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Repetition priming and change in functional ability in older persons without dementia

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Abstract

Adverse consequences such as institutionalization and death are associated with compromised activities of daily living in aging, yet there is little known about risk factors for the development and progression of functional disability. Using generalized linear models, we examined the association between the ability to benefit from repetition and rate of change in functional ability in 160 nondemented elders participating in the Religious Orders Study. Three single-word repetition priming tasks were administered that varied in the degree to which visual-perceptual or conceptual processing is invoked. Decline in functional ability was less rapid, during follow-up of up to 10 years, in persons with better baseline priming performance on a task known to draw on both visual-perceptual and conceptual processing (word-stem completion). By contrast, change in functional ability was not associated with priming on tasks that are known to draw primarily on either visual-perceptual (threshold word-identification) or conceptual (category exemplar production) processing. The results are discussed in terms of a common biological substrate in the inferotemporal neocortex supporting efficient processing of meaningful visual-perceptual experience and proficient performance of activities of daily living.

Keywords

aging; repetition priming; activities of daily living; functional disability; Religious Orders Study

Introduction

The compromised ability of older persons to carry out a wide range of activities of daily living has been associated with a number of adverse outcomes including institutionalization (Aguero-Torres et al., 1998; Fried et al., 1998; Ganguli, Dodge, & Mulsant, 2002; Reuben, Siu, &

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Kimpau, 1992) and death (Allaire & Willis, 2006; Fried et al., 1998; Ganguli, Doge, & Mulsant, 2002; Heyman et al., 1997). Despite these adverse consequences, there remains little known about factors that predict change in functional ability in aging.

Functional ability requires the integration of diverse cognitive, sensory, and motor information. An association between level of cognitive function and ability to carry out activities of daily living has been noted in a number of cross-sectional studies of older persons (reviewed in Barberger-Gateau & Fabrigoule, 1997) with mixed-etiology dementia (Glosser et al., 2002; Hill, Backman, & Fratiglioni, 1995; Vallotti et al., 2001) or probable Alzheimer's disease (AD; Perry & Hodges, 2000; Van Rhijn et al., 2004). These studies showed that the association between cognitive impairment and functional disability is particularly strong on tests that draw on visual-perceptual abilities. Similarly, prospective studies in persons with dementia (Sauvaget et al., 2002) and in persons with probable AD (Sarazin et al., 2005) have found that cognitive status predicts future functional status and dependency, and that the status of specific functions that tap sensory, perceptual, and/or motor domains such as visual-constructive (visual-motor) ability, are particularly robust predictors.

In order to avoid or delay adverse outcomes, however, it is critical to identify factors that put functional ability at risk well before the onset of clinically detectable cognitive impairment. Although it stands to reason that subclinical diminution in the efficiency of particular cognitive operations, such as those that are associated with risk of functional disability in dementia, might be linked to change in functional ability in older persons, this has not been studied longitudinally.

The ability to benefit from repeated exposure to an event is a fundamental cognitive function that may play a critical role in the ability to perform activities of daily living, and thus level of this ability may predict risk of functional disability before frank cognitive compromise occurs. The benefit, or increased processing efficiency (measured as increased speed or accuracy), accrued from a single repetition of an event is termed repetition priming (e.g., Schacter, 1998; Schacter & Buckner, 1998; Schacter & Tulving, 1994; Squire, 2004). Level of repetition priming on tasks that require visual-perceptual processing has been associated with risk of developing motor impairment in aging (Fleischman et al., 2007), suggesting that performance on these tasks may signal early compromise in brain regions dedicated to processing the interface between visual and motor information. Given this association, and that visual-perceptual and visual-motor tasks are potent predictors of functional disability in persons with cognitive impairment, ability to benefit from a single repetition of visual-perceptual information may be an exceptionally early indicator of impending compromise in activities of daily living.

In this study, we examined the extent to which repetition priming is associated with the rate of change in functional ability in older persons without clinical dementia. Repetition priming was measured on three tasks using fully-counterbalanced, single-word stimuli: threshold word-identification, which is known to be strongly driven by visual-perceptual (sensory-based) processing (Roediger & McDermott, 1993), category-exemplar production, which is known to be known to be strongly driven by conceptual (meaning-based) processing (Roediger & McDermott, 1993), and word-stem completion, which is characterized as a strongly visual-perceptual task that additionally draws on conceptual/lexical processing (Roediger & McDermott, 1993; Rueckl & Mathew, 1999). Functional ability was measured annually on three scales, two that emphasized physical activities of daily living and one that emphasized more cognitively-complex instrumental activities of daily living. In generalized linear models, controlling for age, sex, education, and other relevant covariates, we tested the hypothesis that baseline repetition priming ability, specifically on tasks that require visual-perceptual

processing, would be associated with the rate of change in functional ability during follow-up clinical evaluations.

