Published in final edited form as:

Neurobiol Aging. 2009 March ; 30(3): 441–449. doi:10.1016/j.neurobiolaging.2007.07.004.

Visuoperceptual repetition priming and progression of parkinsonian signs in aging

Debra A. Fleischman^{1,2,3}, Aron S. Buchman^{1,2}, Julia L. Bienias^{1,4,5}, and David A. Bennett^{1,2}

¹ Rush University Medical Center, Chicago: Rush Alzheimer's Disease Center

² Neurological Sciences

³ Behavioral Sciences

⁴ Internal Medicine

⁵ Rush Institute on Healthy Aging

Abstract

Parkinsonian signs in older persons are associated with numerous adverse health outcomes, however there is limited information about factors which predict progression of these signs. Using generalized linear models, we examined the association between efficiency in visuoperceptual and conceptual processing, measured by repetition priming, and rate of change in parkinsonian signs in a large sample of older persons without cognitive impairment or Parkinson's disease. Subjects with better visuoperceptual priming, measured by threshold word-identification and word-stem completion, at study baseline, progressed more slowly during follow-up of up to 11 years. Conceptual priming was not associated with change in parkinsonian signs. The findings demonstrate that individual differences in visuoperceptual efficiency, measured by repetition priming, occur in older persons without cognitive impairment and predict important changes in motor function. Reduced visuoperceptual priming in aging may be an early signal of vulnerability in a corticostriatal circuit that contributes to sensorimotor integration.

Keywords

aging; parkinsonian signs; Religious Orders Study; repetition priming; sensorimotor integration

1. Introduction

Despite an extensive literature about the adverse consequences of parkinsonian signs in older persons (4,11,19,20,43,44,45,48,52,58,59,77,78), there is little known about factors which predict their development and progression. Some traditional risk factors for stroke have been related to parkinsonian signs (3,42), however the presence and progression of parkinsonian

Corresponding author: Debra A. Fleischman, Ph.D., Rush Alzheimer's Disease Center, Armour Academic Center Offices, 600 S. Paulina, Suite 1038, Chicago, IL. 60612. Phone: 312-942-2286; facsimile: 312-942-2297; email: Debra_Fleischman@rush.edu.

The authors have no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

signs in older persons is much more common than cerebrovascular disease, suggesting that other factors must also be involved.

Recent electrophysiologic studies in animals (23,24,25,33,60,61) and imaging studies in humans (31,39) suggest that effective movement is not a unitary process but requires the orchestration and integration of diverse sensory, motor and cognitive information in the various stages of planning and execution of movement. This is consistent with recent data suggesting that levels of cognitive function, across multiple domains, are associated with both the presence (19) and progression (78) of most parkinsonian signs. Thus, it is possible that subclinical diminution in certain cognitive abilities might be linked to motor decline in older persons.

The ability to benefit from repeated exposure to an event is a fundamental cognitive function that may play a critical role in purposeful movement. The benefit, or increased processing efficiency (measured as increased speed or accuracy), accrued from a single repetition of an event is termed repetition priming (65,66,67,71). Repetition priming is preserved in healthy aging (17,21), although priming on tasks that require predominantly conceptual (meaning-based) cognitive processing appears to be sensitive to presence of early Alzheimer-type neuropathological changes (22). Although early studies indicated that repetition priming was preserved in idiopathic Parkinson's disease (10,32,38), this view has been recently called into question, particularly on tasks which require predominantly visuoperceptual processing (2).

In the present study we examined the extent to which repetition priming is associated with the rate of change in parkinsonian signs in older persons without clinical dementia or Parkinson's disease. Repetition priming was measured on four tasks: one considered strongly driven by sensory (visuoperceptual) processing, one considered strongly driven by conceptual (meaning-based) processing, and two tasks known to draw upon both visuoperceptual and conceptual processing. The presence of four parkinsonian-signs: gait, rigidity, bradykinesia, tremor, as well as a global score based on these four signs were measured annually. In generalized linear models, controlling for age, sex, education, and other relevant covariates, we tested the hypothesis that baseline repetition priming ability, specifically on visuoperceptual tests, would be associated with the rate of change in parkinsonian signs during follow-up clinical evaluations.

2. Materials and Methods

2.1. 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, that 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 (21). Of these subjects, 17 met criteria for dementia, and one met criteria for idiopathic PD, at baseline and were excluded, leaving a final sample of 160 subjects.

The current study used the baseline scores from a longitudinal study of priming in aging (21). The mean age of the sample 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 (29) 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.

