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Advanced Psychometric Analysis and the Alzheimer's Disease Neuroimaging Initiative:Reports from the 2011 Friday Harbor Conference

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Abstract

This article summarizes a special series of articles from The Advanced Psychometric Methods in Cognitive Aging Research conference, held in June, 2011 at Friday Harbor, Washington. This conference used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to address cognitive change associated with Alzheimer's disease (AD) and how it related to neuroimaging, genetic, and cerebrospinal fluid biomarkers. The 13 articles in this series present innovative approaches to measuring cognition and studying determinants of cognitive decline in AD.

This issue includes a special series of articles that resulted from the June, 2011 Advanced Psychometric Methods in Cognitive Aging Research conference, held in Friday Harbor, Washington. The theme of this conference was "Neuroimaging and Cognition" and the conference and the articles in this series were based on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). This series presents empirical studies that are quite diverse, including psychometric analyses for improved measurement of cognition, neuroimaging-based brain-behavior correlations, genetics of cognitive outcomes, and hypothesis-driven studies of the temporal sequencing of biomarker and clinical changes in Alzheimer's disease (AD).

The Advanced Psychometric Methods in Cognitive Aging Research conference was started in 2004 to share knowledge, skills, and expertise related to psychometric methods and item response theory (IRT). The conference format included a unique blend of lectures and applied data analysis using data from a major study in cognitive aging. The conference has continued on an annual basis, and beginning in 2008 received conference grant funding from the National Institute on Aging (R13 AG 030995, D Mungas, PI). The mission of these meetings is to provide a critical fermenting ground for development and application of research tools to improve the study of cognitive aging, including the determinants and consequences of dementia. The methodology has evolved since 2004 to incorporate broader latent variable modeling and longitudinal data analysis approaches. A defining feature of

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these conferences is that advanced psychometric and statistical methodology is applied to important scientific problems using real data from major studies that have shaped our understanding of aging and cognition. The format continues to include didactic presentations on substantive science and methodology relevant to the conference theme and small workgroups that analyze data to generate scientific presentations and manuscripts. Workgroups continue to meet via teleconference after each annual meeting to complete analyses and manuscripts. There is a different theme for each year, and a different dataset is chosen each year.

There have been 40–50 participants in recent conferences. The model for the conference is to have diversity among participants according to level of training and seniority, areas of substantive and technical expertise, and demographic characteristics such as gender and race/ethnicity. The format promotes training of graduate students, postdoctoral fellows, and junior faculty. A guiding principle is that all participants, regardless of career stage or expertise, will learn skills and knowledge that will enhance their research. Didactic presentations include a scientific symposium related to the conference theme, an overview and scientific summary of the studies that are providing data, and lectures on methodology especially relevant to each conference. Lectures are posted on the conference website (http://alzheimer.ucdavis.edu/fhpsych) and are available to the public.

There were 49 participants in 2011 who divided into workgroups to perform analyses and develop manuscripts. These workgroups collectively produced 13 manuscripts that were peer reviewed and accepted for publication in this issue of Brain Imaging and Behavior. These studies, falling into four broad categories, are summarized in the following sections.

Measurement of Cognition

Availability of reliable and valid assessments of diverse cognitive domains, with sensitivity to change across the range of function, remains a central challenge in research on cognitive aging. Modern approaches to measurement of cognition based on IRT and latent variable modeling have the potential to substantially strengthen dementia research and, for this reason, applications of these tools have been a core theme throughout this conference series. Five of the articles in this series applied these methods to improving measurement in ADNI, and more broadly, AD clinical trials. Skinner and colleagues (“The Alzheimer Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): An expansion of the ADAS-Cog to improve responsiveness in MCI”) applied IRT methods to the problem of improving sensitivity and responsiveness to change of the Alzheimer’s Disease Assessment Scale, Cognitive subtest (ADAS-Cog)(Rosen, Mohs, & Davis, 1984). They combined item content from the ADAS-Cog with additional measures of executive function collected in ADNI and informant-based measures of instrumental activities of daily living. The resulting measure had improved responsiveness to detecting clinical differences and longitudinal change related to AD. Two papers applied modern psychometric methods to optimizing domain-specific composite scores for episodic memory (ADNI-Mem, Crane et al., “Development and assessment of a composite score for memory in the Alzheimer’s Disease Neuroimaging Initiative (ADNI)”) and executive functioning (ADNI-EF, Gibbons et al., “A composite score for executive functioning, validated in Alzheimer’s Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment”) using all related tests and items available within ADNI. They compared reliability and validity using similar validation methods to Skinner et al., and showed that these measures had better psychometric characteristics for measuring episodic memory and executive function, cognitive domains that are especially salient for studying and monitoring the progression of AD.

