Proportion of cognitive loss attributable to terminal decline

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Abstract

Objective

To estimate the proportion of late-life cognitive loss attributable to impending death.

Methods

Older persons ($n = 1,071$) in a longitudinal cohort study without dementia at enrollment underwent annual cognitive assessments (mean 10.6 years, SD 4.6, range 4–24) prior to death. We estimated the onset of terminal acceleration in cognitive decline and rates of decline before and after this point in change point models that allowed calculation of the percent of cognitive loss attributable to terminal decline. Outcomes were composite measures of global and specific cognitive functions. We also estimated dementia and mild cognitive impairment (MCI) incidence before and during the terminal period.

Results

A mean of 3.7 years before death (95% credible interval [CI] -3.8 to -3.5), the rate of global cognitive decline accelerated to -0.313 unit per year (95% CI -0.337 to -0.290), a more than 7-fold increase indicative of terminal decline. The mean global cognitive score dropped 0.377 unit (SD 0.516) assuming no terminal decline and 1.192 units (SD 1.080) with terminal decline. As a result, 71% (95% bootstrapped CI 0.70, 0.73) of overall global cognitive loss was terminal. In subsequent analyses, terminal decline accounted for 70% of episodic memory loss, 65% of semantic memory loss, 57% of working memory loss, 52% of perceptual speed loss, and 53% of visuospatial loss. MCI incidence in the preterminal and terminal periods was similar, but dementia incidence was more than 6-fold higher in the terminal period than preterminal.

Conclusion

Most late-life cognitive loss is driven by terminal decline.

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Glossary

CI = credible interval; MAP = Rush Memory and Aging Project; MCI = mild cognitive impairment; ROS = Religious Orders Study.

According to the terminal decline hypothesis, first proposed more than 50 years ago,¹ rate of cognitive decline sharply accelerates in the last few years of life. The hypothesis has been extensively investigated, with early studies yielding mixed results,^{2,3} but more recent research consistently supporting the hypothesis.^{4–10} The terminal decline hypothesis was proposed as an explanation for age-related differences in cognition. That is, the association of older age with impending death was hypothesized to account for much or all of the association of older age with more rapid rate of cognitive decline.^{1,11,12} To our knowledge, however, there are little published data on this corollary of the terminal decline hypothesis.

In the present study, we estimate the proportion of late-life cognitive loss attributable to impending death. Analyses are based on older participants in 2 longitudinal cohort studies who had annual cognitive testing for up to 24 years and died. In mixed-effects change point models, we estimated person-specific cognitive trajectories (including intercept, preterminal slope, change point, terminal slope) and used these estimates to calculate for each person the proportion of cognitive loss due to terminal decline with composite measures of global cognition and specific cognitive functions as outcomes. In addition, we estimated the incidence of dementia and mild cognitive impairment (MCI) before and during the terminal period.

Methods

Participants

Analyses are based on older participants in 2 ongoing longitudinal clinical-pathologic cohort studies. The Religious Orders Study (ROS) began in 1994 and involves Catholic nuns, priests, and monks from more than 40 orders across the United States; the Rush Memory and Aging Project (MAP) began in 1997 and involves lay persons from the Chicago metropolitan area.¹³ Eligibility for each study requires age ≥ 50 at enrollment, absence of a prior dementia diagnosis, and agreement to annual clinical evaluations and a brain autopsy plus neuropathologic examination at death.

Eligibility for the present analyses required the absence of dementia at the baseline clinical evaluation, completion of at least 5 annual cognitive assessments (to allow observation of non-linear cognitive change), death, and no more than 2 years from the last cognitive assessment to death. As shown in figure 1, 3,469 individuals had completed the baseline clinical evaluation at the time of these analyses. We excluded 204 persons with baseline dementia, 452 persons who died before reaching the fifth annual clinical evaluation, and 659 persons who had enrolled less than 4 years ago. In the remaining 2,154 individuals,

there were 1,160 deaths. We excluded 89 persons without cognitive data in the last 2 years of life, leaving 1,071 in the analytic group. They had a mean age at baseline of 79.4 (SD 6.7, range 62–102) and a mean of 16.5 years of education (SD 3.6, range 3–30); 730 (68.2%) were women and 1,009 (94.3%) were white and not Latino. They were followed a mean of 10.6 years (SD 4.6, range 4–24) before dying at a mean age of 90.1 years (SD 6.3, range 71–108); among survivors, 11,066 of a possible 11,363 clinical evaluations (97.4%) yielded a valid global cognitive score.