2.2. Clinical Assessment

Each participant underwent a structured, uniform evaluation that incorporated the procedures used by the Consortium to Establish a Registry for Alzheimer's Disease (49). The evaluation

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 board-certified or board-eligible neurologist or geriatrician with expertise in the evaluation of older persons with and without dementia. 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 Disorder and Stroke (NINCDS) and the AD and Related Disorders (ADRDA) criteria (46), which require a history of cognitive decline and evidence of impairment in two or more domains of cognition, one of which must be memory for classification of Alzheimer's disease. Details of the diagnostic evaluation have been described previously (7,76,78).

2.3. Cognitive Assessment

Cognitive function was assessed with a set of 21 tests (76). The Mini-Mental State Examination (26) was used for descriptive purposes only. An 8-item version of Complex Ideational Material (29), 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 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 (49), immediate and delayed recall of the East Boston Story (1), and Story A from Logical Memory (73). Semantic memory was assessed with four tests: a 20-item version of the Boston Naming Test (35), a 15-item version of Extended Range Vocabulary (15), a 20-item reading recognition test from the National Adult Reading Test (53) and its modifications (9,30) and Verbal Fluency (49) which involves naming animals and fruits/vegetables in 1-minute epochs. Working memory was assessed with Digit Span Forward and Digit Span Backward (73), Alpha Span (14), and Digit Ordering (13). Two tests of perceptual speed were given: the oral version of the Symbol Digit Modalities Test (70) and Number Comparison (15). Visuospatial ability was assessed with a 15-item version of Judgment of Line Orientation (8) and a 17-item version of Standard Progressive Matrices (57).

Summary measures of the five cognitive domains were formed, based in part on a principal-components factor analysis, as previously described (76). 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.

2.4. Assessment of Parkinsonian Signs

Parkinsonian signs were measured by a modified version (5,6) of the motor portion of the United Parkinson's Disease Rating Scale (UPDRS; 16). The scale was administered by trained nurse clinicians, as previously described (3,5,6,19,69,74,75,78). The modifications were minor and meant to make the scale more applicable to persons without Parkinson's disease and easier to administer and score by non-physicians. Four previously established UPDRS sign scores were derived: gait disorder – postural reflex impairment (based on six UPDRS items), rigidity (based on five items), bradykinesia (based on four items), and tremor (based on two items). Each sign was scored from 0 to 100, and a global UPDRS score was formed by averaging the four sign scores. Scores on each measure range from 0 to 100 and denote the percentage of the total possible item score obtained. In previous research, these measures have been shown to have high inter-rater reliability, short-term temporal stability (6), and be reproducible in men and women in aging and AD (5).

2.5. Assessment of Covariates

Models were adjusted for age, sex, and education, as well as for the potentially confounding variables of global cognitive ability (as described above), presence of other medical conditions, and depressive symptomatology. Number of chronic medical conditions was measured by summing across 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 (37) of the Center for Epidemiological Studies Depression (CES-D, 56).

3. Procedure

3.1. Priming

Materials, design, procedures, and scoring rules for the priming tests used in this study are published in detail elsewhere (21). Briefly, for the study phase, words were read or pictures were named. Four priming tests were administered: threshold word-identification, category-exemplar, word-stem completion, and picture-naming. Threshold word-identification is considered the quintessential perceptual priming task, drawing strongly on perceptual processing resources (62). Category-exemplar is considered the quintessential conceptual priming task, drawing strongly on conceptual processing resources. The status of word-stem completion priming and picture-naming priming along the conceptual/perceptual processing distinction is less clear (40,47), although both tasks are known to draw largely on perceptual processing (62), with contributions from lexical (word-stem completion, 63) and lexical and conceptual (picture-naming) processing resources (54).

In the test phase of 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. In the test phase of 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, or zucchini) as quickly as they could. Priming was measured as the increase in the probability of producing a studied versus an unstudied category exemplar. In the test phase of 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. In the test phase of the picture-naming test, subjects were asked to name pictures as quickly and as accurately as possible. Priming was measured as the difference in milliseconds needed to read or name studied versus unstudied words and pictures.

3.2. Data Analysis

We examined change over time in parkinsonian sign 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 parkinsonian. To fit these data using GEE in SAS®, we used an events/trials" approach, with the maximum number of trials being the maximum value on the parkinsonian sign 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 (79). In addition, GEE models produce estimates even when some data are missing, which is more

flexible than traditional approaches (i.e., standard repeated measures models) that require complete data for each participant. Missing data occurred in this study, but was minimal across annual evaluations: Of the 160 participants at baseline, one died before the first follow-up, and no more than 5 people were missing from the analyses in any subsequent year.

The first step in the analysis was to fit a base model for each parkinsonian sign 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. 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. In these models, the coefficient for time represents the effect of one year of study time on the parkinsonian sign outcome for an average woman. The coefficient for the main effect of age is the effect on the parkinsonian sign outcome of being one year older at baseline. The time-by-age coefficient tests the extent to which annual rate of change of parkinsonian sign varies with each year of baseline age. Similar interpretations apply to the main effects for sex and education and their interactions with time. The priming coefficient is the average effect 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 parkinsonian sign 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, 64).