Materials and Methods

Subjects

All subjects were from the Religious Orders Study, an ongoing longitudinal clinical-pathologic study of aging and AD in older Catholic nuns, priests, and brothers, which involves annual clinical evaluations and brain donation at death. The study was approved by the Institutional Review Board of Rush University Medical Center. 178 subjects of the parent study agreed to a longitudinal substudy of repetition priming (Fleischman et al., 2004). Of these subjects, 17 met criteria for dementia and one met criteria for idiopathic Parkinson's disease at baseline of the substudy and were excluded, leaving a final sample of 160 subjects. The mean age of the sample at the baseline of the substudy was 78.5 years (SD, 6.5 years); mean education was 18.1 years (SD, 3.0 years); and the mean score on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) was 28.5 (SD, 1.4). There were 125 women and 35 men; 158 were white and non-Hispanic, 1 was black and non-Hispanic, and 1 was white and Hispanic. We had as many as ten assessments available for a given person for inclusion in these analyses, with the median number of assessments being 7. To be eligible to be included in the models of change, a person had to have at least two assessments with non-missing outcome data. Thus, the sample size varied across the three primary outcomes, as described below under "Functional Ability Assessment."

Clinical Assessment

Each participant underwent a structured, uniform evaluation that included a medical history, neurological examination, cognitive function testing (detailed below), and a review of a brain scan when available. Participants were evaluated in person by a clinician with expertise in the evaluation of older persons. On the basis of this evaluation, participants were classified with respect to AD, PD, and other common neurologic disorders. The diagnosis of dementia was made by the examining physician on the basis of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the AD and Related Disorders (ADRDA) criteria (McKhann et al., 1984), which require a history of cognitive decline and evidence of impairment in at least two cognitive domains. Details of the diagnostic evaluation have been described previously (Bennett et al., 2002; Bennett et al., 2006).

Cognitive Assessment

Cognitive function was assessed with a set of 21 tests, as previously described (Wilson et al., 2004). The Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) was used for descriptive purposes only. An 8-item version of Complex Ideational Material (Goodglass & Kaplan, 1983), a measure of auditory comprehension, was used to evaluate language function clinically for diagnostic classification but has not been used in analyses because of its highly skewed distribution. The remaining 19 tests were selected to assess five cognitive domains. There were seven episodic memory measures: Word List Memory, Recall, and Recognition (Morris et al., 1989), immediate and delayed recall of the East Boston Story (Albert et al., 1991), and Story A from Logical Memory (Wechsler, 1987). Semantic memory was assessed with four tests: a 20-item version of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), a 15-item version of Extended Range Vocabulary (Ekstrom et al., 1976), a 20-item reading recognition test from the National Adult Reading Test (Nelson, 1982) and its modifications (Blair & Spreen, 1989; Grober & Sliwinski, 1991) and Verbal Fluency (Morris et al., 1989) which involves naming animals and fruits/vegetables in 1-minute epochs. Working memory was assessed with Digit Span Forward and Digit Span Backward (Wechsler, 1987), Alpha Span (Craik, 1986), and Digit Ordering (Cooper et al., 1991). Two tests of perceptual

speed were given: the oral version of the Symbol Digit Modalities Test (Smith, 1982) and Number Comparison (Ekstrom et al., 1976). Visual-spatial ability was assessed with a 15-item version of Judgment of Line Orientation (Benton et al., 1994) and a 17-item version of Standard Progressive Matrices (Raven, Court, & Raven, 1992). Summary measures of the five cognitive domains were formed, based in part on a principal-components factor analysis, as previously described (Wilson et al., 2004). Raw scores on each test were converted to z scores (mean of 0, standard deviation of 1) and then the average z score among tests in a given domain was computed. A global cognitive score was formed by averaging z scores of all 19 tests.

Functional Ability Assessment

Three measures of the ability to carry out activities of daily living were administered. The Katz Physical Activities Scale (Katz, Ford, Moskowitz, Jackson, & Jaffee, 1963) measures six basic physical abilities: bathing, dressing, eating, toileting, walking across a small room, and transferring from bed to chair; 159 persons completed two or more assessments. The Rosow-Breslau Physical Activities scale (Rosow & Breslau, 1966) assesses the ability to carry out three physically-demanding activities that require mobility: performing heavy housework, walking stairs, and walking a half-mile; 159 persons completed two or more assessments. The Instrumental Activities of Daily Living scale (IADL; Lawton & Brody, 1969) measures ten activities of daily living that are more cognitively-demanding: telephone use, meal preparation, light housekeeping, heavy housekeeping, handling medications, handling finances, shopping, and traveling within the community; 144 persons completed two or more assessments on the IADL scale. A participant was considered disabled on a particular item if the participant indicated that he or she could not perform that item without assistance; the total score for the scale was the sum of these individual dichotomous items. Thus, a score of zero on the scale indicated no disability as measured by that scale, and a score of the maximum possible (6 for the Katz ADL scale, 3 for the Rosow-Breslau, and 10 for the IADL scale) indicated 100% disability, as measured by that scale.

