HHS Public Access

Author manuscript

Cogn Behav Neurol. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Cogn Behav Neurol. 2017 September ; 30(3): 81–89. doi:10.1097/WNN.0000000000000131.

Semantic Memory in the Clinical Progression of Alzheimer Disease

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Abstract

Background and Objective—Semantic memory measures may be useful in tracking and predicting progression of Alzheimer disease. We investigated relationships among semantic memory tasks and their 1-year predictive value in women with Alzheimer disease.

Methods—We conducted secondary analyses of a randomized clinical trial of raloxifene in 42 women with late-onset mild-to-moderate Alzheimer disease. We assessed semantic memory with tests of oral confrontation naming, category fluency, semantic recognition and semantic naming, and semantic density in written narrative discourse. We measured global cognition (Alzheimer Disease Assessment Scale, cognitive subscale), dementia severity (Clinical Dementia Rating sum of boxes), and daily function (Activities of Daily Living Inventory) at baseline and 1 year.

Results—At baseline and 1 year, most semantic memory scores correlated highly or moderately with each other and with global cognition, dementia severity, and daily function. Semantic memory task performance at 1 year had worsened one-third to one-half standard deviation. Factor analysis of baseline test scores distinguished processes in semantic and lexical retrieval (semantic recognition, semantic naming, confrontation naming) from processes in lexical search (semantic density, category fluency).The semantic–lexical retrieval factor predicted global cognition at 1 year. Considered separately, baseline confrontation naming and category fluency predicted dementia severity, while semantic recognition and a composite of semantic recognition and semantic naming predicted global cognition. No individual semantic memory test predicted daily function.

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The authors declare no conflicts of interest.

Conclusions—Semantic–lexical retrieval and lexical search may represent distinct aspects of semantic memory. Semantic memory processes are sensitive to cognitive decline and dementia severity in Alzheimer disease.

Keywords

Alzheimer disease; naming; narrative writing; raloxifene; semantic memory

Cognitive processing depends on activity among interconnected nerve cell populations, mediated by synaptic connections. Synapses are lost early in the course of Alzheimer disease (DeKosky et al, 1990; Overk et al, 2014), the most common cause of dementia (Alzheimer's Association, 2016). This loss, more than the pathologic burden of characteristic neuritic plaques and neurofibrillary tangles, is the principal morphologic substrate of cognitive decline in this disorder (DeKosky et al, 1990; Overk et al, 2014).

Impaired episodic memory, a common initial symptom of Alzheimer disease, reflects early pathologic changes in the hippocampus and adjacent entorhinal cortex. Episodic memory—as assessed, for example, by list learning or story recall—reaches a nadir relatively early in the disease course (Locascio et al, 1995; Welsh et al, 1992). Other cognitive domains are increasingly affected as the cerebral association cortex becomes progressively involved (Braak et al, 1991).Semantic memory requires large networks of neurons in the modality-specific association cortex and heteromodal association cortex (Peelle et al, 2014), and measures of semantic memory offer a potentially sensitive window on progression in patients with manifest disease.

Semantic deficits can be assessed in several ways. Common tasks involve confrontation naming (eg, naming a visual stimulus, such an object or the picture of an object) and category fluency (generating word names constrained by semantic relatedness). Other approaches include tests of semantic memory retrieval (eg, retrieval of an object name on the basis of described attributes) and semantic density in structured discourse (number of content words elicited from oral or written narratives).

Here we report secondary analyses of patients with mild–to–moderate dementia from Alzheimer disease, whose assessments at baseline and 1 year later included neuropsychological measures of confrontation naming, category fluency, semantic memory retrieval, and semantic density in written discourse (Henderson et al, 2015). In this study we examined the extent to which these purported measures of semantic memory related to each other and other cognitive measures; the extent to which these measures reflected dementia staging indicated by assessments of global cognition, dementia severity, and daily function; and the extent to which baseline task performance predicted disease progression. We hypothesized that the semantic memory measures would be associated with dementia staging both in baseline cross-sectional analyses and at 1 year in longitudinal analyses.