4. Results

4.1 Distributions and core models

Distributions of the individual priming predictors, parkinsonian sign outcomes, and covariates at baseline are shown in Table 1. Higher scores indicate better priming. Higher scores indicate more parkinsonian signs, and thus worse motor function. Because the parkinsonian signs of rigidity and tremor occurred with low frequency in this sample (at least 50% of the sample having zero scores), we dichotomized these two variables as zero versus greater than zero.

We first examined the relationship of each of the four priming measures at baseline to subsequent change in the global measure of parkinsonian signs in separate core models that adjusted for baseline values of parkinsonian signs, priming, age, sex, education, and all interactions (Table 2, "Global"). Positive and significant coefficients for time in each of the four models indicate that the global measure of parkinsonian signs increased with each year of study time. The positive and significant age coefficients in each of the models represent a significant cross-sectional effect of age on parkinsonian signs, with higher age at baseline being associated with a higher parkinsonian sign score. Parkinsonian signs 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 parkinsonian signs in all models (not shown), indicating worse motor function at baseline for women, but there was no effect of sex on change in parkinsonian signs as a function of time in any model. There were no significant cross-sectional effects, or interactions with time, for education in any model (not shown).

4.2. Priming and Change in a Global Measure of Parkinsonian Signs

Having controlled for the three demographic variables on both starting level and rate of change in parkinsonian signs, we added the main effect of priming and the time-by-priming interaction for each of the four measures in independent models. Threshold word-identification priming had a significant cross-sectional association with the parkinsonian sign score and predicted

change in parkinsonian signs over time. For each one-point increase in baseline threshold word-identification priming, rate of decline in parkinsonian signs decreased by an average of .001 units on the logit scale. Thus, the average annual rate of decline in parkinsonian signs associated with a baseline threshold word-identification score of 21 (75th percentile) for a 75-year-old woman with 18 years of education was 0.107 standard units, an improvement of about 15% compared with the average annual rate of decline (0.126 standard units) associated with a word-identification score of 2 (10th percentile). By contrast, there were no significant cross-sectional or longitudinal associations of the parkinsonian sign score and priming in three of the four models: category-exemplar, word-stem completion, and picture naming.

All models were refit adding the potential confounders of global cognitive ability, other medical conditions, and depressive symptoms. Coefficients did not change substantially with the addition to the models of these variables, with the exception that the association of baseline word-stem completion priming and change in parkinsonian signs became marginally significant ($p = .05$) after controlling for global cognitive ability at baseline.

4.3. Priming and Change in Individual Parkinsonian Signs

Next we performed similar models for the association between each of the four priming measures and the individual parkinsonian signs including parkinsonian gait, rigidity, bradykinesia, and tremor (Table 2). All parkinsonian signs, except tremor, showed main effects of time and age, and no time-by-age interaction, similar to the models described above for the global measure of parkinsonian signs. Threshold word-identification was associated with level of parkinsonian gait and bradykinesia, and with change in gait over time. Thus, the average annual rate of motor decline in gait associated with a baseline threshold word-identification score of 21 (75th percentile) for a 75-year-old woman with 18 years of education was 0.149 standard units, an improvement of about 20% compared with the average annual rate of decline (0.187 standard units) associated with a threshold word-identification score of 2 (10th percentile). In addition, there was a significant modification of the rate of change in gait for word-stem completion priming. The average annual rate of motor decline in gait associated with a baseline word-stem completion score of 7 (75th percentile) for a 75-year-old woman with 18 years of education was 0.143 standard units, an improvement of about 20% compared with the average annual rate of decline (0.179 standard units) associated with a word-stem completion score of 1 (10th percentile). None of the other cross-sectional or longitudinal findings were significant.

All models were refit adding the potential confounders of global cognitive ability, other medical conditions, and depressive symptoms. Coefficients did not change substantially with the addition to the models of these variables.

Given that priming is considered to be unaffected by healthy aging (21), and that significant associations between priming at baseline and change in parkinsonian signs occurred in some models, we examined the possibility that persons with mild cognitive impairment (MCI) may have influenced the results. We identified persons with MCI as those individuals with impairment on cognitive performance testing who did not meet criteria for dementia (7), and reran all models described above 1) excluding MCI at baseline ($N = 38$), and 2) adjusting for MCI at baseline, and for the higher order interactions with MCI (MCI*time, MCI*priming predictor*time). The results remained unchanged in all models.

