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Alzheimer's disease severity, objectively determined and measured

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Abstract

Introduction: With expansion of clinical trials to individuals across the spectrum of Alzheimer disease (AD) from preclinical to symptomatic phases, it is increasingly important to quantify AD severity using methods that capture underlying pathophysiology.
Methods: We derived an AD severity measure based on biomarkers from brain imaging, neuropathology, and cognitive testing using latent variable modeling. We used data from ADNI-1 (N = 822) and applied findings to BIOCARD study (N = 349). We evaluated criterion validity for distinguishing diagnostic groups and construct validity by evaluating rates of change in AD severity.
Results: The AD severity factor cross-sectionally distinguishes cognitively normal participants from MCI (AUC = 0.87) and AD dementia (AUC = 0.94). Among ADNI MCI subjects, worsening scores predict faster progression to AD dementia (HR = 1.17; 95% CI, 1.13–1.22). In ADNI and BIOCARD, the pace of change in AD severity is steepest among progressors, with persisting differences by baseline diagnosis.
Discussion: Our content-valid latent variable measurement model is a reasonable approach for grading AD severity across a broad spectrum beginning at preclinical stages of AD.

Keywords: Alzheimer's disease; Clinical trials; Measurement; Item response theory; Cognitive testing; Imaging; Longitudinal follow-up

1. Introduction

Alzheimer disease (AD) is now recognized to span a spectrum of impairment from normal cognition to dementia, with changes in biomarkers that capture various aspects of the underlying neuropathology [1,2]. AD develops over decades [3,4] and has a long prodromal period [5,6]. The clinical manifestations of AD are often evident only after many years of accumulating neuropathology.

A multitude of AD biomarkers including those derived from brain imaging, cerebrospinal fluid, and neuropsychological testing have been identified which provide distinct information about the pathophysiology and clinical course of AD. A highly influential theoretical model has provided a framework for conceptualizing the pathological cascade of AD [1]. This dynamic biomarkers model proposes that the pathologic cascade of AD begins with abnormal amyloid processing, resulting in build-up of amyloid beta protein

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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($A\beta_{1–42}$) in the brain, accelerating tau deposition, which in combination has neurotoxic effects resulting in cellular dysfunction and death, brain atrophy, and impaired neuropsychological function. This process culminates in clinical symptoms and functional disability [1].

Biomarkers in the dynamic biomarkers model are hypothesized to provide information over a spectrum from preclinical to clinical stages of AD. Evidence suggests, however, that no single biomarker provides sufficient information to capture the underlying severity of disease across the entire spectrum. Several efforts are thus underway to objectively and quantitatively combine multiple biomarkers to characterize the clinico-pathophysiological severity of AD [7,8]. The main goal of this study is to operationalize such a method objectively and quantitatively and to evaluate its validity.

Features of the dynamic biomarkers hypothesis relevant for its operationalization are the prevalence of multiple disease severity markers, thought to represent relationships between disease severity markers and disease stage and the characterization of the phase of disease. First, levels of disease severity markers underlying physiological mechanisms indicate worsening AD severity over time. Different markers worsen from normal to abnormal levels during different phases of AD, ranging from cognitively normal, through mild cognitive impairment (MCI), to clinical dementia. A second feature of the dynamic biomarkers model is the hypothesized sigmoidal (s-shaped) relationship between each disease severity marker and disease stage. In the midrange of the disease severity marker response, its relationship with underlying disease stage is presumed linear, but the distribution at its tails asymptotes toward normal/abnormal response levels. Different disease severity markers have different dynamic ranges. For example, while deposition of $A\beta_{1–42}$ is initially occurring, there may be no change in memory. Later, while memory worsens, it is hypothesized that less $A\beta_{1–42}$ deposition is taking place relative to earlier disease stages. A third key feature of the dynamic biomarkers model is disease stage on the x-axis. Neither time nor age is necessary to describe the advancing disease course, but some quantity (i.e., underlying disease severity) not directly measureable is. Jack et al. [9] suggested a latent variable model, as implemented in this study, may sufficiently represent AD severity and its relationship to disease severity markers.

The dynamic biomarkers model is almost immediately recognizable as a latent variable model. Latent variable models relate item responses on observed variables to a latent, or unobserved, variable using probabilistic models. Severity of underlying pathology is the latent variable. A latent variable is not directly observable but is presumed to causally influence reflective indicators (disease severity markers). The response scale of disease severity markers and sigmoidal response curve shape leads naturally to response variable discretization [10] and graded response variable modeling [11]. Latent variable modeling characterizes aspects of persons (level of latent AD severity) and aspects of latent variable indicators (disease severity markers). This approach quantifies underlying AD pathology in persons without frank impairment.

Our main goal was to operationalize the dynamic biomarkers hypothesis. We present an objective and quantitative method for integrating multiple biomarkers and other disease severity markers of AD into a global measure of AD severity using a latent trait framework based in measures from cerebrospinal fluid, structural neuroimaging, neuropsychological performance, and ratings of functional impairment. We demonstrate the potential utility of the measure of AD severity by using it to describe differences between clinically defined diagnostic groups—normal, MCI, and AD dementia—and to predict future progression to more impaired clinical states. We suggest applications of the model for research and clinical purposes, as well as weaknesses and opportunities for extending the model. We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study to derive the model and applied the findings in the BIOCARD study, both longitudinal studies in which a range of biomarkers was collected.

2. Methods

2.1. Participants

We used data collected in the ADNI and BIOCARD studies. ADNI (adni.loni.usc.edu) was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI was to test whether biological markers could be used to improve measurement of clinical and neuropsychological progression in clinical trials. In these analyses, we used data from ADNI-1. For up-to-date information, see www.adni-info.org.

The BIOCARD study initially recruited 349 cognitively normal middle-aged persons starting in 1995, most of whom by design had a first-degree relative with dementia. The primary goal of the study was to identify early markers of progression to MCI due to AD in cognitively normal people. Participants were recruited by the Geriatric Psychiatry branch of the Intramural Program of the National Institute of Mental Health. The study was stopped in 2005, and in 2009 was reestablished by a research team at the Johns Hopkins School of Medicine. Clinical assessments and cognitive testing were completed annually; MRI scans, cerebrospinal fluid, and blood specimens were collected approximately every 2 years. Further details are available elsewhere [12]. Importantly, BIOCARD is smaller in sample size and has less heterogeneity in AD severity than ADNI, but BIOCARD has greater longitudinal follow-up.

ADNI data could be characterized as a cross-sectional study with longitudinal follow-up in that participants in diagnostic groups were very different from each other at baseline on cognitive, imaging, and cerebrospinal fluid (CSF) outcomes, and the study has not yet followed people long enough