Covariate Assessment

Models were adjusted for age, sex, and education initially, and then also for the potentially confounding variables of global cognitive ability (as described above), presence of other medical conditions, and depressive symptomatology. The number of chronic medical conditions was based upon eight common conditions of aging: self-reported myocardial infarction, congestive heart failure, cancer, diabetes, high blood pressure, thyroid disease, head injury, and clinically-diagnosed stroke. Depressive symptomatology was measured using the 10-item version (Kohout, Berkman, Evans, & Cornoni-Huntley, 1993) of the Center for Epidemiological Studies Depression (CES-D, Radloff, 1977).

Procedure

Priming

Materials, design, procedures, and scoring rules for the priming tests used in this study are published in detail elsewhere (Fleischman et al., 2004). Briefly, for the tasks examined in this study, a pool of 144 words was pseudorandomly assigned to six lists of 24 single words (eight words from each of three categories; Battig & Montague, 1969). In the study phase, 24 words were read twice. In the test phase, 24 studied and 24 unstudied words were presented in each of three tasks: threshold word-identification, category-exemplar, and word-stem completion. All words were fully counterbalanced across lists, appearing equally often as studied and unstudied items and across the three priming tests.

For the threshold word-identification test, subjects were asked to visually identify words that were presented very briefly. For each trial, the target word was presented for 16.7 ms and was

immediately masked with a row of 10 X's. Following a correct identification, the experimenter advanced to the next trial. Following an incorrect identification, the exposure duration of the same word was increased in multiples of 16.7 ms until the word was correctly identified. Priming was the difference in the number of trials (measured in milliseconds) needed to identify studied versus unstudied words. For the category-exemplar test, subjects were told that they would be given the name of a category (e.g., vegetables) and they were to produce eight items that belonged to that category, (e.g., celery, carrot, zucchini) as quickly as they could. Priming was measured as the increase in the probability of producing a studied versus an unstudied category exemplar. For the word-stem completion test, a three-letter word stem cue (e.g., GRA__) was given and subjects were asked to produce the first word that came to mind (e.g., GRAPE) that started with those three letters. Priming was measured as the increase in the probability of producing a studied versus an unstudied word in response to the stem cue. The priming tests were administered consecutively in a fixed order: category-exemplar, word-stem completion, and threshold word-identification.

Data Analysis

We examined change over time in functional ability scores using generalized linear models, fit using the method of generalized estimating equations (GEE). We used a logit link and binomial error structure, considering the observed data to represent a proportion disabled. To fit these data using GEE in SAS®, we used an “events/trials” approach, with the maximum number of trials being the maximum possible value on the given functional ability measure. Our approach allowed us to fit the longitudinal outcome data as a function of follow-up time since baseline, and to account for the correlated structure of these data across repeated measurements (Zeger & Liang, 1986).

The first step in the analysis was to fit a base model for each functional ability outcome, including in the model time since baseline, age (centered at 75), education (centered at 18), sex (0=women, 1=men), and the interactions of age, education, and sex, with time. In these models, the coefficient for time represents the change in the functional ability outcome over one year of study time for an average woman (i.e., a 75-year-old woman with 18 years of education). The coefficient for the main effect of age is the effect on the baseline level of the functional ability outcome of being one year older at baseline. The time-by-age coefficient tests the extent to which annual rate of change in functional ability varies with each year of baseline age. Similar interpretations apply to the main effects for sex and education and their interactions with time. Having thus controlled for the effects of the three demographic variables on both starting level and rate of change, we then entered the main effect of priming and the time-by-priming interaction. The priming coefficient is the effect on baseline functional ability of having a one-unit higher priming score at baseline. A test of the significance of the time-by-priming coefficient indicates the extent to which annual rate of change in the functional ability score varies with priming score at baseline. The final step in the analysis was the addition to the model of potential confounders and their interactions with time. All models were validated graphically and analytically. All analyses were carried out using SAS statistical software (Version 8; SAS Institute, 2000).

Results

Distributions and core models

Distributions of the individual priming predictors and functional ability outcomes at baseline are shown in Table 1. Higher scores indicate better priming and more functional disability. In addition, Table 1 includes distributional information for the outcomes at the final measurement point for each person in the analyses. Using the method of least squares, we estimated within-person rates of change in the Katz, Rosow/Breslau, and IADI scales. The average observed

annual rate of change, and the minimum and maximum rates of change, are presented in the third part of Table 1.

Before running the core models, we confirmed that priming did occur on each task by testing the priming score against 0 using a one-sided t test. Note that 0 is the value that one would expect if no priming occurred (i.e., no difference between performance in the studied and unstudied conditions). All results were significant (word identification: $t(156) = 16.58$; category-exemplar: $t(160) = 14.46$; word stem completion: $t(160) = 18.05$; all $ps < 0.001$). We then examined the relationship of each of the three priming measures at baseline to subsequent change in each functional ability measure in separate core models that adjusted for baseline values of functional ability, priming, age, sex, education, and all interactions. Positive and significant coefficients for time in each of the three models indicate that functional disability increased with each year of study time. The positive and significant age coefficients in each of the models represent the significant cross-sectional effect of age on functional ability, with higher age at baseline being associated with a higher disability score. Functional ability did not change over time significantly as a function of age at baseline, as indicated by non-significant Time-by-Age interactions in all models. There were significant negative cross-sectional associations with sex on functional ability in most models, indicating worse ability at baseline for women, but there was no effect of sex on change in functional ability as a function of time in any model (not shown). There were nonsignificant cross-sectional effects with education in most models, but there was no effect of education on change in functional ability as a function of time in any model (not shown).