5. Discussion

The purpose of this study was to test the hypothesis that efficiency in visuo-perceptual processing, measured by the ability to benefit from repeated exposure to visuo-perceptual information, would be specifically associated with change in motor function, measured by

parkinsonian signs. The results showed that better performance on visuo-perceptual, but not conceptual, repetition priming tasks was associated with a slower rate of progression of parkinsonian signs during up to 11 years of clinical follow-up. Better threshold word-identification ability at study baseline was associated with a slower rate of increase in a global measure of parkinsonian signs, and better threshold word-identification priming and word-stem completion priming were associated with a slower rate of increase in the parkinsonian gait score. All associations remained significant after controlling for the potentially confounding effects of age, education, sex, global cognitive ability, other medical conditions, and depressive symptoms. The finding that priming on these visuo-perceptual tasks was most robustly associated with gait is consistent with other studies that have shown that the associations between cognitive function and parkinsonian signs in persons with and without dementia are often strongest for gait (5,6,19,75,76,78).

The specificity of visuo-perceptual repetition priming measures for predicting the rate of change in parkinsonian signs suggests that these tasks are windows on the complex visual cognitive processes that are linked with movement. This relationship was particularly robust on the threshold word-identification task, which is largely considered the quintessential visuo-perceptual priming task (62). Threshold word-identification requires fast, automatic, item-specific responses that challenge speeded visual detection and discrimination processes (i.e., a typical saccade is less than 100ms, the initial word-identification trial is 16.7 ms). Visual detection and discrimination processes are known to be impaired in idiopathic PD (34,51).

Recent neuropathological and neuroradiological studies offer additional hints regarding the biological bases of parkinsonian signs, visuo-perceptual repetition priming, and their association in aging. Like idiopathic PD, parkinsonian signs are related to pathology in substantia nigra (although the underlying mechanisms may differ, 12, 50, 68, 69). Substantia nigra neurofibrillary pathology is present and is related to parkinsonian signs, particularly gait, in both old persons with and without cognitive impairment (12,41,68,69,72). Although repetition priming has historically been considered a neocortical phenomenon (27), recent exceptions have been published (2,22), and activation-reduction in the striatum associated with long-term repetition priming effects on a task requiring visuospatial transformation of words has been reported in young subjects (55). Furthermore, the striatum has strong reciprocal connections with posterior, higher-order visual processing areas, which have been shown in human lesion (18,28,36) and neuroimaging (66) studies to be engaged by visuo-perceptual repetition priming tasks. Thus, these tasks may gauge the integrity of a corticostriatal circuit that participates in sensorimotor integration. The current findings, taken together with what is known regarding the biological links between vision and various aspects of movement, provide evidence that efficient visuo-perceptual cognition is necessary for normal motor function, and that reduced visuo-perceptual efficiency is a risk factor that predicts change in motor function in the elderly.

Excluding persons with mild cognitive impairment at baseline or accounting for their performance in the models did not change the results of this study. This suggests that individual differences in visuo-perceptual efficiency, measured by repetition priming, occur in older persons without frank cognitive impairment, and that they predict important changes in motor function. Indeed, reduced visuo-perceptual priming may be a very early sign of vulnerability in biological systems that support the interface between cognitive and motor function; a notable finding given that the presence of parkinsonian signs, and in particular, parkinsonian gait, are associated with a two-fold increase in the risk of death in the elderly(4).

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 motor abilities while controlling for potential confounders. Neuropathological and neuroradiological studies are needed that directly examine the brain bases of the association between visuoperceptual repetition priming, motor function, and decline in aging.

Acknowledgements

This work was supported by National Institute on Aging grants R29AG13018, R01AG17133, and P30AG10161 to Rush University Medical Center.

We are indebted to the altruism and support of the hundreds of nuns, priests, and brothers from the following groups participating in the Religious Orders Study: Archdiocesan priests of Chicago, IL and Dubuque, IA; Capuchins; Appleton, WI; Christian Brothers; Chicago; Norbertines; De Pere, WI; Sinsinawa Dominican Sisters, Dubuque; Sisters of Charity, B.V.M.; Chicago and Dubuque, IA; Sisters of Mercy of the Americas; Chicago; Sisters of St. Benedict; St. Cloud; Society of Divine Word; Techny, IL; Trappists Monks, Dubuque, IA.

We thank Julie Bach and Barbara Eubeler, respectively, for coordinating the parent project and this substudy. We also thank the many research assistants that contributed to various phases of this project: Cynthia Caceres, Lisa Dwornik, Joanna Hauser, Kelly Lange, Teresa Moro, Kuheli Mukherjee, and Julie Rinaldi. We also thank Liping Gu and Woojeong Bang for analytic programming.