Standard protocol approvals, registration, and patient consents

Participants signed informed consent forms following discussion with study staff. Each study was approved by the institutional review board of Rush University Medical Center.

Clinical evaluation

At baseline and annually thereafter, participants had a clinical evaluation that included a medical history, neurologic examination, and cognitive testing. As previously reported,¹⁴ the presence of 7 common medical conditions was determined based on medical history (hypertension, diabetes, heart disease, cancer, thyroid disease, head injury) or history plus examination (stroke). We used the number of conditions identified on any evaluation prior to death as a measure of comorbid medical conditions. An experienced clinician used the evaluation results to classify dementia according to the criteria of the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.¹⁵ These criteria require a history of cognitive decline and impairment in at least 2 domains of cognitive function. Persons who had impairment in at least one cognitive domain but did not meet dementia criteria were diagnosed with MCI. Further information on the implementation of the diagnostic criteria for dementia and MCI and their relation to clinical and pathologic outcomes is published elsewhere.¹³

Assessment of cognitive function

A set of 19 cognitive performance tests was administered as part of each annual clinical evaluation. Two tests with skewed distributions (Mini-Mental State Examination, Complex Ideational Material) were not used in analyses. The remaining 17 tests included 7 measures of episodic memory (Word List Memory, Word List Recall, Word List Recognition; immediate and delayed recall of Logical Memory Story A and the East Boston Story), 3 measures of semantic memory (Boston Naming Test, Verbal Fluency, Word Reading), 3 measures of working memory (Digit Span Forward, Digit Span Backward, Digit Ordering), 2 measures of perceptual speed (Symbol Digit

Figure 1 Composition of analytic group

Flow diagram shows the composition of the analytic group.

Modalities Test, Number Comparison), and 2 measures of visuospatial ability (Standard Progressive Matrices, Judgment of Line Orientation). To minimize floor and ceiling artifacts and other sources of measurement error, composites of 2 or more tests were used in analyses. The primary outcome was a measure of global cognition based on all 17 tests. Supported by factor analyses in these^{16–18} and other¹⁹ cohorts, we also formed composite measures of episodic memory (based on 7 tests), semantic memory (3 tests), working memory (3 tests), perceptual speed (2 tests), and visuospatial ability (2 tests). We converted raw test scores to *z* scores, using the baseline mean and SD in the combined ROS and MAP cohorts, and averaged the *z* scores of component tests to obtain each composite score. Previous publications provide additional information on the tests and these composite measures.^{16–19}

Statistical analysis

We estimated change in cognitive outcomes in mixed-effects change point models.^{10,20–22} Specifically, preterminal and terminal changes in cognition were modeled using a piecewise linear trajectory with a random change point. The model follows a structure as below:

$$y_{ij} = (\theta_{i0} + \gamma_{i0}) + (\theta_{i1} + \gamma_{i1})(0, T_{ij} - (\theta_{i3} + \gamma_{i3}))_{\min} + (\theta_{i2} + \gamma_{i2})(T_{ij}, (\theta_{i3} + \gamma_{i3}))_{\max} + e_{ij}$$

