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Neurodegenerative disease and cognitive retest learning

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ABSTRACT

Retest learning impacts estimates of cognitive aging, but its bases are uncertain. Here, we test the hypothesis that dementia-related neurodegeneration impairs retest learning. Older persons without cognitive impairment at enrollment (n = 567) had annual cognitive testing for a mean of 11 years, died, and had a neuropathologic examination to quantify 5 neurodegenerative pathologies. Change point models were used to divide cognitive trajectories into an early retest sensitive component and a later component less sensitive to retest. Performance on a global cognitive measure (baseline mean = 0.227, standard deviation = 0.382) increased an estimated mean of 0.142-unit per year for a mean of 1.5 years and declined an estimated mean of 0.123-unit per year thereafter. No pathologic marker was related to cognitive change before the change point; each was related to cognitive decline after the change point. Results were comparable in analyses that used specific cognitive outcomes, included 220 individuals with mild cognitive impairment at enrollment, or allowed a longer retest learning period. The findings suggest that neurodegeneration does not impact cognitive retest learning.

1. Introduction

Gradually accelerating decline in cognitive function over many years is the primary clinical manifestation of dementia and its precursor, mild cognitive impairment. Assessing these trajectories in individuals requires repeated administration of cognitive tests. However, repeated cognitive testing has long been known to enhance performance (Baltes, 1968; Rabbitt et al., 2004; Schaie, 1965), and some studies have reported that this retest learning is reduced in persons with dementia (Cooper et al., 2001; Hassenstab et al., 2015) and mild cognitive impairment (Cooper et al., 2004; Duff et al., 2011). These observations suggest that estimates of cognitive decline represent an uncertain mix of actual cognitive loss plus ability to benefit from prior test experience.

However, quantifying retest effects in cognitive aging studies poses substantial challenges. The most basic problem is that because "most studies use widely spaced measurement occasions (i.e., of sufficient duration in which systematic change over time is expected to occur) that are relatively constant across individuals, the effects of aging-related change and retest gains within a given individual in such designs are inherently confounded" (Hoffman et al., 2011). Even in data sets with some variation between time and number of measurement occasions, making separation of retest and aging effects possible, it is uncertain whether to specify retest effects as a boost after the initial measurement occasion, as constant or diminishing boosts after multiple measurement occasions, or in some other way (Vivot et al., 2016), and misspecification of retest effects is likely to impact estimates of cognitive aging (Hoffman et al., 2011). In addition to these obstacles to direct assessment of person-specific variation in cognitive retest effects, much prior research is based on relatively short retest intervals (e.g., ≤1 month), but most cognitive aging research uses longer retest intervals (e.g., ≥1 year). Furthermore, with few exceptions (Duff et al., 2014; Galvin et al., 2005) previous research has used cognitive data to characterize the exposure (i.e., mild cognitive impairment, dementia) and the outcome, possibly biasing estimates of the association between them.

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In the present analyses, we use data from 2 longitudinal cohort studies to test the hypothesis that dementia reduces the ability to benefit from prior cognitive test experience. A battery of 17 cognitive tests was administered at annual intervals for a mean of more than a decade. Two study features are noteworthy. First, because of the constant interval between testing occasions, we assessed cognitive retest effects indirectly based on prior observations that the rate of retest learning diminishes with subsequent re-exposures (Baltes, 1968; Bartels et al., 2010; Collie et al., 2003; Hausknecht et al., 2007; Ivnik et al., 2000; Rapport et al., 1997; Schaie, 1965; Theisen et al., 1998; Thorndike, 1922). Specifically, we statistically decomposed each individual cognitive trajectory into an early component assumed to be highly affected by retest learning and a later component assumed to be less affected. Second, at death, all participants underwent a brain autopsy and uniform neuropathologic examination in which we quantified common dementia-related pathologies. Analyses tested the relation of each postmortem pathologic marker to cognitive trajectory components.

2. Methods

2.1. Participants

Analyses are based on participants in 2 longitudinal clinical-pathologic cohort studies. The Religious Orders Study began in 1994 and involves older Catholic nuns, priests, and monks from across the United States (Bennett et al., 2012a; Wilson et al., 2004). The Rush Memory and Aging Project began in 1997 and involves older lay persons from the Chicago metropolitan area (Bennett et al., 2005, 2012b). Eligibility for both studies requires agreement to annual clinical evaluations and brain autopsy and neuropathologic examination at death. The clinical and neuropathologic evaluations in the 2 studies are identical in essential details. After a thorough discussion with study personnel, participants signed informed consent forms and an Anatomical Gift Act. Each study was approved by the institutional review board of Rush University Medical Center.

Inclusion in the present analyses required that participants in the parent studies meet 3 criteria. First, we required a minimum of 5 cognitive assessments to adequately capture nonlinear cognitive change. Second, we required a completed postmortem neuropathologic examination to test the hypothesized association of dementia-related pathologies with cognitive trajectory components. Third, because mild cognitive impairment is a precursor of dementia, we excluded those with the condition at baseline from primary analyses, but we included them in sensitivity analyses to determine whether there was enough pathology in the primary analytic group to support hypothesis testing.

