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Datasets for Special Series on Cognitive Reserve

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INTRODUCTION

The Sixth Annual Advanced Psychometrics Methods Workshop was held August 30 to September 4, 2009 at the University of Washington's Friday Harbor Laboratories in the San Juan Islands, WA. The theme, Cognitive Reserve, focused on identifying variables that influence the association of neuropathology with cognitive function. Functional physiologic systems, for example, pulmonary, renal, hepatic, cardiac, are redundant and a considerable amount of tissue destruction must take place before the system is compromised to the point that signs and symptoms of dysfunction become clinically apparent. The nervous system, though functionally and structurally more complex, has long been recognized to exhibit some type of reserve. Evidence of cognitive reserve comes from a variety of sources. For example, several clinical-pathologic studies have reported widespread Alzheimer's disease (AD) pathology among persons without obvious cognitive impairment suggesting the presence of factors that must influence cognition separate from neuropathology or influence the association of neuropathology with cognition (Crystal et al., 1993; Davis, Schmitt, Wekstein, & Markesbery, 1999; Katzman et al., 1988; Morris et al., 1996). Several factors have been reported to be associated with cognitive reserve such as years of formal education and occupation (Zhang et al., 1990; Stern et al., 1994).

Studies providing data to this workshop included data on a) indicators of cognitive reserve, b) detailed cognitive function, and c) neuropathologic indices. Data were primarily from two studies: The Rush Religious Orders Study and the Rush Memory and Aging Project (MAP). Both are cohort studies of risk factors for common chronic conditions of aging that include organ donation at death. Together, more than 2,500 persons have undergone annual detailed clinical evaluations with up to 17 waves of data, and more than 850 brain autopsies have been performed. Prior work from these studies has reported the relation of neuropathology, including measures of AD pathology, cerebral infarctions, Lewy bodies, and amyloid angiopathy, to cognition (Arvanitakis, Leurgans, Barnes, Bennett, & Schneider, 2011; Arvanitakis, Leurgans, et al., 2010; Bennett, Schneider, Bienias, Evans, & Wilson, 2005; Bennett, Schneider, Arvanitakis, et al., 2006; Schneider, Wilson, Bienias, Evans, & Bennett, 2004; Schneider, Boyle, Arvanitakis, Bienias, & Bennett, 2007; Schneider, Arvanitakis, Bang, & Bennett, 2007; Schneider, Arvanitakis, Leurgans, & Bennett, 2009; Wilson, Leurgans, Boyle, Schneider, & Bennett, 2010). In addition, several experiential and psychological factors have been reported to be related to cognition separate from neuropathology such as neuroticism, loneliness, depression, and cognitive activities (Bennett, Wilson, Schneider, Bienias, & Arnold, 2004; Wilson et al., 2003; Wilson, Scherr,

Schneider, Tang, & Bennett, 2007; Wilson, Arnold, Schneider, Li, & Bennett, 2007; Wilson, Krueger, et al., 2007). Furthermore, several factors have been reported to modify the relation of neuropathology to cognition including years of formal education, social networks, processing resources, conscientiousness, and sex (Barnes et al., 2005; Bennett, Schneider, Wilson, Bienias, & Arnold, 2005; Bennett, Schneider, Arnold, Tang, & Wilson, 2006; Bennett, Wilson, et al., 2009; Boyle, Wilson, Schneider, Bienias, & Bennett, 2008; Wilson, Schneider, Arnold, Bienias, & Bennett 2007). Finally, data collection methods include a large subset of data collected with identical methods in both studies allowing for data to be pooled for clinical and clinical-pathologic analyses in which larger samples are needed to enhance power for associations (Bennett, Schneider, Arvanitakis, et al., 2006; Bennett, Schneider, Aggarwal, et al., 2006b; Bennett, De Jager, Leurgans, & Schneider, 2009; Schneider, Arvanitakis, Bang, & Bennett, 2007; Wilson, Schneider, Boyle, et al., 2007).