References

1. 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. *Int J Neurosci* 1991;57:167–178. [PubMed: 1938160]
2. Arroyo-Anllo EM, Ingrand P, Neau JP, Gil R. Pictorial and lexical priming: Patterns of implicit memory in Alzheimer's and Parkinson's disease patients. *Eur J Cog Psych* 2004;16:535–553.
3. Arvanitakis Z, Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and progression of rigidity and gait disturbance in older persons. *Neurology* 2004;63:996–1001. [PubMed: 15452289]
4. Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, Evans DA. Prevalence of parkinsonian signs and associated mortality in a community population of older people. *N Engl J Med* 1996;334:71–76. [PubMed: 8531961]
5. Bennett DA, Shannon KM, Beckett LA, Wilson R. Dimensionality of parkinsonian signs in aging and Alzheimer's disease. *J Gerontol* 1999;54A:M191–M196.
6. Bennett DA, Shannon KM, Beckett LA, Goetz CG, Wilson RS. Metric properties of nurses' ratings of parkinsonian signs with a modified Unified Parkinson's Disease Rating Scale. *Neurology* 1997;49:1580–1586. [PubMed: 9409350]
7. Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, Barnes LL, Fox JH, Bach J. Natural history of mild cognitive impairment. *Neurology* 2002;59:198–205. [PubMed: 12136057]
8. Benton, AL.; Sivan, AB.; Hamsher, KdeS; Varney, NR.; Spreen, O. Contributions to neuropsychological assessment. Vol. 2. New York: Oxford University Press; 1994.
9. Blair JR, Spreen O. Predicting premorbid IQ: A revision of the National Adult Reading Test. *Clin Neuropsychol* 1989;3:129–136.
10. Bondi MW, Kaszniak AW. Implicit and explicit memory in Alzheimer's disease and Parkinson's disease. *J Clin Exp Neuropsychol* 1991;13:339–358. [PubMed: 1864919]
11. Boyle PA, Wilson RS, Aggarwal NT, Arvanitakis Z, Kelly J, Bienias JL, Bennett DA. Parkinsonian signs in subjects with mild cognitive impairment. *Neurology* 2005;65:1901–1906. [PubMed: 16380610]
12. Burns JM, Galvin JE, Roe CM, Morris JC, McKeel DW. The pathology of the substantia nigra in Alzheimer disease with extrapyramidal signs. *Neurology* 2005;64:1397–1403. [PubMed: 15851730]

13. 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]
14. Craik, FIM. A functional account of age differences in memory. In: Klix, E.; Hagendorf, H., editors. *Human memory and cognitive capabilities: Mechanisms and performances*. Amsterdam: Elsevier Science; 1986. p. 409–422.
15. Ekstrom, RB.; French, JW.; Harman, HH.; Kermen, D. *Manual for kit of factor-referenced tests*. Princeton, NJ: Educational Testing Service; 1976.
16. Fahn, S.; Elton, R. Unified Parkinson's Disease Rating Scale. In: Fahn, S.; Marsden, C.; Goldstein, M.; Calne, D., editors. *Recent Developments in Parkinson's Disease*. Vol. 12. Florham Park, NJ: MacMillan Healthcare Information; 1987. p. 153–163.
17. Fleischman DA. Repetition priming in aging and Alzheimer's disease: An integrative review and future directions. *Cortex*. 2007in press
18. Fleischman DA, Gabrieli JDE, Reminger SL, Rinaldi JA, Morrell F, Wilson RS. Conceptual priming in perceptual identification for patients with Alzheimer's disease and a patient with right occipital lobectomy. *Neuropsychology* 1995;9:187–197.
19. Fleischman DA, Wilson RS, Bienias JL, Bennett DA. Parkinsonian signs and cognitive function in old age. *J Int Neuropsychol Soc* 2005;11:591–597. [PubMed: 16212686]
20. Fleischman DA, Wilson RS, Bienias JL, Schneider JA, Bennett DA. Parkinsonian signs and functional disability in old age. *Exp Aging Res* 2007;33:59–76. [PubMed: 17132564]
21. Fleischman DA, Wilson RS, Gabrieli JDE, Bienias JL, Bennett DA. A longitudinal study of implicit and explicit memory in old persons. *Psychol Aging* 2004;19:617–625. [PubMed: 15584787]
22. 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]
23. Fogassi L, Gallese V, Buccino G, Craighero L, Fadiga L, Rizzolatti G. Cortical mechanism for the visual guidance of hand grasping movements in the monkey: A reversible inactivation study. *Brain* 2001;124:571–586. [PubMed: 11222457]
24. Fogassi L, Luppino G. Motor functions of the parietal lobe. *Cur Op Neurobiol* 2005;15:626–631.
25. Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. Parietal Lobe: From Action Organization to Intention Understanding. *Science* 2005;308:662–667. [PubMed: 15860620]
26. Folstein M, Folstein S, McHugh P. Mini-Mental State: A practical method for grading the mental state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198. [PubMed: 1202204]
27. Gabrieli, JDE. Cognitive neuroscience of human memory. In: Spence, JT.; Darley, JM.; Foss, DJ., editors. *Annual Review of Psychology*, Annual Reviews. Palo Alto, CA: 1998. p. 87–115.
28. Gabrieli JDE, Fleischman DA, Keane MM, Reminger S, Morrell F. Double dissociation between memory systems underlying explicit and implicit memory in the human brain. *Psychol Sci* 1995;6:76–82.
29. Goodglass, H.; Kaplan, D. *The assessment of aphasia and related disorders*. Vol. 2. Philadelphia: Lea & Febiger; 1983.
30. Grober E, Sliwinski M. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *J Clin Exp Neuropsychol* 1991;13:933–949. [PubMed: 1779032]
31. Halsband U, Lange RK. Motor learning in man: A review of functional and clinical studies. *J Phys-Paris* 99:414–424.
32. Heindel WC, Salmon DP, Shults CW, Walicke PA, Butters N. Neuropsychological evidence for multiple memory systems: A comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. *J Neurosci* 1989;9:582–587. [PubMed: 2521896]
33. Hikosama O, Nakamura K, Sakai K, Nakahara H. Central mechanisms of motor skill learning. *Curr Opin Neurobiol* 2002;12:217–222. [PubMed: 12015240]
34. Hikosaka O, Nakamura K, Nakahara H. Basal Ganglia Orient Eyes to Reward. *J Neurophysiol* 2006;95:567–584. [PubMed: 16424448]
35. Kaplan, EF.; Goodglass, H.; Weintraub, S. *The Boston Naming Test*. Philadelphia: Lea & Febiger; 1983.

