Longitudinal cohort study. SETTING: Charles F. and Joanne Knight Alzheimer's Disease Research Center, Washington University, St. Louis, Missouri. PARTICIPANTS: A convenience sample of 197 individuals 50 years and older with normal cognition (Clinical Dementia Rating of 0) at baseline observed for a mean of 3.3 years. MAIN OUTCOME MEASURE: Time to Clinical Dementia Rating >/= 0.5. RESULTS: Three-factor interactions among the baseline biomarker values, education, and nWBV were found for Cox proportional hazards regression models testing tau (P = .02) and p-tau (P = .008). In those with lower tau values, nWBV (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.31-0.91; P = .02), but not education, was related to time to cognitive impairment. For participants with higher tau values, education interacted with nWBV to predict incident impairment (P = .01). For individuals with lower p-tau values, there was no effect of education or nWBV. Education interacted with nWBV to predict incident cognitive impairment in those with higher p-tau values (P = .02). CONCLUSION: In individuals with normal cognition and higher levels of cerebrospinal fluid tau and p-tau at baseline, time to incident cognitive impairment is moderated by education and brain volume as predicted by the cognitive/brain reserve hypothesis.

4 Price, J. L., McKeel, D. W., Buckles, V. D., Roe, C. M., Xiong, C., Grundman, M., ..., & Morris, J. C. (2009). Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. Neurobiology of Aging, 30, 1026-1036. Notes: OBJECTIVE: To determine the frequency and possible cognitive effect of histological Alzheimer's disease (AD) in autopsied older nondemented individuals. DESIGN: Senile plaques (SPs) and neurofibrillary tangles (NFTs) were assessed quantitatively in 97 cases from 7 Alzheimer's Disease Centers (ADCs). Neuropathological diagnoses of AD (npAD) were also made with four sets of criteria. Adjusted linear mixed models tested differences between participants with and without npAD on the quantitative neuropathology measures and psychometric test scores prior to death. Spearman rank-order correlations between AD lesions and psychometric scores at last assessment were calculated for cases with pathology in particular regions. SETTING: Washington University Alzheimer's Disease Research Center. PARTICIPANTS: Ninety-seven nondemented participants who were age 60 years or older at death (mean=84 years). RESULTS: About 40% of nondemented individuals met at least some level of criteria for npAD; when strict criteria were used, about 20% of cases had npAD. Substantial overlap of Braak neurofibrillary stages occurred between npAD and no-npAD cases. Although there was no measurable cognitive impairment prior to death for either the no-npAD or npAD groups, cognitive function in nondemented aging appears to be degraded by the presence of NFTs and SPs. CONCLUSIONS: Neuropathological processes related to AD in persons without dementia appear to be associated with subtle cognitive dysfunction and may represent a preclinical stage of the illness. By age 80-85 years, many nondemented older adults have substantial AD pathology.

5 Morris, J. C., Roe, C. M., Grant, E. A., Head, D., Storandt, M., Goate, A. M. et al. (2009). Pittsburgh compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease. Archives of Neurology, 66, 1469-1475. Notes: OBJECTIVE: To determine whether preclinical Alzheimer disease (AD), as detected by the amyloid-imaging agent Pittsburgh Compound B (PiB) in cognitively normal older adults, is associated with risk of symptomatic AD. DESIGN: A longitudinal cohort study of cognitively normal older adults assessed with positron emission tomography (PET) to determine the mean cortical binding potential for PiB and followed up with annual clinical and cognitive assessments for progression to very mild dementia of the Alzheimer type (DAT). SETTING: The Alzheimer's Disease Research Center, Washington University, St. Louis, Missouri. PARTICIPANTS: One hundred fifty-nine participants with a mean age of 71.5 years with a Clinical Dementia Rating (CDR) of 0 on a PET PiB scan at baseline. MAIN OUTCOME MEASURE: Progression from CDR 0 to CDR 0.5 status (very mild dementia). RESULTS: Twenty-three participants progressed to CDR 0.5 at follow-up assessment (range, 1-5
assessments after PET PiB). Of these, 9 also were diagnosed with DAT. Higher mean cortical binding potential values for PiB (hazard ratio, 4.85; 95% confidence interval, 1.22-19.01; P = .02) and age (hazard ratio, 1.14; 95% confidence interval, 1.02-1.28; P = .03) predicted progression to CDR 0.5 DAT. The CDR 0.5 DAT group showed decline in 3 cognitive domains (episodic memory, semantic memory, and visuospatial performance) and had volume loss in the parahippocampal gyrus (includes entorhinal cortex) compared with individuals who remained at CDR 0. CONCLUSION: Preclinical AD as detected by PET PiB is not benign, as it is associated with progression to symptomatic AD Alzheimer's Disease Research Center, St Louis, Missouri 63108, USA. morrisj@abraxas.wustl.edu


Notes: BACKGROUND: Detection of the earliest cognitive changes signifying Alzheimer disease is difficult. OBJECTIVE: To model the cognitive decline in preclinical Alzheimer disease. DESIGN: Longitudinal archival study comparing individuals who became demented during follow-up and people who remained nondemented on each of 4 cognitive factors: global, verbal memory, visuospatial, and working memory. SETTING: Alzheimer Disease Research Center, Washington University School of Medicine, St Louis, Missouri.