A third study, the Minority Aging Research Study, also contributed clinical data to the workshop. This is a cohort study of risk factors for common chronic conditions with more than 350 older African Americans. Data collection methods include a large subset of data collected with identical methods as those used in the Religious Orders Study and the Rush Memory and Aging Project, which include nearly 200 African Americans, allowing for data to be pooled for clinical analyses across race (Arvanitakis, Bennett, Wilson, & Barnes, 2010; Boyle, Barnes, Buchman, & Bennett, 2009; Boyle, Buchman, Barnes, James, & Bennett, 2010; Buchman, Boyle, Barnes, Leurgans, & Bennett, 2010).

This special Series on Cognitive Reserve in the Journal of the International Neuropsychological Society highlights four manuscripts produced by conference participants. The first, by Jones, et al. examined latent variable modeling approaches for quantifying reserve, with an emphasis on their application to data from observational studies. The second paper, by Dowling, et al., used latent variable modeling to examine clinical-pathologic relationships with data from the Religious Orders Study and Rush Memory and Aging Project. The third paper, by Reed et al., also used a latent variable modeling approach to estimate domain-specific cognitive reserve and then sought to identify potential determinants of reserve using data from the same two studies. Finally, the paper by Fyffe et al., assessed differential item functioning, demographic characteristics, and factors associated with cognitive reserve to determine whether they account for racial differences in episodic memory performance using data from the Rush Memory and Aging Project and the Minority Aging Research Study.

COHORTS PROVIDING DATA TO WORKSHOP

Rush Religious Orders Study

The Religious Orders Study enrolls nuns, priests, and brothers without known dementia, from across the United States. Participants must agree to an annual detailed clinical evaluation and brain donation at the time of death. Each subject signs a consent form and an Anatomical Gift Act. The study was approved by the Institutional Review Board of Rush University Medical Center. The study primarily recruits clergy living in more than 40 communities, including three predominantly African American communities, and Hispanic sisters primarily from communities in San Antonio. Clinical data collection began in January of 1994. The study has a rolling admission with participants enrolling each year. To date, more than 1150 participants have enrolled, approximately 30% are men and approximately 90% are white, non-Hispanic. The mean age at entry is approximately 75 years with an average education of approximately 18 years. Follow-up clinical evaluations are conducted annually with a 95% follow-up rate of survivors. More than 500 brain autopsies have been performed with an autopsy rate nearly 95%.

Rush Memory and Aging Project

The Memory and Aging Project enrolls older lay persons from across northeastern Illinois (Bennett, Buchman, et al., 2005). Participants must agree to an annual detailed clinical evaluation and donation of brain, spinal cord, nerve, and muscle at the time of death. Each subject signs a consent form and an Anatomical Gift Act. The study was approved by the Institutional Review Board of Rush University Medical Center. The study primarily recruits from more than 40 communities. It also recruits from Section 8 and Section 202 housing, retirement homes, and through local Churches and social service agencies serving minorities and low-income elderly. Clinical data collection began in the fall of 1997. The study has a rolling admission with participants enrolling each year. To date, more than 1450 participants have enrolled, approximately 30% are men and approximately 90% are white, non-Hispanic. The mean age at entry is approximately 80 years with an average education of approximately 14 years with more than a third with 12 or fewer years of education. Follow-up clinical evaluations are conducted annually with a follow-up rate in excess of 90% of survivors. More than 375 autopsies have been performed with an autopsy rate over 80%.

Rush Minority Aging Research Study

The Minority Aging Research Study recruits older African Americans from the Chicago area using the same methodology as used by the Rush Memory and Aging Project. Each subject signs a consent form agreeing to an annual detailed clinical evaluation and participation in an organ donation component is encouraged but not required. The study was approved by the Institutional Review Board of Rush University Medical Center. Clinical data collection began in 2004. The study has a rolling admission with participants enrolling each year. To date, more than 350 participants have enrolled, approximately 30% are men. The mean age at entry is approximately 73 years with an average education of approximately 14 years with more than a third with 12 or fewer years of education. Follow-up clinical evaluations are conducted annually with a follow-up rate in excess of 90% of survivors.