Priming and Change in Functional Ability

We next added the main effect of priming and the time-by-priming interaction for each of the three measures in independent models (all models are shown in Table 2). Word-stem completion priming predicted change in functional ability over time on the Rosow/Breslau and the IADL scales. For each one-point increase in baseline word-stem completion priming, rate of decline in functional ability measured by the Rosow/Breslau scale decreased by an average of 0.014 units on the logit scale. To get an estimate of this on the original scale, we first computed predicted values at each of 10 years (baseline through 9th follow-up) for a given set of covariates. We then computed the average change over one year by averaging the 9 one-year differences. Thus, the average annual rate of decline in functional ability on the Rosow/Breslau scale associated with a baseline word stem completion score of 9 (90th percentile) for a 75-year-old woman with 18 years of education was .05, an improvement of more than two times that of the average annual rate of decline (.12) associated with a baseline word-stem completion score of 1 (10th percentile). On the IADL scale, the difference between the 90th and 10th percentile word-stem completion priming scores represented 2.6 times more improvement in average annual decline (0.08 and 0.20, respectively). No other significant longitudinal associations occurred.

All models were refit adding the potential confounders of global cognitive ability, other medical conditions, and depressive symptoms. Cross-sectional and longitudinal associations between functional ability and priming remain unchanged with addition of these covariates, except that the longitudinal association between word-stem completion priming and functional ability on the IADL scale became borderline significant when adding to the model medical conditions ($p = .08$) and the time by medical conditions interaction ($p = .07$).

Finally, to determine the specificity of the priming predictors to the functional disability outcomes, all models were refit adding, separately, scores on each of the five cognitive domains measures: episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. Adding these scores to the models resulted in no differences in any of the

results with the exception that the longitudinal association between word-stem completion priming and IADL was reduced ($p = .15$) by the addition of the perceptual speed measure.

Discussion

This study showed that the ability to benefit from repetition was associated with a slower rate of progression of functional disability during up to 10 years of clinical follow-up. This association was specific to the word-stem completion priming task and to the Rosow-Breslau and IADL activity scales. The association between word-stem completion priming and change in Rosow-Breslau activities remained significant after controlling for the potentially confounding effects of age, education, sex, global cognitive ability, other medical conditions, and depressive symptoms. The association between word-stem completion priming and change in IADL activities remained significant after controlling for all of the above factors except medical conditions, which slightly reduced the association to borderline significance.

Repetition priming, on all tasks, was unrelated to change in performing rudimentary activities of living as measured by the Katz scale. Although the lack of associations with the Katz outcome may appear to be due to a lack of variability in this disability scale because the average starting value for the scale was close to 0 (0.30), at baseline the values ranged from 0 to 5, and at the last data point for each person, the range was up to 6. Furthermore, the average yearly rate of change on the scale was 0.11 with a standard deviation of 0.38 (Table 1), which is comparable to the variability of the other disability outcomes. Thus, the lack of associations between the priming predictors and the Katz scale are unlikely to be due to truncation of variance in this outcome measure. Rather, the finding suggests that the ability to benefit from repetition may be most critical in the earliest stages of cognitive change when more physically and cognitively challenging, as opposed to rudimentary, activities of daily living are being performed.

We hypothesized that the association between repetition priming and change in functional ability would occur specifically for tasks that invoke visual-perceptual processing. Indeed, category-exemplar priming which draws strongly on conceptual, and not on visual-perceptual, processing did not predict change in functional ability. However, the predicted association between visual-perceptual repetition priming and functional ability occurred for one visual-perceptual priming task, word-stem completion, but did not occur for another, threshold word-identification. Although both tasks are considered to be largely driven by visual-perceptual processing, they differ in important ways. Threshold word-identification priming requires fast, automatic, item-specific responses that challenge speeded visual detection and discrimination. It is considered the quintessential visual-perceptual priming task because it draws strongly on visual-perceptual, and not on nonperceptual (lexical and/or conceptual), processes (Roediger & McDermott, 1993). Threshold word-identification priming is not associated with cognitive function in aging or Alzheimer's disease (reviewed in Fleischman & Gabrieli, 1998; Fleischman, 2007; Light et al., 2000; Meiran & Jelicic, 1995; Mitchell & Bruss, 2003), but it is associated with change in motor function (Fleischman et al., 2007), suggesting that the task may gauge the integrity of a posterior corticostriatal circuit that controls sensory-motor coordination. By contrast, word-stem completion priming draws on visual-perceptual processes, but also invokes nonperceptual processes [Roediger & McDermott, 1993; Rueckl & Mathew, 1999]. Word-stem completion priming is often, but not always, associated with cognitive function in aging and Alzheimer's disease (reviewed in Fleischman & Gabrieli, 1998; Fleischman, 2007; Light et al., 2000; Meiran & Jelicic, 1995; Mitchell & Bruss 2003), and is also related to change in motor function, albeit less strongly than threshold word-identification (Fleischman et al., 2007). Priming on this task is known to be largely supported by anterior, higher level visual areas in the temporal lobe, particularly inferotemporal cortex (Buckner, Koustaal, Schacter, & Rosen 2000; Nielsen-Bohlman, Ciranni, Shimamura &