Here, the outcome y_{ij} is the longitudinal cognitive measure for individual i at visit j , $i = 1, \dots, m$ and $j = 1, \dots, n_i$. T_{ij} is time (in years relative to death) for individual i at visit j . In order to differentiate the rate of change in cognition before and after the change point (denoted by $\theta_{i3} + \gamma_{i3}$), we specify 2 separate

column vectors of time. The first column vector is defined as the minimum of $(0, T_{ij} - [\theta_{i3} + \gamma_{i3}])$ and the second column vector as the maximum of $(T_{ij} [\theta_{i3} + \gamma_{i3}])$. $\theta_{i0} + d_{i0}$, $\theta_{i1} + \gamma_{i1}$, and $\theta_{i2} + \gamma_{i2}$ represent the subject-specific intercept (i.e., the level of cognition at death), preterminal slope, and terminal slope, respectively. θ_{i0} , θ_{i1} , θ_{i2} , and θ_{i3} are parameterized as linear functions of age at death, sex, and education. The random effects γ_{i0} , γ_{i1} , γ_{i2} , and γ_{i3} follow a multivariate normal distribution with means 0 seconds and unknown variance covariance structure $\sum_{4 \times 4}$. The residual error e_{ij} assumes a normal distribution with mean 0 and unknown variance σ^2 .

Parameter estimation was implemented in OpenBUGS software,²³ and used a Bayesian Monte Carlo Markov Chain approach²⁴ with diffuse conjugate priors. Specifically, β coefficient for each fixed effect assumes normal prior with mean 0 and variance 10,000. Inverse of variance covariance matrix for random effects $\sum_{4 \times 4}$ assumes a Wishart ($R, 4$) prior, where R is a 4×4 diagonal matrix of 0.1. Inverse of residual variance σ^2 assumes a γ prior with shape and rate parameters of 0.001 seconds. As shown in our prior analyses, since diffuse priors were used, the estimation is not sensitive to specific distributions of the priors.²⁵ Initial values for person-specific intercept and preterminal and terminal slopes were set at $-0.1, 0$, and -0.1 , respectively; initial values for the location of person-specific change point were set at the midpoint of individuals' follow-up length. Initial values for regression coefficients for θ s were all set at 0. Initial value for the inverse of residual variance σ^2 was 0.1 and the inverse of initial variance covariance matrix for random effects was a 4×4 diagonal matrix of 0.1. History of Markov chain Monte Carlo iterations, density distribution, and autocorrelation for each measure were visually examined to determine convergence. Posterior means from the sampling chain were used as the point estimates and posterior 2.5 and 97.5 quantiles were used to construct 95% credible intervals.

From the model results, we extracted for each individual the model-based estimates for the preterminal slope, onset of terminal decline, terminal slope, and intercept. These estimates were used to calculate for individual i cognitive level at baseline (Y_{i0}), cognitive level at death assuming no terminal decline (Y_{i1}), and cognitive level at death assuming terminal decline (Y_{i2}). Person-specific total cognitive loss was estimated by the difference between predicted scores of cognition at baseline and death. Of note, cognitive level without terminal decline was obtained using the estimates from the same model except that cognitive scores in the terminal phase were predicted using preterminal slope. It follows that total cognitive loss is $Y_{i2} - Y_{i0}$ and cognitive loss due to terminal decline $Y_{i2} - Y_{i1}$. This allowed us to calculate the proportion of cognitive loss due to terminal decline as $(Y_{i2} - Y_{i1}) / (Y_{i2} - Y_{i0})$. The CI for the mean proportion of cognitive loss due to terminal decline was calculated by bootstrapping. Briefly, we sampled with replacement 10,000 times the original dataset that contains the person-specific proportions of cognitive loss. We calculated the mean proportion from each sample to obtain the corresponding sampling distribution. The 95% confidence intervals (CIs)

were obtained by taking the 2.5 and 97.5 percentiles of the sampling distributions. The composite measure of global cognition was the initial outcome. Separate subsequent analyses used measures of specific cognitive functions.

Data availability

The data used in these analyses and descriptions of the parent studies can be accessed at the Rush Alzheimer's Disease Center Research Resource Sharing Hub at radc.rush.edu. After logging in, qualified users can request deidentified data.