DATA USED IN PAPERS IN SPECIAL ISSUE

Three types of data were used in analyses: (a) indicators of cognitive reserve, (b) detailed cognitive function, and (c) neuropathologic indices. These are summarized in Tables 1–3 for each study.

Demographics, Indicators of Reserve, and Clinical Diagnoses

Sex, race, and ethnicity are ascertained using the 1990 U.S. Census questions.

Indicators of reserve included direct and indirect measures. Direct measures included years of formal education, and early, mid-, and late life cognitive activities (Barnes, Wilson, Mendes de Leon, & Bennett, 2006; Bennett, Schneider, Wilson, Bienias, & Arnold, 2005; Bennett, Wilson, et al., 2003; Wilson, Mendes de Leon, et al., 2002; Wilson, Scherr, Schneider, Tang, & Bennett, 2007). We also measure height (Buchman, Schneider, Wilson, Bienias, & Bennett, 2006). Indirect measures included parental education, income, occupation, and father's occupation; in addition, birth addresses were linked to 1920 census data to determine early-life socioeconomic status including literacy rates and Duncan socioeconomic status of head of household for county or census track (Wilson et al., 2005; Wilson, Scherr, Schneider, Tang, & Bennett, 2007).

The diagnostic process for Alzheimer's disease and mild cognitive impairment included a decision tree designed to mimic expert clinical judgment, implemented by computer (Bennett, Schneider, Aggarwal, et al., 2006). It combines data reduction techniques for the

cognitive performance testing (see below) with a series of discrete clinical judgments made in series by a neuropsychologist and a clinician. The evaluation is designed to reduce costs and enhance uniformity of diagnostic decisions over time and space (Weir et al., 2011).

Apolipoprotein E allele status was performed by Agencourt Bioscience Corporation (Beverly, MA) using high throughput sequencing (Bennett, De Jager, Leurgans, & Schneider, 2009).

Measures of Cognition

A battery of cognitive performance tests is administered each year (Barnes et al., 2006; Boyle, Barnes, Buchman, & Bennett, 2009; Wilson, Beckett, et al., 2002). The Mini-Mental State Examination (MMSE) is primarily used to describe the cohort. Eleven tests are used for diagnostic classification, including complex ideational material. The remaining tests assess a range of cognitive abilities and are used to construct separate summary measures of five cognitive domains, including episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. Semantic memory can be separated into word knowledge and word generation (fluency). There are nineteen tests in common across the three studies. Seven tests can be administered by telephone. This version yields composites for episodic memory, semantic memory, and working memory (Wilson & Bennett, 2005).

Measures of Neuropathology

The brain is removed and weighed. The post-mortem neuropathologic evaluation includes a uniform structured assessment of AD pathology, cerebral infarcts, Lewy body disease, and other pathologies common in aging and dementia. Brain tissue stained with modified Bielschowsky is used to count neuritic plaques, diffuse plaques, and neurofibrillary tangles in five brain regions, including the mesial temporal lobe (hippocampal formation and entorhinal cortex) and neocortex (superior frontal and middle temporal gyri, and parietal lobe) (Bennett, Schneider, Arnold, Tang, & Wilson, 2006; Bennett et al., 2003). The location, size, and age of each macroscopic infarct are recorded as described (Schneider et al., 2004; Schneider, Boyle, et al., 2007). Microscopic infarctions are identified on H&E stained sections (Arvanitakis et al., 2011). Lewy bodies are identified on alpha-synuclein immunostained sections from six brain regions (Bennett, Schneider, et al., 2005; Schneider, Arvanitakis, et al., 2007; Schneider, Arvanitakis, et al., 2007).

