Pre-clinical Cognitive Phenotypes for Alzheimer Disease: A Latent Profile Approach

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Background: *Cognitive profiles for pre-clinical Alzheimer disease (AD) can be used to identify groups of individuals at risk for disease and better characterize pre-clinical disease. Profiles or patterns of performance as pre-clinical phenotypes may be more useful than individual test scores or measures of global decline.* **Objective:** *To evaluate patterns of cognitive performance in cognitively normal individuals to derive latent profiles associated with later onset of disease using a combination of factor analysis and latent profile analysis.* **Methods:** *The National Alzheimer Coordinating Centers collect data, including a battery of neuropsychological tests, from participants at 29 National Institute on Aging–funded Alzheimer Disease Centers across the United States. Prior factor analyses of this battery demonstrated a four-factor structure comprising memory, attention, language, and executive function. Factor scores from these analyses were used in a latent profile approach to characterize cognition among a group of cognitively normal participants (N = 3,911). Associations between latent profiles and disease outcomes an average of 3 years later were evaluated with multinomial regression models. Similar analyses were used to determine predictors of profile membership.* **Results:** *Four groups were identified; each with distinct characteristics and significantly associated with later disease outcomes. Two groups were significantly associated with development of cognitive impairment. In post hoc analyses, both the Trail Making Test Part B, and a contrast score (Delayed Recall - Trails B), significantly predicted group membership and later cognitive impairment.* **Conclusions:** *Latent profile analysis is a useful method to evaluate patterns of cognition in large samples for the identification of preclinical AD phenotypes; comparable results, however, can be achieved with very sensitive tests and contrast scores.* (Am J Geriatr Psychiatry 2013; ■:■–■)

Key Words: Latent profile analysis, factor analysis, neuropsychological test, longitudinal study

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Alzheimer disease (AD) is neurodegenerative disease that has a gradual onset and progressive course. Without an effective prevention or cure, the prevalence of AD is expected to increase dramatically in the coming years.[1] The challenge of identifying individuals who are asymptomatic yet at increased risk for developing AD has been identified as a critical, rate-limiting factor that is delaying the development and validation of preventive therapies for mild cognitive impairment (MCI) and AD.[2] Preventive interventions must take place long before the disease is clinically apparent because the pathology accumulates over many years. For this reason, the focus of research has now shifted to very early detection and characterization of pre-clinical disease (in cognitively normal individuals) in order to facilitate prevention trials. The hope is that new treatments may be effective if applied early, before the level of pathology is too great to overcome.

AD is fundamentally a disease of clinical presentation; therefore, neurocognitive testing is an important tool in the early identification of individuals at risk for MCI and AD. In the absence of an adequate blood test for AD biomarkers, neurocognitive testing with brief, targeted cognitive batteries may be one of the best ways to identify appropriate subjects for research studies and clinical trials because it is less invasive and potentially less expensive to measure than other biomarkers such as amyloid imaging. Furthermore, studies have shown that neuropsychological testing does a better job of predicting conversion to AD than other biomarkers.[3,4] Batteries of neurocognitive tests are designed to measure function in various cognitive domains, nine of which were specifically identified by the original NINCDS-ADRDA criteria as being important in AD.[5] To date, there have been few studies of the overall latent patterns of cognitive performance in normal individuals across different cognitive domains (see Mavandadi et al.[6] for an example in Parkinson disease). Patterns of performance have been studied by examining multiple cognitive measures concurrently and declines on memory measures and executive function are generally accepted early harbingers of decline to MCI due to AD.[7,8] Contrasts or differences between tests that measure various cognitive domains have also been found to be predictive.[9] Contrasts can demonstrate asymmetric cognitive function and have been associated with differences in cortical thickness.[10] Given the evidence suggesting that cognitive changes take place years before diagnosis, we sought to identify subtypes of cognitively normal individuals with different patterns of cognition, which may suggest later AD or dementia onset. Using data from the National Alzheimer Disease Coordinating Center (NACC), we tested the hypotheses that distinct latent profiles can be identified and distinguished from each other, and that group membership will predict later onset of MCI, AD, or dementia.

METHODS

Participants and Setting

The NACC is charged with the aggregation of standardized data collected from 29 Alzheimer Disease Centers (ADCs) across the United States.[11] Recruitment methods vary from center to center and participants are generally drawn from the surrounding community. Approximately 36% of participants were referred by friend or relative, 21% by clinician or clinic sample, 14% by ADC solicitation, 4% by non-ADC media appeal, and the remaining 25% from other sources.[12] All protocols are approved by local institutional review boards. Evaluations may take place in a clinical facility or in research participants' homes.

Basic demographic information, medical history, medication history, and family history of dementia are collected from participants in addition to behavioral and functional assessments. The Uniform Data Set (UDS) neuropsychological battery[12] is administered at each annual visit by trained psychometricians either in the clinic or in the home. Clinicians review participant's records and assign a global Clinical Dementia Rating (CDR) score. CDR scores are assigned and diagnoses are made according to standard criteria.[13–15] (See Morris et al.[15] for a description of clinical and cognitive variables collected for the NACC.)

The UDS Neuropsychological Battery

The neuropsychological battery administered as part of the UDS has nine neuropsychological tests that are used to characterize normal aging, mild impairments in cognition, and dementia. The battery was designed to be brief and is administered in a fixed fashion (standard administration and order of tests)

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