36. Keane MM, Gabrieli JDE, Mapstone HC, Johnson KA, Corkin S. Double dissociation of memory capacities after bilateral occipital-lobe or medial temporal-lobe lesions. *Brain* 1995;118:1129–1148. [PubMed: 7496775]
37. Kohout FJ, Berman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D depression symptoms index. *J Aging Health* 1993;5:179–193. [PubMed: 10125443]
38. Koivisto M, Portin R, Rinne JO. Perceptual priming in Alzheimer's and Parkinson's diseases. *Neuropsychologia* 1996;34:449–557. [PubMed: 9148201]
39. Lehericy S, Bardinet E, Tremblay L, Van de Moortele PF, Pochon JB, Dormont D, Dae-Skik K, Yelnik J, Ugurbil K. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. *Cerebral Cortex* 2006;16:149–161. [PubMed: 15858164]
40. 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*. London: Oxford University Press; 2000. p. 239-299.
41. Liu Y, Stern Y, Chun M, Jacobs D, Yau P, Goldman J. Pathological correlates of extrapyramidal signs in Alzheimer's disease. *Ann Neurol* 1997;41:368–374. [PubMed: 9066358]
42. Louis ED, Luchsinger JA. History of vascular disease and mild parkinsonian signs in community-dwelling elderly. *Arch Neurol* 2006;63:717–722. [PubMed: 16682541]
43. Louis ED, Schupf N, Manly J, Marder K, Tang MX, Mayeux R. Association between mild parkinsonian signs and mild cognitive impairment in a community. *Neurology* 2005;64:1157–1161. [PubMed: 15824340]
44. Louis ED, Tang MX, Mayeux R. Parkinsonian signs in older people in a community-based study: risk of incident dementia. *Arch Neurol* 2004;61:1273–1276. [PubMed: 15313847]
45. Louis ED, Tang MX, Schupf N, Mayeux R. Functional correlates and prevalence of mild parkinsonian signs in a community population of older people. *Arch Neurol* 2005;62:297–302. [PubMed: 15710859]
46. McKhann, G.; Drachman, D.; Folstein, M.; Katzman, R.; Price, D.; Stadlan, E. *Neurology*. Vol. 34. 1984. 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; p. 939-944.
47. Mitchell DB, Bruss PJ. Age differences in implicit memory: Conceptual, perceptual, or methodological? *Psychol Aging* 2003;18:897–822.
48. Mitchell SL, Rockwood K. The association between parkinsonism, Alzheimer's disease, and mortality: A comprehensive approach. *Journal of the American Geriatric Society* 2000;48:422–425.
49. Morris J, Heyman A, Mohs R, Hughes 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]
50. Morris JC, Price AL. Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *J Mol Neurosci* 2001;17:101–118. [PubMed: 11816784]
51. Mosimann UP, Muri RM, Burn DJ, Felblinger J, O'Brien JT, McKeith IG. Saccadic eye movement changes in Parkinson's disease dementia and dementia with Lewy bodies. *Brain* 2005;128:1267–1276. [PubMed: 15774501]
52. Murray AM, Bennett DA, Mendes de Leon CF, Beckett LA, Evans DA. A longitudinal study of parkinsonism and disability in a community population of older people. *J Gerontol Med Sci* 2004;59A:864–870.
53. Nelson HE. *National Adult Reading Test (NART. Test manual*. Windsor, UK: NFER Nelson; 1982.
54. Park SM, Gabrieli JDE. Perceptual and nonperceptual components of implicit memory for pictures. *J Exp Psychol Learn Mem Cogn* 1995;21:1583–1594. [PubMed: 7490580]
55. Poldrack RA, Gabrieli JD. Characterizing the neural mechanisms of skill learning and repetition priming: evidence from mirror reading. *Brain* 2001;124:67–82. [PubMed: 11133788]
56. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Appl Psychol Measure* 1977;1:385–401.
57. Raven, JC.; Court, JH.; Raven, J. *Manual for Raven's progressive matrices and vocabulary: Standard Progressive Matrices*. Oxford: Oxford Psychologists Press; 1992.