Results

Terminal decline in global cognition

At baseline, the composite measure of global cognition had a mean of 0.020 (SD 0.499), with higher scores indicating better function, and the mean Mini-Mental State Examination score was 28.1 (SD 1.9). Younger age ($r = -0.34, p < 0.001$) and higher educational attainment ($r = 0.31, p < 0.001$) were associated with a higher cognitive score at baseline; the scores of women and men did not differ (mean of 0.012 vs 0.037, $t [1,069] = 0.7, p = 0.470$). Participants died after a mean of 10.6 years of observation (SD 4.6). The last cognitive assessment took place a mean of 7.6 months before death (SD 4.8) at which time the mean global cognitive score was -0.913 (SD 1.373) and the mean Mini-Mental State Examination score was 20.5 (SD 9.2).

We assessed global cognitive change in a mixed-effects model that allowed rate of cognitive decline to accelerate at some variable point before death. In this analysis, the composite measure of global cognition declined a mean of 0.040 unit per year (95% credible interval [CI] -0.045 to -0.035) until a mean of 3.7 years before death (95% CI -3.8 to -3.5) when the rate of global cognitive decline accelerated to a mean loss of 0.313 unit per year (95% CI -0.337 to -0.290), a more than 7-fold increase. The cognitive trajectory predicted by the model for a typical participant (upper portion of figure 1) shows the acceleration of cognitive loss in the last 3–4 years of life.

The lower portion of figure 1 shows how the analytic results were used to estimate cognitive loss due to terminal decline for an exemplary participant i . The model predicted trajectory of global cognitive change in this individual (black line, overlaid with observed global cognitive scores represented by black dots) allowed us to calculate the initial cognitive level at baseline, designated Y_{i0} (0.624 in this participant); the final cognitive level assuming no terminal decline is extrapolated using only the preterminal slope and designated Y_{i1} (0.202 in this participant); and the final cognitive level with terminal decline is designated Y_{i2} (-1.818 in this participant). So, the proportion of cognitive loss attributable to terminal decline for participant i is $(Y_{i2} - Y_{i1}) / (Y_{i2} - Y_{i0}) = 0.827$ (or 82.7%). The means and SDs of these estimates are provided in table 1. Based on these values, the mean percent of overall global cognitive loss attributable to terminal decline was 71.2% (95% bootstrapped CI 0.699–0.726).

Table 1 Separation of global cognitive decline into terminal and preterminal components^a

Cognitive trajectory component	Component label	Mean	SD	95% CI
Initial cognitive level	Y_0	0.150	0.479	
Final cognitive level without terminal decline	Y_1	-0.227	0.775	
Final cognitive level with terminal decline	Y_2	-1.042	1.242	
Terminal percent of cognitive decline	$(Y_2 - Y_1) / (Y_2 - Y_0)$	71.2		0.699–0.726

Abbreviation: CI = credible interval.

^a Mean and SD or 95% CI of cognitive trajectory components in 1,071 persons estimated from a mixed-effects change point model adjusted for age at death, education, and sex.

To account for medical comorbidities, we repeated the mixed-effects model with a term added for the number of common chronic conditions present during follow-up (mean 2.23, SD 1.26, range 0–6). In this analysis, the mean percent of global cognitive loss attributable to terminal decline was identical to the original analysis (mean 71.2%; 95% bootstrapped CI 0.698–0.725).

Terminal decline in cognitive domains

Although terminal decline tends to globally affect cognitive function, preterminal cognitive change is often domain-specific,²⁶

suggesting that the proportion of loss attributable to terminal decline may vary across cognitive domains. To address this issue, we repeated analyses separately with composite measures of specific cognitive domains as the outcomes instead of the global cognitive measure (table 2). Figures 2 and 3, which are based on these models, show that the rate of decline in each cognitive domain markedly accelerated a mean of 3–4 years before death. On the basis of these analyses, terminal decline accounted for a mean of 70% of episodic memory loss, 65% of semantic memory loss, 57% of working memory loss, 52% of perceptual speed loss, and 53% of visuospatial ability loss (table 3).