Knight, , 1997; Schacter & Buckner, 1998; Schott et al., 2005; Yasuno et al., 2000). The current findings suggest that performance on neither category-exemplar priming, a primarily conceptual task mostly mediated by far anterior neural regions, nor performance on threshold word-identification priming, a primarily visual-perceptual task mostly mediated by far posterior neural regions (e.g., for reviews see Buckner et al., 2000; Fleischman & Gabrieli, 1998; Fleischman, 2007), captures the association between cognitive efficiency and change in functional ability in aging. Rather, word-stem completion priming, which is known to draw on both conceptual and visual-perceptual processes mediated by inferotemporal neocortex (e.g., Buckner et al., 2000; Schacter & Buckner, 1998), does capture this important association.

The neurobiological and information processing commonalities and distinctions between priming on threshold word-identification and word-stem completion suggest that these two tasks may be windows on the integrity of two different, but interactive (Milner & Goodale, 1995; Grady et al., 1994) visual processing pathways, the dorsal versus the ventral processing streams (Milner & Goodale, 1995; Ungerleider & Mishkin, 1982; Valyear et al., 2006), respectively. Both streams begin with primary visual cortex (calcarine cortex, BA 17) and then move anteriorly, either dorsally to the posterior inferior parietal lobe (BA 39) which mediates the nonsemantic interface between vision and movement (such as the guidance of saccades) or ventrally to the inferior temporal lobe (BA 20) where perceptual objects (including words) are first linked with semantic (conceptual) information. Both threshold word-identification priming and motor ability in aging may be associated with the functional integrity of regions along the dorsal (and to a lesser extent, ventral) stream (Fleischman et al., 2007). Both word-stem completion priming (Buckner & Koustal, 2000; Nielsen-Bohlman et al., 1997; Schacter & Buckner, 1998; Schott et al., 2005; Yasuno et al., 2000) and performance of activities of daily living in aging (Glosser et al., 2002; Van Rhijn et al., 2004) are associated with the functional integrity of regions along the ventral stream, in particular, the inferotemporal cortex. Taken together with the results of the current study, these findings suggest that efficiency of processing visual information in the dorsal stream and visual plus conceptual information in the ventral stream, measured by threshold word-identification and word-stem completion priming, respectively, can predict age-related change in motor and functional proficiency. It is important to note as a caveat to this notion that neuroimaging studies suggest that the distinction between these processing streams may blur with aging, as older adults, compared to younger adults, tend to harness the power of both streams in the service of processing visual information (Grady et al., 1992, 1994).

The association between word-stem completion priming and change on the IADL scale was not influenced by the addition of a measure of episodic memory to the model. It was influenced, however, by the addition of a measure of perceptual speed. This suggests that a subtle reduction in cognitive efficiency, particularly in the perceptual domain, predicted change in the ability to perform instrumental activities of daily living in older persons in this study, whereas episodic memory status did not. This finding has important implications for the early identification of those older individuals who are at risk for developing Alzheimer's disease (AD). Episodic memory impairment is thought to be the earliest cognitive symptom of the disease (e.g., Albert et al., 1991) and ability to perform instrumental activities of daily living is common in the earliest stages (e.g., Perry & Hodges, 2000). Although age-related repetition priming has been shown to remain robust over time on a group level (Fleischman et al., 2004), it may identify those individuals who are in the earliest stage of AD neuropathology deposition (Fleischman et al., 2005). Thus, word-stem completion priming performance might signal the early presence of AD neuropathology in regions along the ventral processing stream and identify those individuals who are at risk of developing functional disability and clinically-diagnosed AD before the disease has devastated episodic memory.

This study had important strengths and limitations. A large sample of old persons was used that was exceptionally well-characterized neuropsychologically, neurologically, and medically. These old persons were religious orders' members, however, and thus do not represent the US population in terms of education and lifestyle. Multiple predictor, outcome, and covariate measures, all of which have been well-established in previous research, were used, allowing for an in-depth examination of the association between specific cognitive processes and specific functional abilities while controlling for potential confounders. A limitation is that the functional ability outcome measures are based on self-report. Neuropathological and neuroradiological studies are needed that directly examine the brain bases of the association between visual-perceptual repetition priming and functional disability in aging.