Quitania Park et al. (“Confirmatory Factor Analysis of the ADNI Neuropsychological Battery”) used confirmatory factor analysis to examine the dimensions of cognition measured in the ADNI battery. They specified a five-factor structure that corresponded to previous studies based on different test batteries, and importantly, showed the same factor structure at each level of impairment (normal, MCI, dementia). Johnson et al. (“Longitudinal Change in Neuropsychological Performance Using Latent Growth Models: A Study of Mild Cognitive Impairment”) performed a latent growth model to characterize cognitive change in patients with normal cognition and mild cognitive impairment (MCI) using the factors identified by Quitania Park et al. Results showed that among cognitively normal participants, average episodic memory declined but other factors did not. Among study participants with MCI at the baseline evaluation, all five factors declined, with greater decline in executive function than memory.

Neuroimaging-Cognition Relationships

Nho et al. (“Voxel and Surface-Based Topography of Memory and Executive Deficits in Mild Cognitive Impairment and Alzheimer’s Disease”) applied voxel-based and surface-based quantitative methods to structural MRI to evaluate associations of gray matter density and cortical thickness with episodic memory and executive functioning among people with normal cognition, MCI, and AD using ADNI-Mem and ADNI-EF. Habeck et al. (“Association between brain metabolism and cognitive function in prodromal and early Alzheimer’s disease”) performed similar analyses with FDG-PET scan data to identify voxels in which basal metabolic activity was associated with ADNI-Mem and ADNI-EF. Gross et al. (“Cortical Signatures of Cognition and their Relationship to Alzheimer’s Disease”) identified regions in which cortical thickness was associated with the cognitive factors from Quitania Park et al. They found that cognition and cortical thickness in these regions were independent predictors of risk for converting from MCI to dementia.

Sequencing of Biomarker and Cognitive Changes

Two papers used the Jack et al. (Jack et al., 2010) conceptual model of temporal sequences of biomarker and clinical change in AD to generate hypotheses about longitudinal relations among CSF biomarkers, MRI measures of brain structure, PET measures of brain metabolism, and cognition. Stricker et al. (“CSF biomarker associations with change in hippocampal volume and precuneus thickness: implications for the Alzheimer’s pathological cascade”) examined CSF Aβ and tau as predictors of change in hippocampal volume and precuneus thickness. They showed that the two CSF biomarkers jointly predicted changes in these brain structures, which are central to AD. Han et al. (“Beta Amyloid, Tau, Neuroimaging, and Cognition: Sequence Modeling of Biomarkers for Alzheimer’s Disease”) examined how CSF Aβ and tau individually and jointly relate to brain structure, brain metabolism, and cognition, and how CSF biomarkers, brain structure, and brain function relate to cognition. Results showed a complex pattern of associations in the hypothesized pathway from Aβ changes to cognitive decline. These findings suggest that Aβ effects on cognition are largely mediated by tau and imaging variables, but tau effects on cognition independent of neuroimaging characteristics were observed.

Genetic Contributions to Cognition

A group of articles present innovative approaches to using high-dimensional genetic data to explain cognitive outcomes. Mukherjee et al. (“Genetic architecture of resilience of executive functioning”) modeled genetic predictors of resilience in executive function. They defined resilience as the degree to which ADNI-EF scores were better or worse than expected on the basis of brain imaging and demographic variables. Ramanan et al. (“Genome-wide pathway analysis of memory impairment in the Alzheimer’s Disease

Neuroimaging Initiative (ADNI) cohort implicates gene candidates, pathways, and networks") studied variation in genetic pathways associated with ADNI-Mem performance. Processes classically understood to be involved in memory consolidation, such as neurotransmitter receptor-mediated calcium signaling and long-term potentiation, were highly represented among the enriched pathways. In addition pathways related to cell adhesion, neuronal differentiation and guided outgrowth, and glucose- and inflammation-related signaling were enriched. Mukherjee et al. ("Dysexecutive and amnesic AD subtypes defined by single indicator and modern psychometric approaches: relationships with SNPs in ADNI") differentiated amnesic and dysexecutive people with AD using a conventional approach (Dickerson & Wolk, 2011) and the ADNI-Mem and ADNI-EF composites. They then evaluated associations with single nucleotide polymorphisms (SNPs) associated with AD (Naj et al., 2011), with MRI-defined infarcts (Debette et al., 2010), and with white matter hyperintensities (Fornage et al., 2011). They found higher proportions of SNPs associated with dysexecutive vs. amnesic groups in predicted directions using the modern psychometric approach than using the conventional approach.

This special series takes advantage of the ADNI dataset that provides comprehensive characterization of brain imaging, CSF, and genetic biomarkers along with detailed measurement of cognition in a sample designed to span a broad spectrum of AD severity from normal to preclinical AD to mild dementia. The articles in this series all used state of-the-art methods for measuring cognition, and many shared core cognitive measures. These studies varied greatly in the types of biomarkers used to explain cognition and in the hypotheses being tested and the analytic approaches. This series presents innovative approaches to measurement of cognition and modeling the complexities of genetic and brain determinants of the cognitive changes of AD to address important clinical and scientific challenges presented by AD.

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