Methods

Participants

The participants were 42 community-dwelling women aged 68 to 89 years with probable Alzheimer disease (McKhann et al, 1984) of mild or moderate severity. They had enrolled in a three-site randomized clinical trial of oral raloxifene hydrochloride versus placebo in women with Alzheimer disease (Henderson et al, 2015). Raloxifene is a selective estrogen receptor modulator approved to treat osteoporosis in postmenopausal women.

The trial protocol is registered at ClinicalTrials.gov (NCT00368459), and the study was approved by the Stanford University Institutional Review Board. Participants provided written informed consent, or assent with the written consent of their next of kin or a legally authorized representative.

We gave the treatment and placebo groups cognitive and noncognitive tests at baseline and 1 year. The primary clinical trial endpoint was change in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog). Results at 1 year failed to suggest cognitive, global, or functional benefit for the women in the raloxifene group (Henderson et al, 2015).

Cognitive Tasks

We assessed semantic memory with five verbal measures:

- **Oral confrontation naming:** 30-item version of the Boston Naming Test (Mack et al, 1992). We scored the number of line drawings correctly named without phonemic cues.
- **Oral category fluency:** animal naming. We scored the number of unique animal names generated in 60 seconds (Troyer, 2000).
- **Oral semantic memory retrieval (two measures):** Semantic Object Retrieval Test (Kraut et al, 2006, 2007). Participants first judge semantic associations by deciding whether the combination of two object features leads to the retrieval of a specific object memory and, for any *yes* response, they then name the object. We scored separately for semantic recognition (the number of correct *yes* [eg, desert and humps] and *no* [eg, propeller and ink]responses) and for semantic naming (for correct *yes* responses, the correct name of the object suggested by the two features [eg, “camel” for desert and humps]).
- **Semantic density in a written narrative:** the cookie theft picture from the Boston Diagnostic Aphasia Examination (Goodglass et al, 2001).We showed the participants a line drawing that depicts children stealing cookies. We gave the participants a blank sheet of paper and instructed, “In the space provided, write as much as you can about what you see going on in this picture” (Appendix A).We scored the number of key people, objects, and actions (Henderson et al, 1992) that the participants wrote in their description.

We evaluated other cognitive domains with these tests:

- East Boston Memory Test: immediate and delayed recall of a paragraph story (Scherr et al, 1988)
- List learning: immediate and delayed recall of the ADAS-cog word list (Rosen et al, 1984)
- A digit ordering task (MacDonald et al, 2001)
- Trail Making Test, Parts A and B (Reitan, 1958)
- Maze completion and number cancellation developed as supplemental tasks for the ADAS-cog (Mohs et al, 1997)
- A visuoconstructive (drawing) task embedded within the ADAS-cog (Rosen et al, 1984)
- The narrative writing score from the cookie theft picture, based on writing mechanics, vocabulary access, syntax, and adequacy of content (Goodglass et al, 2001)
- Mini-Mental State Examination (Folstein et al, 1975)

We determined global cognition psychometrically with the:

- ADAS-cog total score (Rosen et al, 1984). The ADAS-cog is a common cognitive endpoint in clinical trials of patients with Alzheimer disease

Noncognitive Endpoints

In addition to global cognition assessed with the ADAS-cog, our other endpoints were dementia severity and daily function. A certified examiner used information from each participant and a knowledgeable informant to rate her dementia severity with the Clinical Dementia Rating sum of boxes score (Morris, 1993). We assessed her daily function during the preceding 4 weeks with the informant-based Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory of basic and instrumental activities (Galasko et al, 1997).

Statistical Analyses

We examined Pearson correlations among cognitive variables and trial endpoints. For semantic memory measures, we calculated standardized 1-year change scores using baseline standard deviations. Because semantic recognition and semantic naming scores correlated highly (see below), we also calculated a semantic retrieval composite score as a simpler single measure. The composite score took into account a chance score of 16 on the recognition task. We calculated the semantic retrieval composite score as semantic recognition minus 16 (minimum value set at 0) plus semantic naming (range of possible scores = 0 to 32).