58. Richards M, Stern Y, Mayeux R. Subtle extrapyramidal signs can predict the development of dementia in elderly individuals. *Neurology* 1993;43:2184–2188. [PubMed: 8232926]63/64 need to be turned around
59. Richards M, Touchon J, Ledesert B, Ritchie K. Mild extrapyramidal signs and functional impairment in ageing. *International Journal of Geriatric Psychiatry* 2002;17:150–153. [PubMed: 11813278]
60. Rizzolatti G, Ferrari PF, Rozzi S, Fogassi L. The inferior parietal lobule: where action becomes perception. *Novartis Found Symp* 2006;270:129–140. [PubMed: 16649712]
61. Rizzolatti G, Luppino G. The cortical motor system. *Neuron* 2001;31:889–901. [PubMed: 11580891]
62. Roediger, HL.; McDermott, KB. Implicit memory in normal human subjects. In: Spinnler, H.; Boller, F., editors. *Handbook of Neuropsychology*. Vol. 8. Amsterdam: Elsevier; 1993. p. 63-131.
63. Rueckl JG, Mathew S. Implicit memory for phonological processes in visual stem completion. *Mem Cognit* 1999;27:1–11.
64. SAS Institute Inc. SAS/STAT® user guide, Version 8. Cary, NC: SAS Institute Inc.; 2000.
65. Schacter DL. Neuroscience: Memory and Awareness. *Science* 1998;280:59–60. [PubMed: 9556454]
66. Schacter DL, Buckner RL. Priming and the brain. *Neuron* 1998;20:185–195. [PubMed: 9491981]
67. Schacter, DL.; Tulving, E. What are the memory systems of 1994?. In: Schacter, DL.; Tulving, E., editors. *Memory systems 1994*. Cambridge, MA: MIT Press; 1994. p. 1-38.
68. Schneider JA, Bienias JL, Gilley DW, Kvarnberg DE, Mufson EJ, Bennett DA. Improved detection of nigral pathology in AD. *J Histochem Cytochem* 2002;50:99–106. [PubMed: 11748299]
69. Schneider JA, Li J-L, Li Y, Wilson RS, Kordower JH, Bennett DA. Substantia nigra tangles are related to gait impairment in older persons. *Ann Neurol* 2006;59:166–173. [PubMed: 16374822]
70. Smith, A. *Symbol Digit Modalities Test Manual-Revised*. Los Angeles: Western Psychological Services; 1982.
71. Squire LR. Memory systems of the brain: A brief history and current perspective. *Neurobiol Learn Mem* 2004;82:171–177. [PubMed: 15464402]
72. Stern Y, Jacobs D, Goldman J, Gomez-Tortosa E, Hyman BT, Liu Y, Troncoso J, Marder K, Tang MX, Brandt J, Albert M. An investigation of clinical correlates of Lewy bodies in autopsy-proven Alzheimer's disease. *Arch Neurol* 2001;58:460–465. [PubMed: 11255450]
73. Wechsler, D. *Wechsler Memory Scale-Revised manual*. San Antonio, TX: Psychological Corporation; 1987.
74. Wilson RS, Bennett DA, Gilley DW, Beckett LA, Schneider JA, Evans DA. Progression of parkinsonism and loss of cognitive function in Alzheimer's disease. *Arch Neurol* 2000a;57:855–860. [PubMed: 10867783]
75. Wilson RS, Bennett DA, Gilley DW, Beckett LA, Schneider JA, Evans DA. Progression of parkinsonian signs in Alzheimer's disease. *Neurology* 2000;54:1284–1289. [PubMed: 10746599]
76. Wilson RS, Bienias JL, Evans DA, Bennett DA. Religious Orders Study: Overview and Change in Cognitive and Motor Speed. *Aging Neuropsychol Cogn* 2004;11:28–303.
77. Wilson RS, Schneider JA, Beckett LA, Evans DA, Bennett DA. Progression of gait disorder and rigidity and risk of death in older persons. *Neurology* 2002;58:1815–1819. [PubMed: 12084882]
78. Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Parkinsonianlike signs and risk of incident Alzheimer's disease in older persons. *Arch Neurol* 2003;60:539–544. [PubMed: 12707067]
79. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121–130. [PubMed: 3719049]