At the time of these analyses, 3072 individuals without dementia had completed a baseline clinical evaluation. We excluded 822 persons with mild cognitive impairment. Of the remaining 2250 individuals without cognitive impairment, 242 had died before the fourth annual follow-up evaluation and 474 had enrolled less than 3 years earlier, leaving 1534 persons with sufficient follow-up data. Of these, 729 had died and 670 (92%) had a brain autopsy. The neuropathologic examination was pending in 20 cases and 83 had some missing data. This left 567 persons in the primary analytic group. They had a mean age of 78.7 [standard deviation (SD) = 6.6; range: 64.5–96.9] at baseline, a mean age of 89.7 (SD = 6.3; range: 71.3–104.3) at death, and a mean of 11.0 years of follow-up (SD = 4.2; range: 3.7–21.8). They had completed a mean of 16.5 years of education (SD = 3.7), and 393 (69.3%) were women.

In sensitivity analyses, we included 220 individuals who had mild cognitive impairment at baseline but otherwise met eligibility criteria. Compared to the 567 individuals in the primary analytic group, the additional 220 individuals were older (81.0 vs. 79.0, t [785] = 4.5, $p < 0.001$) and had fewer years of follow-up (9.9 vs. 11.0, x^2 [1] = 11.1, $p < 0.001$); they had a similar level of education (16.3 vs. 16.5, x^2 [1] = 0.1, $p = 0.776$) and percent of women (69.1 vs. 69.3, x^2 [1] = 0.0, $p = 0.952$); and aside from Lewy bodies (24.8% vs. 22.2%, x^2 [1] = 0.5, $p = 0.486$), they had higher postmortem levels of pathology, including tangles (8.89 vs. 5.33, x^2 [1] = 36.5, $p < 0.001$), amyloid (1.90 vs. 1.64, x^2 [1] = 7.4, $p = 0.007$), transactive response DNA-binding protein 43 (TDP-43) pathology (x^2 [3] = 8.1, $p = 0.044$), and hippocampal sclerosis (15.9% vs. 8.3%, x^2 [1] = 9.9, $p = 0.002$).

2.2. Clinical evaluation

At annual intervals, participants had a uniform clinical evaluation that included a medical history, neurological examination, and assessment of cognitive function, as previously described (Bennett et al., 2006a, 2012a, b). On the basis of this evaluation, diagnoses of dementia, mild cognitive impairment, and other common conditions were rendered. The diagnosis of dementia followed the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984), which require a history of cognitive decline and impairment in at least 2 domains of cognition. Those who had impairment in at least 1 cognitive domain but did not meet dementia criteria were classified as mild cognitive impairment. Further information on these diagnostic criteria and their relation to clinical and pathologic outcomes is published elsewhere (Bennett et al., 2006b).

2.3. Assessment of cognitive function

A battery of cognitive performance tests was administered each year in an approximately 1 hour session. There were 7 episodic memory measures: Word List Memory, Word List Recall, and Word List Recognition (Welsh et al., 1994; Wilson et al., 2002) and immediate and delayed recall of Logical Memory Story A (Wechsler, 1987) and the East Boston Story (Albert et al., 1991; Wilson et al., 2002). Semantic memory was assessed with a category fluency test (Welsh et al., 1994; Wilson et al., 2002), 15-item version (Welsh et al., 1994) of the Boston Naming Test (Kaplan et al., 1983), and a brief word reading test (Wilson et al., 2002). There were 3 working memory tests: Digit Span Forward and Digit Span Backward (Wechsler, 1987) plus a modified form (Wilson et al., 2002) of Digit Ordering (Cooper et al., 1991). Modified versions (Wilson et al., 2002) of the Symbol Digit Modalities Test (Smith, 1982) and Number Comparison (Ekstron et al., 1976) were used to assess perceptual speed, and short forms of Judgment of Line Orientation (Benton et al., 1994) and Standard Progressive Matrices (Raven et al., 1992) assessed visuospatial ability. In analyses, these individual measures were used to create composite measures of global cognition (based on all 17 tests), episodic memory (7 tests), and perceptual speed (2 tests). In each case, raw scores on individual tests were converted to z scores using the baseline mean and SD from the pooled parent cohorts, and z scores on component tests were averaged to yield the composite scores. Further information on the individual tests and development of the composite measures is published elsewhere (Wilson et al., 2002, 2003, 2005).

2.4. Neuropathologic examination

A standard protocol was used for removal of the brain and sectioning and preservation of the tissue (Bennett et al., 2006b; Schneider et al., 2009). Density of tau-immunoreactive neurofibrillary tangles was assessed in 8 brain regions (CA1/subiculum,