We performed a factor analysis on baseline scores of the cognitive tests to reduce these correlated variables to a smaller set of factors that might represent distinct cognitive abilities. We standardized the 17 baseline test scores to a mean of 0 and a standard deviation of 1 before performing the factor analysis. The only missing baseline scores were baseline maze

scores from five participants. We imputed those missing scores using single imputation by fitting a linear regression model to the sample, with baseline maze score as the outcome and baseline composite cognitive score as the main predictor. We then calculated a baseline composite cognitive score using all 17 baseline scores, as described previously (Henderson et al, 2012). We used an orthogonal varimax rotation procedure to make factors more interpretable.

We modeled associations between cognitive factors and outcome measures separately using multivariable linear regression analysis. We adjusted the analyses for participant age, education, raloxifene versus placebo group, and baseline value of the outcome variable. Similar analyses considered the relation between baseline scores on semantic memory tasks and 1-year outcomes, again adjusting for age, education, raloxifene versus placebo group, and baseline value of the outcome variable.

For the analyses we used Statistical Analysis System (SAS®) Version 9.4 (SAS Institute, Inc, Cary, North Carolina).

We set two-tailed statistical significance at $P < 0.05$.

Results

As shown in Table 1, all 42 of the participants contributed data for our baseline analyses, and 39 contributed data for the analyses at 1 year.

At baseline, most semantic memory measures correlated highly (large effect size, $r \geq 0.50$) or moderately (medium effect size, $0.50 > r \geq 0.30$) with each other; with global cognition (ADAS-cog), dementia severity (Clinical Dementia Rating sum of boxes), and daily function (Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory) (Table 2); and with most other cognitive test scores (Appendix B). All correlations were in the expected direction. Semantic recognition and semantic naming from the Semantic Object Retrieval Test were highly correlated ($r = 0.84$).

At 1 year, correlations among semantic memory measures and between semantic memory measures and outcome measures were generally similar to those at baseline (Table 2). As expected, outcome measures also correlated highly with each other at baseline (r absolute values =0.59 to 0.81) and 1 year (0.66 to 0.81).

For semantic memory tests, mean standardized 1-yearchange scores ranged from one-third to one-half standard deviation for the patients assessed at both time points (Table 3). These change scores were higher than most, but not all, of the standardized change scores for the other neuropsychological tests (Appendix C).

In the factor analysis, a five-factor solution accounted for 97% of the variance (Table 4). The first of these uncorrelated factors (eigenvalue = 8.08, 67% of the variance explained) reflected search of the semantic lexicon as well as aspects of visual attention. We found high loadings for (in descending order) semantic density, narrative writing, and Part A of the Trail

Making Test; number cancellation, category fluency, and maze completion also loaded on this factor.

Factor 2 (eigenvalue = 1.34, 11% of variance) represented semantic retrieval and lexical retrieval, with the high loadings on semantic naming, semantic recognition, digit ordering, and confrontation naming.

Factor 3 (eigenvalue = 1.04, 8% of variance) incorporated aspects of executive functions, particularly those dependent on visuoconstruction and visual attention. The high loadings were on drawings, maze completion, digit ordering, and Parts A and B of the Trail Making Test. Confrontation naming and the Mini-Mental State Examination also loaded on this factor.

The fourth (eigenvalue =0.85, 7% of variance) and fifth (eigenvalue = 0.67, 5%of variance) factors primarily represented aspects of episodic memory. Factor 4, which we designated *learning*, had high loadings on the East Boston Memory Test paragraph immediate recall, number cancellation, word list immediate recall, and the Mini-Mental State Examination. Factor 5, which we designated *memory,* had high loadings on word list delayed recall and the East Boston Memory Test paragraph delayed recall; category fluency also loaded on this factor.

In linear regression models to predict 1-year global cognition, dementia severity, and daily function, only the executive functions factor (factor 3) predicted all three outcomes (Table 5). The semantic–lexical retrieval factor (factor 2) independently predicted change in global cognition, and the memory factor (factor 5) independently predicted change in dementia severity.

In the models that considered baseline values of each of the semantic memory measures separately, significant predictors of 1-year outcomes were semantic recognition (for global cognition), category fluency (for dementia severity), and confrontation naming (also for dementia severity) (Table 6).The baseline value of the semantic retrieval composite score also predicted change in global cognition. None of the baseline semantic memory measures were related to daily function1year later.