Incident cognitive disorders during terminal period

The association of terminal decline with incident dementia, another indicator of cognitive loss, has been difficult to establish.^{5–7,27} During follow-up, 524 individuals (48.9%) developed incident dementia. To determine how often the diagnosis was made proximate to death, we used the estimates of each person's preterminal and terminal periods derived from the initial mixed-effects analysis of the composite measure of global cognition. Of the 524 diagnoses, 180 (34.4%) were made during the preterminal period and 344 (65.7%) were made during the terminal period. The dementia incidence rate per 1,000 person-years during the terminal period was 134.6 (95% confidence interval 121.3–148.9), more than 6 times the rate during the preterminal period (20.4, 95% confidence interval 17.2–23.9).

Little is known about the association of terminal decline with MCI, the precursor of dementia. At study baseline, 296

Figure 2 Terminal decline in global cognition

Figure 3 Terminal decline in cognitive domains

persons had MCI, leaving 775 with no cognitive impairment. During follow-up, 582 individuals (75.1%) developed incident MCI, 380 (65.3%) during the preterminal period and 202 (34.7%) during the terminal period. The MCI incidence rates per 1,000 person-years during the preterminal (85.3, 95% confidence interval 77.0–94.4) and terminal (96.9, 95% confidence interval 84.0–111.3) periods were similar.

Discussion

In a group of more than 1,000 older persons without dementia at study enrollment, we assessed cognitive function at annual intervals for up to 24 years before death. There was a more than 7-fold increase in rate of global cognitive decline beginning a mean of 3–4 years before death, consistent with the terminal decline hypothesis. Analyses suggested that this terminal acceleration accounted for approximately 71% of late-life global cognitive decline in this cohort. The results suggest that most cognitive decline in old age is related to mortality.

The terminal decline hypothesis was originally formulated to help explain loss of cognition in old age. Thus, Kleemeier¹ proposed that age differences in cognition “may be accounted for to a substantial degree by the presence of terminal drop or decline” (page 294). Similarly, Riegel and Riegel¹¹ argued that age-related cognitive decline “is an artifact produced by the increasing occurrence of terminal drops during the later years” (page 314). However, little data on the proportion of cognitive aging attributable to impending death have been published.

Current knowledge is based primarily on studies comparing rates of cognitive change in decedents and survivors,^{4,9,28,29} but this approach assumes that decedents and survivors are comparable, which is unlikely,⁵ and lacks information on distance to death in survivors, complicating interpretation of subgroup differences. By contrast, the approach in the present study is based on person-specific estimates of rates of terminal and preterminal decline, allowing us to directly calculate the proportion of each individual’s cognitive trajectory associated with impending mortality.

There was evidence of terminal decline in each of the 5 cognitive domains assessed, consistent with previous analyses suggesting that terminal cognitive decline is predominantly global.²⁶ However, we are not aware of published data on the terminal proportion of loss in different cognitive domains. In the present analyses, terminal decline accounted for approximately 50%–70% of loss in specific cognitive domains. Although there was substantial terminal decline in perceptual speed, it accounted for only about half of total perceptual speed loss because during the preterminal period, perceptual speed declined at approximately twice the rate of other cognitive functions (table 3), consistent with prior research in these²⁶ and other^{30–32} cohorts suggesting that loss of perceptual speed tends to precede loss of other cognitive functions in adulthood and old age.