PARTICIPANTS: One hundred thirty-four individuals who became demented during follow-up and 310 who remained nondemented. MAIN OUTCOME MEASURES: Inflection point in longitudinal cognitive performance. RESULTS: The best-fitting model for each of the 4 factors in the stable group was linear, with a very slight downward trend on all but the Visuospatial factor. In contrast, a piecewise model with accelerated slope after a sharp inflection point provided the best fit for the group that progressed. The optimal inflection point for all 4 factors was prior to diagnosis of dementia: Global, 2 years; Verbal and Working Memory, 1 year; and Visuospatial, 3 years. These results were also obtained when data were limited to the subset (n = 44) with autopsy-confirmed Alzheimer disease. CONCLUSIONS: There is a sharp inflection point followed by accelerating decline in multiple domains of cognition, not just memory, in the preclinical period in Alzheimer disease when there is insufficient cognitive decline to warrant clinical diagnosis using conventional criteria. Early change was seen in tests of visuospatial ability, most of which were speeded. Research into early detection of cognitive disorders using only episodic memory tasks may not be sensitive to all of the early manifestations of disease.


Notes: OBJECTIVE: We previously used exploratory analyses across the entire cortex to determine that mild Alzheimer disease (AD) is reliably associated with a cortical signature of thinning in specific limbic and association regions. Here we investigated whether the cortical signature of AD-related thinning is present in individuals with questionable AD dementia (QAD) and whether a greater degree of regional cortical thinning predicts mild AD dementia. METHODS: Participants included 49 older adults with mild impairment consistent with mild cognitive impairment (Clinical Dementia Rating [CDR] = 0.5) at the time of structural MRI scanning. Cortical thickness was measured in nine regions of interest (ROIs) identified previously from a comparison of patients with mild AD and controls. RESULTS: Longitudinal clinical follow-up revealed that 20 participants converted to mild AD dementia (progressors) while 29 remained stable (nonprogressors) approximately 2.5 years after scanning. At baseline, QAD participants showed a milder degree of cortical thinning than typically seen in mild AD, and CDR Sum-of-Boxes correlated with thickness in temporal and parietal ROIs. Compared to nonprogressors, progressors showed temporal and parietal thinning. Using receiver operating characteristic curves, the thickness of an aggregate measure of these regions predicted progression to mild AD with 83% sensitivity and 65% specificity. CONCLUSIONS: Thinning in specific cortical areas known to be affected by Alzheimer disease (AD) is detectable in individuals with questionable AD dementia (QAD) and predicts conversion to mild AD dementia. This method could be useful for identifying individuals at
relatively high risk for imminent progression from QAD to mild AD dementia, which may be of value in clinical trials.


9 Morris, J. C., Weintraub, S., Chui, H. C., Cummings, J., DeCarli, C., Ferris, S. et al. (2006). The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Disease and Associated Disorders, 20, 210-216. Notes: Washington University, St. Louis, MO 63108, USA. morrisj@abraxas.wustl.edu A Clinical Task Force, composed of clinical leaders from Alzheimer’s Disease Centers (ADC), was convened by the National Institute on Aging to develop a uniform set of assessment procedures to characterize individuals with mild Alzheimer disease and mild cognitive impairment in comparison with nondemented aging. The resulting Uniform Data Set (UDS) defines a common set of clinical observations to be collected longitudinally on ADC participants in accordance with standard methods. The UDS was implemented at all ADCs on September 1, 2005. Data obtained with the UDS are submitted to the National Alzheimer’s Coordinating Center and represent a unique and valuable source of data to support and stimulate collaborative research.