Discussion

During the raloxifene randomized clinical trial (Henderson et al, 2015), values of most semantic memory tasks—oral confrontation naming, oral semantic fluency, oral semantic memory retrieval (recognition and naming), and written semantic density—correlated significantly with each other, but these five measures did not load on a common factor. Instead, they loaded on two uncorrelated factors and thus appear to distinguish two distinct aspects of semantic memory. The first aspect concerns processes in semantic retrieval and lexical retrieval: semantic recognition, semantic naming, and confrontation naming, ie, factor 2 of this study, semantic–lexical retrieval. The second aspect relates to processes in lexical search: semantic density in written discourse and category fluency, ie, factor 1 of this study, lexical search–visual attention. This dichotomy was not absolute, however, as

confrontation naming contributed to a second factor, executive functions (factor 3), and category fluency contributed to a second factor, memory (factor 5).

Global cognition, dementia severity, and daily function are related concepts used for dementia staging. Global cognition is a direct neuropsychological measure, daily function reflects the real-world consequences of neuropsychological and behavioral deficits, and dementia severity incorporates aspects of both. As we had hypothesized, in cross-sectional analyses semantic memory measures were significantly associated with dementia staging at baseline and—apart from nonsignificant correlations of confrontation naming and category fluency with daily function—with dementia staging at 1 year. Also, as hypothesized, some—although not most—baseline semantic memory test scores were closely related to global cognition and dementia severity at 1 year. Contrary to our prediction, none of the baseline semantic memory test scores were related to daily function at 1 year.

Of the five unrelated cognitive factors, semantic–lexical retrieval predicted global cognition 1 year after baseline assessment, but lexical search–visual attention did not. Activities of daily living are closely related to neuropsychological measures of executive function (Martyr et al, 2012). We found that the executive functions factor was the best overall predictor, in that it related not only to daily function, but also to global cognition and dementia severity outcomes. The memory factor (although not the learning factor) predicted dementia severity but, consistent with other reports (Locascio et al, 1995; Welsh et al, 1992), neither the learning nor the memory factor predicted global cognitive decline in our sample of women with mild or moderate dementia.

Of the individual semantic memory measures, baseline values of both confrontation naming and category fluency predicted dementia severity at 1 year, and semantic recognition from the Semantic Object Retrieval Test predicted global cognition. Confrontation naming and category fluency, but not semantic recognition, are widely used in neuropsychological batteries to assess patients with Alzheimer disease in both clinical and research settings. At baseline, the semantic retrieval composite score—derived from semantic recognition and semantic naming scores—also predicted global cognition.

These results suggest that aspects of semantic memory may be sensitive predictors of disease severity and cognitive decline in patients with mild-to-moderate dementia from Alzheimer disease but do not predict functional decline. One-year change scores of one-third to one-half standard deviation for our individual semantic memory measures suggest that these tests should be sensitive to therapeutic interventions targeting cognitive impairment in patients at similar stages of their illness. We also found large mean 1-year change scores for immediate recall on the East Boston Memory Test and for maze completion. Semantic deficits can start earlier in the course of Alzheimer disease (Kraut et al, 2007; Verma et al, 2012), but we did not study participants with preclinical disease. Our results also support the usefulness of some executive function tasks in predicting and monitoring disease progression.

We derived each factor from correlated neuropsychological test scores, and the failure of our lexical search–visual attention factor to predict 1-year outcomes could be explained by the

inclusion of variables unrelated to lexical search. The sample size in this study was small, and our factor structure requires replication in larger cohorts of older adults at similar stages of dementia. Factor loadings might differ for cognitively normal women or for women with severe dementia. We did not include men in our sample, and patterns of cognitive impairment in dementia may differ between men and women (Buckwalter et al, 1996; Henderson et al, 1994; Moreno-Martinez et al, 2008).

Although half of our participants received raloxifene as part of the clinical trial, treatment should not have affected our findings. The intervention had no effect on the participants' cognition, disease severity, or daily function at 1 year, and we adjusted our analyses for whether participants were in the raloxifene or placebo group.