A novel feature of the parent studies from which these data were drawn is that clinical diagnosticians were blinded to previously collected data, making change in cognitive function

Table 2 Trajectories of change in cognitive domains^a

Cognitive domain	Model term	Estimate	95% Credible interval
Episodic memory	Intercept	-1.312	-1.427, -1.195
	Preterminal time	-0.041	-0.048, -0.033
	Change point	-3.7	-3.9, -3.5
	Terminal time	-0.324	-0.351, -0.296
Semantic memory	Intercept	-1.413	-1.533, -1.293
	Preterminal time	-0.043	-0.048, -0.037
	Change point	-3.0	-3.2, -2.8
	Terminal time	-0.367	-0.407, -0.331
Working memory	Intercept	-1.003	-1.099, -0.905
	Preterminal time	-0.036	-0.042, -0.030
	Change point	-3.3	-3.5, -3.0
	Terminal time	-0.234	-0.267, -0.204
Perceptual speed	Intercept	-1.689	-1.796, -1.582
	Preterminal time	-0.072	-0.080, -0.065
	Change point	-3.8	-4.0, -3.6
	Terminal time	-0.328	-0.357, -0.300
Visuospatial ability	Intercept	-1.025	-1.120, -0.927
	Preterminal time	-0.036	-0.043, -0.029
	Change point	-3.2	-3.5, -2.9
	Terminal time	-0.188	-0.221, -0.157

^a From mixed-effects change point models adjusted for age at death, education, and sex. The terms for preterminal and terminal time indicate the mean annual rate of change in the cognitive outcome measure.

and incident cognitive conditions relatively independent outcomes. Based on the person-specific estimates of the onset of the terminal period derived from the core mixed-effects model, we calculated that the incidence rate of dementia during the terminal period was more than 6-fold higher than the rate during the preterminal period, underscoring the

severe loss of cognition occurring during the terminal period. An unexpected finding was that MCI incidence during the preterminal and terminal periods was similar, possibly reflecting the relatively brief duration of the terminal period in conjunction with very gradual worsening of cognition in the prodromal phase of MCI.³³

Table 3 Terminal and preterminal components of decline in different cognitive domains^a

Cognitive domain	Initial level, mean (SD)	Final level no TD, Mean (SD)	Final level with TD, Mean (SD)	Terminal percent, mean (95% CI)
Episodic memory	0.171 (0.605)	-0.194 (1.134)	-1.034 (1.452)	70.3 (0.684–0.722)
Semantic memory	0.150 (0.547)	-0.262 (0.796)	-1.062 (1.446)	65.1 (0.637–0.664)
Working memory	0.126 (0.596)	-0.211 (0.653)	-0.795 (1.012)	57.3 (0.558–0.588)
Perceptual speed	0.034 (0.728)	-0.674 (1.031)	-1.438 (1.231)	51.7 (0.502–0.532)
Visuospatial ability	-0.031 (0.620)	-0.347 (0.770)	-0.742 (0.934)	53.3 (0.513–0.552)

Abbreviations: CI = credible interval; TD = terminal decline.

^a Person-specific estimates from 5 mixed-effects change point models adjusted for age at death, education, and sex.

The factors underlying the association of impending death with accelerated cognitive decline are uncertain. In clinical-pathologic studies, postmortem markers of common neurodegenerative and cerebrovascular conditions have been associated with more rapid terminal cognitive decline.^{34–36} Thus, the link between mortality and cognitive decline is probably due in part to the lethal nature of these underlying neurodegenerative and cerebrovascular conditions. However, these conditions account for less than half of the variability in terminal cognitive decline and account for as much as or more of the variability in preterminal cognitive decline.^{34,35} Therefore, factors other than these pathologic conditions must be contributing to the marked acceleration in cognitive decline during the last years of life. It is likely that increasing frailty³⁷ and the adverse consequences of precipitous cognitive decline (e.g., reduced self-care, awareness of symptoms, treatment/medication compliance) also contribute to the association of mortality with cognitive decline.

That most late-life loss of cognition is attributable to mortality-related and neuropathology-related factors rather than aging per se has important implications. Perhaps the most important is that evidence of cognitive decline in older persons should be interpreted as a sign of illness rather than a sign of getting older. In addition, although demographic variables (i.e., age,^{38,39} race/ethnicity²⁸) and personality⁴⁰ have been associated with terminal cognitive decline, there is limited knowledge of factors contributing to individual differences in its onset or rate. Better understanding of the sources of variability in terminal cognitive decline might suggest novel therapeutic targets.