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References

- Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B. Prognostic factors in very old demented adults: A seven-year follow-up study from a population-based survey in Stockholm. *Journal of the American Geriatric Society* 1998;46:444–452.
- Albert M, Smith L, Scherr P, Taylor J, Evans D, Funkenstein H. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. *International Journal of Neuroscience* 1991;57:167–178. [PubMed: 1938160]
- Allaire JC, Willis SL. Competence in everyday activities as a predictor of cognitive risk and mortality. *Aging, Neuropsychology, and Cognition* 2006;13:207–224.
- Barberger-Gateau P, Fabrigoule C. Disability and cognitive impairment in the elderly. *Disability Rehabilitation* 1997;19:175–193.
- Battig WF, Montague WE. Category norms of verbal items in 56 categories: A replication and extension of the Connecticut category norms. *Journal of Experimental Psychology Monographs* 1969;80:1–45.
- Bennett DA, Schneider JA, Aggarwal NT, Arvanitakis Z, Shah R, Kelly JF, Fox JH, Cochran EJ, Arends D, Treinkman A, Wilson RS. Decision rules guiding the clinical diagnosis of Alzheimer's disease in two community-based cohort studies compared to standard practice in a clinic-based cohort study. *Neuroepidemiology* 2006;27:169–176. [PubMed: 17035694]
- Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, Barnes LL, Fox JH, Bach J. Natural history of mild cognitive impairment in older persons. *Neurology* 2002;59:198–205. [PubMed: 12136057]
- Benton, AL.; Sivan, AB.; Hamsher, KS.; Varney, NR.; Spreen, O. Contributions to neuropsychological assessment. Vol. 2nd ed.. Oxford University Press; New York: 1994.
- Blair JR, Spreen O. Predicting premorbid IQ: A revision of the National Adult Reading Test. *Clinical Neuropsychology* 1989;3:129–136.
- Buckner RL, Koutstaal W, Schacter DL, Rosen BR. Functional MRI evidence for a role of frontal and inferior temporal cortex in amodal components of priming. *Brain* 2000;123:20–40.

- Cooper JA, Sagar HJ, Jordan N, Harvey NS, Sullivan EV. Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain* 1991;114:2095–2122. [PubMed: 1933236]
- Craik, FIM. A functional account of age differences in memory. In: Klix, E.; Hagendorf, H., editors. *Human memory and cognitive capabilities: Mechanisms and performances*. Elsevier Science; Amsterdam: 1986. p. 409-422.
- Ekstrom, RB.; French, JW.; Harman, HH.; Kermen, D. *Manual for kit of factor-referenced tests*. Educational Testing Service; Princeton, NJ: 1976.
- Fleischman DA. Repetition priming in aging and Alzheimer's disease: An integrative review and future directions. *Cortex* 2007;43:889–897. [PubMed: 17941347]
- Fleischman DA, Gabrieli JDE. Repetition priming in normal aging and Alzheimer's disease: A review of findings and theories. *Psychology and Aging* 1998;13:88–119. [PubMed: 9533193]
- Fleischman DA, Wilson RS, Bienias JL, Schneider JA, Bennett DA. Parkinsonian signs and functional disability in old age. *Experimental Aging Research* 2007;33:59–76.
- Fleischman DA, Wilson RS, Gabrieli JDE, Bienias JL, Bennett DA. A longitudinal study of implicit and explicit memory in old persons. *Psychology & Aging* 2004;19:617–625. [PubMed: 15584787]
- Fleischman DA, Wilson RS, Gabrieli JDE, Schneider JA, Bienias JL, Bennett DA. Implicit memory and Alzheimer's disease neuropathology. *Brain* 2005;128:2006–2015. [PubMed: 15975947]
- Fried LP, Kronmal RA, Newman AB, Bild DE, Mittelmark MB, Polak JF, Robbins JA, Gardin JM. Risk factors for 5-year mortality in older adults: The Cardiovascular Health Study. *Journal of the American Medical Association* 1998;279:585–592. [PubMed: 9486752]
- Folstein MF, Folstein SE, McHugh PR. Mini-Mental State Examination: A practical method for grading the mental state of patients for the clinician. *Journal of Psychiatric Research* 1975;12:189–198. [PubMed: 1202204]
- Gabrieli JDE, Desmond JE, Demb JB, Wagner AD. Functional magnetic resonance imaging of semantic memory processes in the frontal lobes. *Psychological Science* 1996;7:278–283.
- Ganguli M, Dodge HH, Mulsant BH. Rates and predictors of mortality in an aging, rural, community-based cohort: The role of depression. *Archives of General Psychiatry* 2002;59:1046–1053. [PubMed: 12418938]
- Glosser G, Gallo J, Duda N, de Vries JJ, Clark CM, Grossman M. Visual perceptual functions predict instrumental activities of daily living in patients with dementia. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* 2002;3:198–206.
- Goodglass, H.; Kaplan, D. *The assessment of aphasia and related disorders*. Vol. 2nd ed.. Lea & Febiger; Philadelphia: 1983.
- Grady CL, Haxby JV, Horwitz B, Ungerleider LG, Schapiro MB, Carson RE, Herscovitch P, Mishkin M, Rapoport SI. Dissociation of object and spatial vision in human extrastriate cortex: age-related changes in activation of regional cerebral blood flow measured with [¹⁵O]water and positron emission tomography. *Journal of Cognitive Neuroscience* 1992;4:23–34.
- Grady CL, Maisog JM, Horwitz B, Ungerleider LG, Mentis MJ, Salerno JA, Pietrini P, Wagner E, Haxby JV. Age-related changes in cortical blood flow activation during visual processing of faces and location. *Journal of Neuroscience* 1994;14:1450–1462. [PubMed: 8126548]
- Grober E, Sliwinski M. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *Journal of Clinical and Experimental Neuropsychology* 1991;13:933–949. [PubMed: 1779032]
- Heyman JA, Peterson B, Lillenbaum G, Pieper C. Predictors of time to institutionalization of patients with Alzheimer's disease. *Neurology* 1997;48:1304–1309. [PubMed: 9153462]
- Hill RD, Backman L, Fratiglioni L. Determinants of functional abilities in dementia. *Journal of the American Geriatrics Society* 1995;43:1092–1097. [PubMed: 7560697]
- Kaplan, EF.; Goodglass, H.; Weintraub, S. *The Boston Naming Test*. Lea & Febiger; Philadelphia: 1983.
- Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffee MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psych-social function. *Journal of the American Medical Association* 1963;185:914–923. [PubMed: 14044222]
- Kohout FIJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D depression symptoms index. *Journal of Aging and Health* 1993;5:179–193. [PubMed: 10125443]

- Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179–86. [PubMed: 5349366]
- Light, LL.; Prull, MW.; La Voie, D.; Healy, MR. Dual-process theories of memory in older age. In: Perfect, T.; Maylor, E., editors. *Models of cognitive aging*. Oxford University Press; London: 2000. p. 239-299.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Standlan E. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–944. [PubMed: 6610841]
- Meiran N, Jelicic M. Implicit memory in Alzheimer's disease: A meta-analysis. *Neuropsychology* 1995;9:291–303.
- Milner, AD.; Goodale, MA. *The Visual Brain in Action*. Oxford University Press; Oxford: 1995.
- Mitchell DA, Bruss PJ. Age differences in implicit memory: Conceptual, perceptual, or methodological? *Psychology & Aging* 2003;18:897–822.
- Morris J, Heyman A, Mohs R, Huges J, van Belle G, Fillenbaum G, Mellits E, Clark C, Investigators C. The consortium to establish a registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 1989;39:1159–1165. [PubMed: 2771064]
- Nelson, HE. *National Adult Reading Test (NART): Test manual*. NFER Nelson; Windsor, UK: 1982.
- Nielsen-Bohlman L, Ciranni M, Shimamura AP, Knight RT. Impaired word-stem priming in patients with temporal-occipital lesions. *Neuropsychologia* 1997;35:1087–92. [PubMed: 9256373]
- Perry RJ, Hodges JR. Relationship between functional and neuropsychological performance in early Alzheimer disease. *Alzheimer's Disease and Associated Disorders* 2000;14:1–10.
- Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement* 1977;1:385–401.
- Raven, JC.; Court, JH.; Raven, J. *Manual for Raven's progressive matrices and vocabulary: Standard Progressive Matrices*. Oxford Psychologists Press; Oxford: 1992.
- Reuben DB, Siu AL, Kimpau S. The predictive validity of self report and performance-based measures of function and health. *Journal of Gerontology: Biological and Medical Sciences* 1992;47:M106–M110.
- Roediger, HL.; McDermott, KB. Implicit memory in normal human subjects. In: Spinnler, H.; Boller, F., editors. *Handbook of Neuropsychology*. Vol. 8. Elsevier; Amsterdam: 1993. p. 63-131.
- Rosow I, Breslau N. A Guttman health scale for the aged. *Journals of Gerontology* 1966;21:556–559. [PubMed: 5918309]
- Rueckl JG, Mathew S. Implicit memory for phonological processes in visual stem completion. *Memory & Cognition* 1999;27:1–11.
- SAS Institute Inc.. *SAS/STAT® user guide*. Vol. Version 8. SAS Institute Inc.; Cary, NC: 2000.
- Sarazin M, Stern Y, Berr C, Riba A, Albert M, Brandt J, Dubois B. Neuropsychological predictors of dependency in patients with Alzheimer disease. *Neurology* 2005;64:1027–1031. [PubMed: 15781821]
- Sauvaget C, Yamada M, Fujiwara S, Sasaki H, Mimori Y. Dementia as a predictor of functional disability: A four-year follow-up study. *Gerontology* 2002;48:226–233. [PubMed: 12053112]
- Schacter DL. Neuroscience: Memory and Awareness. *Science* 1998;280:59–60. [PubMed: 9556454]
- Schacter DL, Buckner RL. Priming and the brain. *Neuron* 1998;20:185–195. [PubMed: 9491981]
- Schacter, DL.; Tulving, E. What are the memory systems of 1994?. In: Schacter, DL.; Tulving, E., editors. *Memory systems 1994*. MIT Press; Cambridge, MA: 1994. p. 1-38.
- Schott BH, Henson RN, Richardson-Klavehn A, Becker C, Thoma V, Heinze HJ, Duzel E. Redefining implicit and explicit memory: The functional neuroanatomy of priming, remembering, and control of retrieval. *PNAS* 2005;102:1257–1262. [PubMed: 15657126]
- Smith, A. *Symbol Digit Modalities Test Manual-Revised*. Western Psychological Services; Los Angeles: 1982.
- Squire LR. Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory* 2004;82:171–177. [PubMed: 15464402]