Acknowledgments

The authors thank the anonymous reviewers for their constructive comments and John Hart, Jr, MD, for helpful comments on an early draft of the manuscript. The authors are especially grateful to the participants in the raloxifene clinical trial.

Supported in part by National Institutes of Health grants R01 AG023038 and P50 AG047366 (V.W.H.).

Appendix A

Scoring the Test of Narrative Writing Semantic Density

Scoring Template for the Cookie Theft Picture: Key People, Objects, and Actions					
	✓		Examples and Explanation	Exclusions	Comments
Key Categories: People and Objects					
1		**Introduction**	Kitchen [scene], domestic setting, scene from the 1950s, story [of a distracted housewife]		
2		**Boy**	Son, brother, lad (accept “children” if girl is mentioned; accept “child” or “youngster” if girl is not mentioned)		
3		**Girl**	Sister, daughter (accept “children” if boy is mentioned)		
4		**Woman**	Mother, mom, Mrs., wife, lady, older sister, adult, grown-up		
5		**Cookie**		Not: cookie jar	
6		**Jar**	Container, canister		
7		**Stool**	Chair	Not: ladder, bench	
8		**Sink**	Faucet, drain		
9		**Water**		Not: water faucet	
10		**Dishes**	Plate (the plate held by the woman, stated or implied)		
11		**Window**	Curtain, drapes		
12		**Outside**	Something outside the window (eg, tree, yard, sidewalk, hedges, nice day)		
13		**Clothing**	Article of clothing (eg, apron, shoe, shorts) or comment on personal appearance of woman, boy, or girl (eg, short hair, neat, well-groomed)		

Scoring Template for the Cookie Theft Picture: Key People, Objects, and Actions					
	✓		**Examples and Explanation**	**Exclusions**	**Comments**
14		**Cabinet**	Cupboard, closet, shelf, lid		
15		**Counter**	Sideboard, items on counter (cups, dishes, counter plate [but not the plate held by the woman])		
Key Categories: Actions					
16		**Stealing** [boy]	Grabbing, taking, reaching, holding, getting [cookie]	Not: eating [cookie]	
17		**Falling** [boy or stool]	Tilting, losing balance, slipping, toppling	Not: dangerous, reckless, be careful, accident	
18		**Overflowing** [water]	Spilling, has too much water		
19		**Washing** [woman]	Drying, wiping, cleaning, doing [dishes]		
20		**Action** [girl]	Any depicted action by the girl: shushing, gesturing for quiet, girl receiving cookie (or, equivalently, boy giving cookie to girl), girl eating cookie		
21		**Unawareness** [woman]	Unconcern, ignoring, daydreaming, distracted, not paying attention, mind is somewhere else, thinking of something else		
Total /21 semantic density score					

Appendix B

Baseline Pearson Correlations Among Neuropsychological Test Scores

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1 Confrontation naming[1]															
2 Category fluency[2]	**0.40**														
3 Semantic recognition[3]	**0.53**	**0.47**													
4 Semantic naming[3]	**0.48**	**0.48**	**0.84**												
5 Semantic density[4]	0.24	**0.62**	**0.54**	**0.40**											
6 EBMT, immediate recall[5]	0.17	**0.39**	**0.45**	0.24	**0.36**										
7 EBMT, delayed recall[5]	0.29	**0.47**	**0.32**	**0.39**	**0.31**	0.27									
8 List-learning, immediate recall[6,7]	**0.42**	**0.57**	**0.61**	**0.60**	**0.52**	**0.60**	**0.35**								
9 List-learning, delayed recall[6,7]	0.18	**0.32**	0.18	0.19	**0.34**	**0.45**	**0.46**	**0.53**							
10 Digit ordering[8]	**0.56**	**0.49**	**0.67**	**0.59**	**0.39**	**0.51**	**0.32**	**0.66**	0.22						