Advantages of These Cohort Studies for Examining Cognitive Reserve

The neurobiologic basis of cognitive reserve is not well understood. Although there is evidence to suggest that the modest association between cognition and neuropathology may reflect the inter-individual variability of cognitive reserve, it has been challenging to operationalize or measure reserve directly. As noted by Jones et al. (this issue), if reserve is defined as the difference between expected and observed impairment for a given level of pathology, then good measures of performance and pathology are needed to measure reserve. The observational studies used in three of the current papers have several advantages that advance the study of reserve and the sophisticated latent variable modeling techniques used by the authors allow a better understanding of both the neural underpinnings of reserve and the experiential factors that may influence reserve. The combination of large, clinically well-characterized older adults with high rates of follow-up participation, comprehensive well-established cognitive performance measures, and a wide spectrum of neuropathology in prospective longitudinal studies provide a unique opportunity to directly link common indicators of reserve (e.g., education, occupation, cognitive activities) to measures of neuropathology. Furthermore, the substantial overlap in clinical and cognitive measures across the three epidemiologic studies allows investigators to pool data across studies increasing power to not only examine clinical-pathologic correlations but to address

issues across race and ethnicity as well. Together, the set of papers in this special series represents an important contribution to the study of cognitive reserve.

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Table 1

Demographic characteristics, measures of reserve, and clinical diagnoses in the Religious Orders Study (ROS), Memory and Aging Project (MAP), and the Minority Aging Research Study (MARS)

Demographic characteristics	ROS	MAP	MARS
Age	X	X	X
Gender	X	X	X
Race	X	X	X
Ethnicity	X	X	X
Indicators of reserve			
Education (years and quality (as measured in Fyffe)	X	X	X
Early life cognitive activities		X	X
Parental education	X	X	X
Age 40 cognitive activities		X	X
Late life cognitive activities (at study baseline)	X	X	X
Age 40 income		X	X
Current income (at study baseline)	X	X	X
Occupational history	X	X	X
Father's occupation	X	X	X
County or census tract literacy rate	X	X	X
County or census tract Duncan head of household	X	X	X
Clinical diagnoses			
Alzheimer's disease	X	X	X
Mild cognitive impairment	X	X	X
No cognitive impairment	X	X	X

Table 2

Cognitive function tests in the Religious Orders Study (ROS), Memory and Aging Project (MAP), and the Minority Aging Research Study (MARS)

	ROS	MAP	MARS
MMSE	X	X	X
Complex Ideational Material	X	X	X
Episodic Memory			
Logical Memory Ia	X	X	X
Logical Memory IIa	X	X	X
East Boston Story Immediate recall	X	X	X
East Boston Story Delayed recall	X	X	X
Word List Memory	X	X	X
Word List Recall	X	X	X
Word List Recognition	X	X	X
Semantic Memory			
Boston Naming Test	X	X	X
Verbal Fluency	X	X	X
Wide Range Achievement Test			X
National Adult Reading Test	X	X	
Extended Range Vocabulary Test	X		
Working Memory			
Digit Span Forward	X	X	X
Digit Span Backward	X	X	X
Digit Span Ordering	X	X	X
Alpha Span Ordering	X		
Perceptual (Processing) Speed			
Symbol Digit	X	X	X
Number Comparison	X	X	X
Stroop Word Reading		X	X
Stroop Word Color Naming		X	X
Visuospatial Ability (Perceptual Organization)			
Line Orientation	X	X	X
Progressive Matrices	X	X	X
Executive Function			
Trails A			X
Trails B			X

Table 3

Neuropathologic indices available in the Religious Orders Study (ROS) and Memory and Aging Project (MAP)

	ROS	MAP
Alzheimer's disease pathology		
Neuritic plaque counts	X	X
Diffuse plaque counts	X	X
Neurofibrillary tangle counts	X	X
Cerebrovascular disease		
Macroscopic infarcts	X	X
Microscopic infarcts	X	X
Lewy body disease pathology		
Lewy bodies	X	X
Other pathology		
Brain weight	X	X