- Ungerleider, LG.; Mishkin, M. Two cortical visual systems. In: Ingle, DJ.; Goodale, MA.; Mansfield, RJW., editors. *Analysis of Visual Behavior*. MIT Press; Cambridge, MA: 1982. p. 549-586.
- Vallotti B, Mossello E, Cantini C, Moretti G, Fumagalli S, Caleri V, Ungar A, Bruscoli M, Tilli S, Masotti G. Determinants of functional status in Alzheimer's disease and vascular dementia. *Archives of Gerontology and Geriatrics* 2001;(suppl 7):419-428. [PubMed: 11431094]
- Valyear KF, Culham JC, Sharif N, Westwood D, Goodale MA. A double dissociation between sensitivity to changes in object identity and object orientation in the ventral and dorsal visual streams: A human fMRI study. *Neuropsychologia* 2006;44:218-228. [PubMed: 15955539]
- Van Rhijn SJ, Glosser G, de Vries JJ, Clark CM, Newberg AB, Alavi A. Visual processing impairments and decrements in regional brain activity in Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology* 2004;26:11-23. [PubMed: 14972690]
- Wechsler, D. Wechsler Memory Scale-Revised manual. Psychological Corporation; San Antonio, TX: 1987.
- Wilson RS, Bienias JL, Evans DA, Bennett DA. Religious Orders Study" Overview and change in cognitive and motor speed. *Aging, Neuropsychology, and Cognition* 2004;11:280-303.
- Yasuno F, Nishikawa T, Tokunaga H, Yoshiyama K, Nakagawa Y, Yoshitaka I, et al. The neural basis of perceptual and conceptual word priming - a PET study. *Cortex* 2000;36:59-69. [PubMed: 10728897]
- Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-130. [PubMed: 3719049]

Table 1

Distributions of the predictor and outcome variables

<u>Predictors</u>	<u>Mean</u>	<u>SD</u>	<u>Range</u>
Word Identification	14.6	11.0	-9 to 55
Category Exemplar Production	2.9	2.5	-5 to 9
Word Stem Completion	4.7	3.3	-3 to 14
<u>Outcomes at Baseline</u>			
Katz	0.30	0.91	0 to 5
Rosow-Breslau	0.93	1.0	0 to 3
Instrumental Activities	1.1	1.7	0 to 11
<u>Outcomes at Final Observation</u>			
Katz	1.21	1.83	0 to 6
Rosow-Breslau	1.61	1.22	0 to 3
Instrumental Activities	2.47	2.85	0 to 11
<u>Outcomes: Within-Person Change/Year</u> *			
Katz	0.11	0.38	-2.06 to 1.54
Rosow-Breslau	0.09	0.20	-1.12 to 1.04
Instrumental Activities	0.22	0.83	-4.49 to 4.96

* Computed from within-person estimated rates of change over the period of observation for each person.

Table 2

Summary of GEE models evaluating the association of time, age, individual priming predictors, and their interactions, with each of the functional disability sign outcomes (Parameter Estimate, SD)

<u>Variable</u>	<u>Katz</u>	<u>Rosow-Breslau</u>	<u>Instrumental Activities</u>
Time	0.276(0.078) **	0.163(0.028) **	0.113(0.034) **
Age	0.167(0.038) **	0.101(0.021) **	0.088(0.018) **
Time $\times$ Age	0.002(0.007)	0.005(0.003)	0.005(0.004)
WI	0.027(0.017)	0.035(0.010) **	0.015(0.009)
WI $\times$ Time	-0.003(0.003)	-0.002(0.001)	-0.000(0.002)
Time	0.231(0.090) **	0.128(0.026) **	0.102(0.032) **
Age	0.181(0.039) **	0.102(0.022) **	0.087(0.018) **
Time $\times$ Age	-0.001(0.007)	0.005(0.003)	0.005(0.003)
CEPR	0.005(0.078)	-0.019(0.042)	-0.047(0.045)
CEPR $\times$ Time	0.003(0.014)	0.002(0.006)	0.002(0.007)
Time	0.247(0.082) **	0.197(0.028) **	0.154(0.031) **
Age	0.181 (0.039) **	0.099(0.022) **	0.084(0.018) **
Time $\times$ Age	-0.001(0.007)	0.006(0.003)	0.006(0.003)
WSC	0.013(0.065)	0.078(0.032) **	0.038(0.035)
WSC $\times$ Time	-0.001(0.010)	-0.014(0.005) **	-0.010(0.005) *

Notes: Table data represent estimated regression coefficients (β), adjusted for sex and education, based on generalized estimated equation models. WI = Word-Identification priming; CEPR = Category-Exemplar priming; WSC = Word-Stem Completion priming.

*
p<.05

**
p<.01