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
11 Trail Making Test, Part A[9]	**0.32**	**0.58**	**0.54**	**0.42**	**0.64**	**0.38**	0.24	**0.53**	0.13	**0.62**						
12 Trail Making Test, Part B[9]	**0.39**	0.28	0.17	0.08	**0.36**	0.23	0.00	**0.44**	0.25	**0.40**	0.25					
13 Maze completion[10]	0.25	**0.40**	**0.39**	0.27	**0.54**	**0.35**	0.16	**0.51**	0.19	**0.60**	**0.72**	**0.42**				
14 Number cancellation[10]	0.22	**0.42**	**0.56**	**0.49**	**0.63**	**0.53**	0.13	**0.63**	0.29	**0.63**	**0.66**	**0.31**	**0.67**			
15 Drawings[6,7]	**0.35**	**0.41**	0.23	0.22	**0.41**	0.20	0.15	**0.41**	0.19	**0.51**	**0.73**	0.30	**0.62**	**0.49**		
16 Narrative writing[11]	**0.31**	**0.60**	**0.55**	**0.40**	**0.92**	**0.39**	0.27	**0.58**	**0.39**	**0.43**	**0.67**	**0.36**	**0.55**	**0.60**	**0.51**	
17 Mini-Mental State Examination[12]	**0.48**	**0.63**	**0.65**	**0.51**	**0.62**	**0.66**	**0.36**	**0.76**	**0.47**	**0.65**	**0.68**	**0.38**	**0.56**	**0.68**	**0.54**	**0**

Bold type indicates correlations with nominally significant probabilities of $P < 0.05$. Correlations of ≥0.31 were nominally significant at $P < 0.05$; correlations of ≥0.40, at $P < 0.01$; correlations of ≥0.49, at $P < 0.001$; and correlations of ≥0.56, at $P < 0.0001$.

[1] Mack et al, 1982.

[2] Troyer, 2000

[3] Kraut et al, 2006, 2007.

[4] Henderson et al, 1992.

[5] Scherr et al, 1988.

[6] Rosen et al, 1984.

[7] Henderson et al, 2015.

[8] MacDonald et al, 2001.

[9] Reitan, 1958.

[10] Mohs et al, 1997.

[11] Goodglass et al, 2001.

[12] Folstein et al, 1973.

EBMT = East Boston Memory Test.

Appendix C

Standardized 1-YearChange Scores for Neuropsychological Tests Other Than Semantic Memory Measures

	Mean (Standard Deviation)	Median (Interquartile Range)
East Boston Memory Test, immediate recall[1]	-0.65 (0.94)	-0.41 (-1.2 to 0.00)
East Boston Memory Test, delayed recall[1]	-0.04 (1.02)	0.00 (-0.42 to 0.00)
Word list, immediate recall[2,3]	-0.07 (0.77)	0.00 (-0.43 to 0.43)
Word list, delayed recall[2,3]	0.07 (1.12)	0.00 (0.00 to 0.00)
Digit ordering span[4]	-0.19 (0.87)	0.00 (-0.52 to 0.00)
Trail Making Test, Part A[5]	-0.24 (0.67)	-0.05 (-0.25 to 0.01)
Trail Making Test, Part B[5]	0.01 (1.24)	0.00 (-0.37 to 0.09)
Maze completion[6]	-0.59 (1.17)	-0.04 (-1.71 to 0.06)
Number cancellation[6]	-0.24 (0.68)	-0.22 (-0.45 to 0.11)

	Mean (Standard Deviation)	Median (Interquartile Range)
Drawings[2,3]	-0.20 (0.56)	-0.27 (-0.55 to 0.00)
Narrative writing[7]	-0.23 (0.77)	-0.33 (-0.66 to 0.33)
Mini-Mental State Examination[8]	-0.36 (0.66)	-0.18 (-0.89 to 0.25)

Calculated as the difference between mean scores at 1 year and baseline, divided by the baseline standard deviation. Negative values indicate cognitive decline.

[1] Scherr et al, 1988.

[2] Rosen et al, 1984.

[3] Henderson et al, 2015.

[4] MacDonald et al, 2001.

[5] Reitan, 1958.

[6] Mohs et al, 1997.

[7] Goodglass et al, 2001.

[8] Folstein et al, 1973.

