ELSEVIER

Neurobiology of Aging 33 (2012) 1556–1563

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Modeling regional vulnerability to Alzheimer pathology

Donald R. Royall[a,b,c,d,*], Raymond F. Palmer[c], Helen Petrovitch[e], G. Webster Ross[f], Kamal Masaki[g,h], Lon R. White[g,h]

[a] Department of Psychiatry, The University of Texas Health Science Center, San Antonio, TX, USA
[b] Department of Medicine, The University of Texas Health Science Center, San Antonio, TX, USA
[c] Department of Family and Community Medicine, The University of Texas Health Science Center, San Antonio, TX, USA
[d] South Texas Veterans' Health System, Audie L. Murphy Division GRECC, San Antonio, TX, USA
[e] Pacific Health Research and Education Institute, Honolulu, HI, USA
[f] Honolulu Department of Veterans Affairs, Honolulu, HI, USA
[g] Department of Geriatric Medicine, John A. Burns School of Medicine at Kakaako, Honolulu, HI, USA
[h] Kuakini Medical Center, HonoluluKuakini Medical Center, Honolulu, HI, USA

Received 7 September 2010; received in revised form 14 April 2011; accepted 13 May 2011

Abstract

Latent growth curve (LGC) models estimate change over time in a cohort's serially obtained measurements. We have applied LGC techniques to a spatial distribution of Alzheimer's disease (AD) pathology using autopsy data from 435 participants in the Honolulu-Asia Aging Study. Neurofibrillary tangle (NFT) and neuritic plaques (NP) were distributed across differently ordered sets of anatomical regions. The gradient of spatial change in neuritic plaque (dNP), was significantly associated with that of neurofibrillary tangle (dNFT), but weakly and inversely ($r = -0.12$; $p < 0.001$). Both dNFT and dNP correlated significantly and inversely with Braak stage. Sixty-one percent of the variance in Braak stage was explained by dNFT independent of covariates. Only dNFT was significantly associated with longitudinal change in cognition. Only dNP was associated with apolipoprotein (APOE) e4 burden. This is the first application of LGC models to spatially-ordered data. The result is a quantification of the interindividual variation in the interregional vulnerability to Alzheimer's disease lesions.

Keywords: Old age; Neuropathology; Alzheimer's disease

1. Introduction

Latent "class" or growth curve (LGC) and growth mixture models (GMM) represent the state of the art in longitudinal data analysis. LGC estimate the trajectory of change over time in a cohort's serially-obtained measurements (Willet and Sayer, 1994). GMM can be used to define subsets among a cohort with homogenous trajectory parameters. Through them, it is possible to use intra- and interindividual change over time as outcome variables or as predictors, e.g., in structural equation models (SEM) (McArdle and Epstein, 1987; Willet and Sayer, 1994). This allows one to assess mediating/moderating effects on longitudinal outcomes. Another valuable feature of LGC models is that measurement error is explicitly assessed, and removed from the latent construct. This can strengthen statistical power and improve model fit.

However, it may also be possible to extend the application of these techniques beyond temporally ordinal datasets, i.e., to measures repeated across spatial dimensions. Particularly useful applications might be in the analysis of neuropathological or neuroimaging data (Royall, 2007). For example, Braak and others have suggested that neurofibrillary tangles (NFT) and Lewy body lesions propagate transynaptically within neuronal networks (Braak and Braak,

* Corresponding author at: Department of Psychiatry, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284-7792, USA. Tel.: +1 210 567 1255; fax: +1 210 567 5507.
E-mail address: royall@uthscsa.edu (D.R. Royall).

0197-4580/$ – see front matter © 2012 Published by Elsevier Inc.
10.1016/j.neurobiolaging.2011.05.028

1991; Braak et al., 2006; Pearson and Powell, 1989; Saper et al., 1985). The interconnections of those networks may thus determine the exquisite regional, and even laminar vulnerability of neuronal populations to NFT (Armstrong et al., 2001; Arnold et al., 1991). These networks can be conceived as an ordinally arranged sequence of anatomical regions along a hierarchical gradient of interregional vulnerability. As such, the 3-dimensional propagation of neuropathology through the network may be amenable to modeling with LGC and GMM techniques.