This study has important limitations and strengths. The main limitation is that participants were selected and so the generalizability of the findings remains to be determined. In particular, further study of terminal cognitive decline in groups with a broader representation of socioeconomic strata and racial and ethnic minorities is needed. The main strength is that participants were assessed annually for a mean of more than 10 years with psychometrically sound cognitive outcomes, a high rate of follow-up participation, and final assessments proximate to death, enhancing our ability to track nonlinear cognitive change during the last years of life.

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Disclosure

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Sue E. Leurgans, PhD	Rush University Medical Center	Author	Critical revision of manuscript for intellectual content
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Continued

Appendix (continued)

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References

- Kleemeier RW. Intellectual change in the senium. In: Proceedings of the Social Statistic Section of the American Statistical Association. Washington, DC: American Statistical Association; 1962:290–295.
- Siegler IC. The terminal drop hypothesis: fact or artifact? *Exp Aging Res* 1975;1: 169–185.
- Bosworth HB, Siegler IC. Terminal change in cognitive function: an updated review of longitudinal studies. *Exp Aging Res* 2002;28:299–315.
- Wilson RS, Beckett LA, Bienias JL, Evans DA, Bennett DA. Terminal decline in cognitive function. *Neurology* 2003;60:1782–1787.
- Sliwinski MJ, Stawski RS, Hall CB, Katz M, Verghese J, Lipton R. Distinguishing preterminal and terminal cognitive decline. *Eur Psychol* 2006;11:172–181.
- Laukka EJ, MacDonald SW, Backman L. Terminal-decline effects for select cognitive tasks after controlling for preclinical dementia. *Am J Geriatr Psychiatry* 2008;26: 355–365.
- Thorvaldsson V, Hofer SM, Berg S, Skoog I, Sacuiu S, Johansson B. Onset of terminal decline in cognitive abilities in individuals without dementia. *Neurology* 2008;71: 882–887.
- MacDonald SWS, Hultsch DF, Dixon RA. Aging and the shape of cognitive change before death: terminal decline or terminal drop? *J Gerontol B Psychol Sci Soc Sci* 2011;66:292–301.
- Wilson RS, Beck TL, Bienias JL, Bennett DA. Terminal cognitive decline: accelerated loss of cognition in the last years of life. *Psychosom Med* 2007;69:131–137.
- Karr JE, Graham RB, Hofer SM, Muniz-Terrera G. When does cognitive aging begin? A systematic review of change point studies on accelerated decline in cognitive and neurological outcomes preceding mild cognitive impairment, dementia, and death. *Psychol Aging* 2018;33:195–218.
- Riegel KF, Riegel RM. Development, drop, and death. *Develop Psychol* 1976;6: 306–319.
- Small BJ, Backman L. Time to death and cognitive performance. *Curr Dir Psychol Sci* 1999;8:168–172.
- Bennett DA, Buchman AS, Boyle PA, Barnes LL, Wilson RS, Schneider JA. Religious orders study and memory and aging project. *J Alzheimers Dis* 2018;64:S161–S189.
- Wilson RS, Mendes de Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA* 2002;287:742–748.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984;34:939–944.
- Wilson RS, Beckett LA, Barnes LL, et al. Individual differences in rates of change in cognitive abilities of older persons. *Psychol Aging* 2002;17:179–193.
- Wilson RS, Barnes LL, Bennett DA. Assessment of lifetime participation in cognitively stimulating activities. *J Clin Exp Neuropsychol* 2003;25:634–642.