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Glossary

ADAS-cog Alzheimer's Disease Assessment Scale, cognitive subscale

Table 1
Participant Characteristics at Baseline and 1 Year Later

	Baseline (N = 42)	1 Year* (N = 39)
Age (years)	75.9 (5.1)	75.7 (4.8)
Education (years)	13.6 (2.2)	—
Dementia severity†		
Mild	25 (60)	22 (56)
Moderate	17 (40)	10 (26)
Severe	0	7 (18)
Confrontation naming[1] (0–30)	18.9 (6.1)	17.2 (7.3)
Category fluency[2] (≥ 0)	10.2 (4.8)	8.3 (4.4)
Semantic recognition[3] (16–32‡)	26.7 (3.9)	25.9 (4.8)
Semantic naming[3] (0–16)	11.0 (3.7)	9.9 (4.5)
Semantic density[4] (≥ 0)	11.5 (4.8)	10.0 (4.9)
ADAS-cog[5§] (70–0)	25.1 (11.4)	27.4 (14.4)
CDR-SOB[6§] (18–0)	6.1 (3.1)	8.0 (4.5)
ADL Inventory[7] (0-78)	60.9 (13.7)	55.2 (17.0)

Values are shown as number (percent) or mean (standard deviation). For semantic memory measures and outcome variables, the range of potential scores is shown in parentheses.

*1-year values were missing for confrontation naming (5 participants), category fluency (4), semantic recognition and naming (6), and semantic density (5).

†Defined by Mini-Mental State Examination score: mild = 20–26, moderate = 12–19, severe <12.

‡16 indicates a chance score.

§Higher values indicate greater impairment.

[1]Mack et al, 1982.

[2]Troyer, 2000.

[3]Kraut et al, 2006, 2007.

[4]Henderson et al, 1992.

[5]Rosen et al, 1984.

[6]Morris, 1993.

[7]Galasko et al, 1997.

ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive subscale. **CDR-SOB** = Clinical Dementia Rating sum of boxes. **ADL Inventory** =Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory.

Table 2

Pearson Correlations Among Semantic Memory Measures and With Outcome Measures

	Confrontation Naming[1]	Category Fluency[2]	Semantic Recognition[3]	Semantic Naming[3]	Semantic Density[4]	Semantic Retrieval Composite*
Baseline						
Category fluency	**0.40**					
Semantic recognition	**0.53**	**0.47**				
Semantic naming	**0.48**	**0.48**	**0.84**			
Semantic density	0.24	**0.62**	**0.54**	**0.40**		
Semantic retrieval composite*	**0.66**	**0.44**	**0.88**	**0.86**	**0.48**	
ADAS-cog[5†]	**-0.55**	**-0.63**	**-0.56**	**-0.51**	**-0.58**	**-0.56**
CDR-SOB[6†]	**-0.34**	**-0.59**	**-0.59**	**-0.56**	**-0.66**	**-0.55**
ADL Inventory[7]	**0.32**	**0.50**	**0.53**	**0.39**	**0.61**	**0.48**
1 Year						
Category fluency	**0.60**					
Semantic recognition	**0.70**	**0.53**				
Semantic naming	**0.75**	**0.70**	**0.82**			
Semantic density	**0.49**	**0.63**	**0.58**	**0.75**		
Semantic retrieval composite*	**0.59**	**0.54**	**0.81**	**0.85**	**0.59**	
ADAS-cog[5†]	**-0.71**	**-0.71**	**-0.67**	**-0.85**	**-0.73**	**-0.66**
CDR-SOB[6†]	**-0.57**	**-0.56**	**-0.64**	**-0.71**	**-0.74**	**-0.59**
ADL Inventory[7]	0.27	0.25	**0.38**	**0.47**	**0.59**	**0.46**

Bold type indicates correlations with nominally significant probabilities of $P < 0.05$. At baseline, correlations of ≥0.31 were nominally significant at $P < 0.05$; correlations of ≥0.40 at $P < 0.01$; correlations of ≥0.49 at $P < 0.001$; and correlations of ≥0.56 at $P < 0.0001$. At 1 year, correlations of ≥0.32 were nominally significant at $P < 0.05$; correlations of ≥0.41 at $P < 0.01$; correlations of ≥0.51 at $P < 0.001$; and correlations of ≥0.59 at $P < 0.0001$.