If applied to NFT counts, this approach would result in 2 latent parameters, the network's "intercept" (e.g., the estimated mean NFT count within the first in a hierarchically arranged sequence of anatomical regions that together define the Braak neuropathological hierarchy) and its "slope" (e.g., the mean change in NFT counts across regions, from the most to the least vulnerable in the sequence). Both parameters would have associated estimates of variability about their means, and both linear and nonlinear gradients in NFT counts across the network could be independently estimated. These "slope" parameters can be interpreted as representing the network's "vulnerability" to, or alternatively, its resistance against, penetration by the Alzheimer's disease (AD) process. Biomarkers, genes, or other variables could then be tested as determinants of this vulnerability.

If there is significant variability about the estimated mean change in NFT counts across the network, then GMM could be employed to identify homogeneous subgroups within the cohort with significantly different network intercepts and vulnerability gradients. These could be interpreted as subpopulations within the cohort with differing risks of AD pathology. Thus, the variables responsible for those differences could also be identified, in regression models of trajectory class membership. Associating these gradients with longitudinal change in cognitive measures, i.e., in SEM, may eventually allow the direct quantification of cognitive reserve and its related biomarkers. In this report, we demonstrate the feasibility of this approach using autopsy and clinical data from the Honolulu-Asia Aging Study (HAAS).

2. Methods

2.1. HAAS

Autopsy tissue and clinical data were obtained from HAAS (White et al., 2005). HAAS began in 1991 as an add-on to the Honolulu Heart Program (HHP). It is a longitudinal study of heart disease and stroke established in 1965 with the examination of 8006 Japanese-American men born 1900–1919. Brain autopsy and cognitive examinations have been performed continuously since 1991.

2.2. HAAS autopsy material

Eight hundred thirty-eight autopsies had been performed prior to May (2010). These represent approximately 20% of HAAS deaths since 1991. The current analyses are limited to autopsies obtained between 1991 and 2001. Microscopic examinations performed since 2001 have been done by a different team of neuropathologists, and have not yet been pooled for common analyses. Complete microscopic data generated by the first team are available in 493. Four hundred thirty-seven of those with complete microscopic data also have premorbid clinical information related to dementia and neuropsychological test performance. Results presented here are from these 437 decedents. The generalizability of autopsied decedents to the larger HAAS sample has been detailed elsewhere (White et al., 2002).

2.3. Pathological materials

The HAAS pathological methods have been detailed elsewhere (Petrovitch et al., 2001). Brains were fixed by submersion in 10% neutral formalin. Tissue samples were embedded in paraffin. Slides were cut at 8-μm thicknesses and stained as mentioned. Modified Bielschowsky, Gallyas, hematoxylin and eosin (H&E), and α-synuclein-stained slides were examined to quantify diffuse plaques (DP), neuritic plaques (NP), neurofibrillary tangle (NFT), cortical Lewy bodies (CLB), and to determine Braak stage. NP were defined as extracellular accumulations of abnormal agyrophilic and antiamyloid staining aggregates containing a central amyloid core and identifiable neurites (abnormal dark, coarse, tangled, or irregular neuritic processes). DP were defined as unformed and amorphous plaques that lack identifiable neurites. NFT were defined by intraneuronal, cytoplasmic dense accumulations of agyrophilic (Bielschowsky or Gallyus stain) filamentous material that may be globoid, circumferential, or flame-shaped. Extracellular or "tombstone" neurofibrillary tangles were interpreted as indicating that the neuron in which the NFT had developed had died and deteriorated. CLBs were defined by round to oval, single or multiple intraneuronal, cytoplasmic accumulations of synuclein immunoreactive material.

NP, DP, and NFT were enumerated in 5 fields for each anatomical region, with postassessment adjustment to produce counts standardized to areas of 1 square millimeter. Fields with the highest counts (2-dimensional densities) were selected for either the total plaque count (neuritic plus diffuse) or the total NFT count. Mean NP, DP, and NFT counts were calculated across 20 isocortical fields, from the left (L), frontal (F), parietal (P), temporal (T), and occipital (O) lobes. Total CLBs were counted in defined segments of the cortical gray ribbon of the 4 main lobes, plus the insula and anterior cingulate cortex, in order to create a total cortical Lewy body score and a standard McKeith Lewy body score (McKeith et al., 1996).

2.4. Cognitive abilities screening instrument (CASI)

The CASI was developed by merging an expanded Mini Mental State Examination (MMSE) (the 3 MS) with the Hasegawa dementia scale (Hasegawa et al., 1986). The