12 Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H. et al. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. Archives of Neurology, 58, 397-405. Notes: Alzheimer’s Disease Research Center, Washington University School of Medicine, 4488 Forest Park Ave, Suite 130, St Louis, MO 63178, USA. BACKGROUND: Mild cognitive impairment (MCI) is considered to be a transitional stage between aging and Alzheimer disease (AD). OBJECTIVE: To determine whether MCI represents early-stage AD by examining its natural history and neuropathologic basis. DESIGN: A prospective clinical and psychometric study of community-living elderly volunteers, both nondemented and minimally cognitively impaired, followed up for up to 9.5 years. Neuropathologic examinations were performed on participants who had undergone autopsy. SETTING: An AD research center. PARTICIPANTS: All participants enrolled between July 1990 and June 1997 with Clinical Dementia Rating (CDR) scores of 0 (cognitively healthy; n = 177; mean age, 78.9 years) or 0.5 (equivalent to MCI; n = 277; mean age, 76.9 years). Based on the degree of clinical confidence that MCI represented dementia of the Alzheimer type (DAT), 3 subgroups of individuals with CDR scores of 0.5 were identified: CDR 0.5/DAT, CDR 0.5/incipient DAT, and CDR 0.5/uncertain dementia. MAIN OUTCOME MEASURE: Progression to the stage of CDR 1, which characterizes mild definite DAT. RESULTS: Survival analysis showed that 100% of CDR 0.5/DAT participants progressed to greater dementia severity over a 9.5-year period. At 5 years, rates of progression to a score of CDR 1 (or greater) for DAT were 60.5% (95% confidence interval [CI], 50.2%-70.8%) for the CDR 0.5/DAT group, 35.7% (95% CI, 21.0%-50.3%) for the CDR 0.5/incipient DAT group, 19.9% (95% CI, 8.0%-31.8%) for the CDR 0.5/uncertain dementia group, and 6.8% (95% CI, 2.2%-11.3%) for CDR 0/controls. Progression to greater dementia severity correlated with degree of cognitive impairment at baseline. Twenty-four of the 25 participants with scores of CDR 0.5 had a neuropathologic dementing disorder, which was AD in 21 (84%). CONCLUSIONS: Individuals currently characterized as having MCI progress steadily to greater stages of dementia severity at rates dependent on the level of cognitive...
impairment at entry and they almost always have the neuropathologic features of AD. We conclude that MCI generally represents early-stage AD


Notes: Department of Neurology, Washington University School of Medicine, St. Louis, MO 63110, USA; ABSTRACT: Global staging measures for dementia of the Alzheimer type (DAT) assess the influence of cognitive loss on the ability to conduct everyday activities and represent the "ultimate test" of efficacy for antidementia drug trials. They provide information about clinically meaningful function and behavior and are less affected by the "floor" and "ceiling" effects commonly associated with psychometric tests. The Washington University Clinical Dementia Rating (CDR) is a global scale developed to clinically denote the presence of DAT and stage its severity. The clinical protocol incorporates semistructured interviews with the patient and informant to obtain information necessary to rate the subject's cognitive performance in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR has been standardized for multicenter use, including the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and the Alzheimer's Disease Cooperative Study, and interrater reliability has been established. Criterion validity for both the global CDR and scores on individual domains has been demonstrated, and the CDR also has been validated neuropathologically, particularly for the presence or absence of dementia. Standardized training protocols are available. Although not well suited as a brief screening tool for population surveys of dementia because the protocol depends on sufficient time to conduct interviews, the CDR has become widely accepted in the clinical setting as a reliable and valid global assessment measure for DAT


Notes: AD: Washington University School of Medicine, Memory and Aging Project, St. Louis, MO 63110 AB: Reliable information on rate of progression of cognitive impairment in probable Alzheimer's disease (AD) is important for evaluating possible beneficial effects of therapeutic agents and in planning long-term care for patients with this chronic illness. However, wide variability exists in published rates of change for psychometric measures of the dementing process, and there is need for an accurate analysis of large numbers of persons with the disorder studied over long periods. Utilizing the large, well-characterized sample of the Consortium to Establish a Registry for Alzheimer's Disease and employing a least squares regression method to adjust for different levels of impairment and periods of observation, we report rates of change on the Short Blessed Test, Mini-Mental State Examination, Blessed Dementia Scale, Clinical Dementia Rating, and other cognitive measures in 430 patients with probable AD (mean age at entry = 70.9 +/- 8.0 SD years) studied for up to 4 years. We found that rate-of-change determinations are less reliable when the observation period is 1 year or less, that dementia progression may be nonlinear when described by certain measures, and that simple change scores do not accurately characterize the rate of decline. We also found that rate of progression in AD is determined by the severity of cognitive impairment: the less severe the dementia, the slower the rate of decline


Notes: Department of Neurology, Washington University School of Medicine, St. Louis, MO 63110 The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) has developed brief, comprehensive, and reliable batteries of clinical and neuropsychological tests for assessment of patients with the clinical diagnosis of Alzheimer's disease (AD). We
administered these batteries in a standardized manner to more than 350 subjects with a diagnosis of AD and 275 control subjects who were enrolled in a nationwide registry by a consortium of 16 university medical centers. The tests selected for this study measured the primary cognitive manifestations of AD across a range of severity of the disorder, and discriminated between normal subjects and those with mild and moderate dementia. The batteries also detected deterioration of language, memory, praxis, and general intellectual status in subjects returning for reassessment 1 year later. Interrater and test-retest reliabilities were substantial. Long-term observations of this cohort are in progress in an effort to validate the clinical and neuropsychological assessments and to confirm the diagnosis by postmortem examinations. Although information on validation is limited thus far, the CERAD batteries appear to fill a need for a standardized, easily administered, and reliable instrument for evaluating persons with AD in multicenter research studies as well as in clinical practice.