Table 1
Distributions of Priming and Parkinsonian Sign Measures and Correlations with Covariates

Mean (SD)		Correlations					
		Age	Education	Sex ^b	GlobCog ^c	CES-D ^d	Medical ^e
<u>Priming:</u>							
Category Exemplar	2.9(2.5)	.010	-.015	-.054	.065	-.099	.033
Word Stem Completion	4.7(3.3)	.026	-.014	.100	.004	.052	.038
Word Identification	14.6(11.0)	.041	-.078	.054	-.157	.023	-.029
Picture Naming	73.7(175.7)	-.092	.045	.037	.068	.084	-.007
<u>Parkinsonian Sign:</u>							
Global ^d	8.2(6.1)	.645***	-.023	-.384***	-.381***	.188*	.285***
Gait	17.5(15.4)	.659***	-.062	-.387***	-.350***	.180**	.269***
Rigidity	1.8(4.5)	.266***	.108	.144	-.207**	-.069	.127
Bradykinesia	10.8(9.1)	.470***	-.059	-.489***	-.315***	.218**	.246***
Tremor	2.7(4.4)	.006	.104	.104	-.011	.027	-.010

^a Possible 100 points

^b Female

^c Global Cognitive function

^d Depressive symptoms

^e Chronic Medical conditions

* p<.05

** p<.01

*** p<.001

Table 2

Summary of GEE models evaluating the association of time, age, individual priming predictors, and their interactions, with each of the parkinsonian sign outcomes

Variable	Global	Gait	Rigidity	Bradykinesia	Tremor
Time	0.111(0.014)**	0.162(0.015)**	0.201(0.038)**	0.071(0.020)**	-0.045(0.039)
Age	0.078(0.007)**	0.111(0.011)**	0.098(0.023)**	0.056(0.010)**	0.026(0.022)
TimeXAge	-0.001(0.001)	0.000(0.001)	-0.001(0.004)	-0.002(0.002)	0.000(0.004)
CEPR	-0.002(0.019)	0.010(0.028)	-0.002(0.048)	-0.022(0.031)	0.022(0.052)
CEPRXTime	0.000(0.003)	-0.002(0.008)	0.003(0.006)	0.000(0.004)	-0.002(0.009)
Time	0.126(0.014)**	0.185(0.015)**	0.220(0.043)**	0.079(0.019)**	-0.018(0.047)
Age	0.078(0.007)**	0.110(0.010)**	0.097(0.023)**	0.056(0.010)**	0.026(0.022)
TimeXAge	-0.001(0.001)	0.000(0.001)	-0.001(0.004)	-0.002(0.002)	0.001(0.004)
WSC	0.011(0.014)	0.021(0.020)	0.023(0.040)	-0.008(0.019)	-0.003(0.043)
WSCXTime	-0.003(0.002)	-0.006(0.002)*	-0.006(0.006)	-0.002(0.003)	-0.008(0.007)
Time	0.128(0.012)**	0.191(0.014)**	0.162(0.049)**	0.087(0.018)**	-0.059(0.040)
Age	0.076(0.007)**	0.108(0.010)**	0.098(0.020)**	0.055(0.010)**	0.023(0.022)
TimeXAge	-0.000(0.001)	0.000(0.001)	0.000(0.004)	-0.001(0.002)	0.003(0.003)
WI	0.011(0.003)**	0.018(0.005)**	-0.006(0.012)	0.011(0.005)*	-0.006(0.002)
WIXTime	-0.001(0.001)**	-0.002(0.001)**	0.002(0.002)	-0.001(0.001)	0.001(0.002)
Time	0.115(0.011)**	0.165(0.012)**	0.200(0.035)**	0.076(0.014)**	-0.055(0.032)
Age	0.080(0.008)**	0.113(0.011)**	0.098(0.024)**	0.058(0.010)**	0.025(0.022)
TimeXAge	-0.001(0.001)	-0.000(0.001)	-0.002(0.004)	-0.002(0.002)	0.000(0.004)
PN	0.000(0.000)	0.000(0.000)	-0.001(0.000)	-0.000(0.000)	-0.000(0.001)
PNXTime	-0.000(0.000)	-0.000(0.000)	-0.000(0.000)	0.000(0.000)	0.000(0.000)

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

* p<.05

** p<.01