- Wilson RS, Barnes LL, Krueger KR, Hoganson G, Bienias JL, Bennett DA. Early and late life cognitive activity and cognitive systems in old age. *J Int Neuropsychol Soc* 2005;11:400–407.
- Wilson RS, Aggarwal NT, Barnes LL, Bienias JL, Mendes de Leon CF, Evans DA. Biracial population study of mortality in mild cognitive impairment and Alzheimer's disease. *Arch Neurol* 2009;66:767–772.
- Hall CB, Lipton RB, Sliwinski M, Stewart WF. A change point model for estimating the onset of cognitive decline in preclinical Alzheimer's disease. *Stat Med* 2000;19:1555–1566.
- McArdle JJ, Wang L. Modeling age-based turning points in longitudinal life-span growth curves of cognition. In: Cohen P, editor. *Applied Data Analytic Techniques for Turning Points Research*. New York: Routledge; 2008.
- Wilson RS, Segawa E, Boyle PA, Anagnos SE, Hizez LP, Bennett DA. The natural history of cognitive decline in Alzheimer's disease. *Psychol Aging* 2012;27: 1008–1017.
- Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: evolution, critique and future directions (with discussion). *Stat Med* 2009;28:3049–3082.
- Gelman A, Carli JB, Stern HS, Rubin DB. *Bayesian Data Analysis*. New York: Chapman and Hall; 2004.
- Yu L, Boyle P, Wilson RS, et al. A random change point model for cognitive decline in Alzheimer's disease and mild cognitive impairment. *Neuroepidemiol* 2012;39:73–83.
- Wilson RS, Segawa E, Hizez LP, Boyle PA, Bennett DA. Terminal dedifferentiation of cognitive abilities. *Neurology* 2012;78:1116–1122.
- Laukka EJ, MacDonald SWS, Backman L. Contrasting cognitive trajectories of impending death and preclinical dementia in the very old. *Neurology* 2006;66:833–838.
- Wilson RS, Rajan KB, Barnes LL, et al. Terminal decline of episodic memory and perceptual speed in a biracial population. *Neuropsychol Dev Cogn B Aging Neuro-psychol Cogn* 2018;25:378–389.
- Bosworth HB, Schaie KW, Willis SL, Siegler IC. Age and distance to death in the Seattle Longitudinal Study. *Res Aging* 1999;21:723–738.
- Salthouse TA. The processing-speed theory of adult aged differences in cognition. *Psychol Rev* 1966:403–428.
- Finkel D, Reynolds CA, McArdle JJ, Pedersen NL. Age changes in processing speed as a leading indicator of cognitive aging. *Psychol Aging* 2007;22:558–568.
- Deary IJ, Ritchie SJ. Processing speed differences between 70- and 83-year olds matched on childhood IQ. *Intelligence* 2016;55:28–33.
- Wilson RS, Leurgans SE, Boyle PA, Bennett DA. Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. *Arch Neurol* 2011;68:351–356.
- Wilson RS, Leurgans SE, Boyle PA, Schneider JA, Bennett DA. Neurodegenerative basis of age-related cognitive decline. *Neurology* 2010;75:1070–1078.
- Boyle PA, Wilson RS, Yu L, et al. Much of late life cognitive decline is not due to common neurodegenerative pathologies. *Ann Neurol* 2013;74:478–489.
- Wilson RS, Capuano AW, Bennett DA, Schneider JA, Boyle PA. Temporal course of neurodegenerative effects on cognition in old age. *Neuropsychology* 2016;30: 591–599.
- Wallace LMK, Theou O, Godin J, Andrew MK, Bennett DA, Rockwood K. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. *Lancet Neurol* 2019;18:177–184.
- Muniz-Terrera G, van den Hout A, Piccinin AM, Matthews FE, Hofer SM. Investigating terminal decline: results from a UK population-based study of aging. *Psychol Aging* 2013;28:377–385.
- Muniz-Terrera G, Matthews FE, Steohan B, Brayne C, CC75C Collaboration Group. Are terminal decline and its potential indicators detectable in population studies of the oldest old? *Int J Geriatr Psychiatry* 2011;26:S84–S92.
- Wilson RS, Boyle PA, Yu L, Segawa E, Sytsma J, Bennett DA. Conscientiousness, dementia related pathology, and trajectories of cognitive aging. *Psychol Aging* 2015; 30:74–82.