*Calculated post hoc from semantic recognition and semantic naming, as described in the text.

†Higher values indicate greater impairment.

1Mack et al, 1982.

2Troyer, 2000.

[3] Kraut et al, 2006, 2007.

[4] Henderson et al, 1992.

[5] Rosen et al, 1984.

[6] Morris, 1993.

[7] Galasko et al, 1997.

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Table 3
Standardized 1-Year Change Scores for Semantic Memory Measures

	Mean (Standard Deviation)	Median (Interquartile Range)
Confrontation naming[1]	-0.35 (0.63)	-0.49 (-0.66 to 0.16)
Category fluency[2]	-0.52 (0.77)	-0.42 (-0.84 to 0.00)
Semantic recognition[3]	-0.34 (0.89)	-0.26 (-0.77 to 0.38)
Semantic naming[3]	-0.41 (0.96)	0.00 (-0.83 to 0.28)
Semantic density[4]	-0.45 (0.93)	-0.64 (-1.06 to 0.00)
Semantic retrieval composite	-0.38 (0.87)	-0.31 (-1.05 to 0.21)

Calculated as the difference between mean scores at 1 year and baseline, divided by the baseline standard deviation. Negative values indicate cognitive decline.

[1] Mack et al, 1982.

[2] Troyer, 2000.

[3] Kraut et al, 2006, 2007.

[4] Henderson et al, 1992.

Table 4

Factor Loadings for Baseline Neuropsychological Test Scores

Factor	1	2	3	4	5
	Lexical Search–Visual Attention	**Semantic-Lexical Retrieval**	**Executive Functions**	**Learning**	**Memory**
Confrontation naming[1]	-0.03	0.52	0.47	-0.06	0.32
Category fluency[2]	0.45	0.33	0.29	0.11	0.44
Semantic recognition[3]	0.31	0.83	0.08	0.30	0.10
Semantic naming[3]	0.21	0.87	0.04	0.13	0.17
Semantic density[4]	0.85	0.18	0.16	0.18	0.27
East Boston Memory Test, immediate recall[5]	0.15	0.15	0.13	0.72	0.26
East Boston Memory Test, delayed recall[5]	0.14	0.30	0.02	0.04	0.57
List learning, immediate recall[6,7]	0.24	0.39	0.35	0.53	0.38
List learning, delayed recall[6,7]	0.12	-0.03	0.09	0.39	0.63
Digit ordering span[8]	0.14	0.56	0.55	0.37	0.09
Trail Making Test, Part A[9]	0.61	0.32	0.52	0.20	-0.06
Trail Making Test, Part B[9]	0.09	-0.01	0.54	0.19	0.21
Maze completion[10]	0.45	0.14	0.59	0.32	-0.08
Number cancellation[10]	0.48	0.29	0.33	0.57	-0.07
Drawings[6,7]	0.39	0.09	0.71	0.06	0.01
Narrative writing[11]	0.81	0.18	0.25	0.20	0.29
Mini-Mental State Examination[12]	0.37	0.36	0.42	0.50	0.34

Values represent correlation coefficients between neuropsychological tests and factors.

[1]Mack et al, 1982.

[2]Troyer, 2000.

[3]Kraut et al, 2006, 2007.

[4]Henderson et al, 1992.

[5] Scherr et al, 1988.
[6] Rosen et al, 1984.
[7] Henderson et al, 2015.
[8] MacDonald et al, 2001.
[9] Reitan, 1958.
[10] Mohs et al, 1997.
[11] Goodglass et al, 2001.
[12] Folstein et al, 1973.

Table 5

Baseline Cognitive Factors as Predictors of 1-Year Outcomes

	Global Cognition (ADAS-cog[1])		Dementia Severity (CDR-SOB[2])		Daily Function (ADL Inventory[3])	
Factor	**β**	***P***	**β**	***P***	**β**	***P***
1 Lexical search–visual attention	-0.72	0.64	-0.11	0.84	2.88	0.22
2 Semantic-lexical retrieval	-3.59	0.02 *	-0.43	0.37	-1.36	0.51
3 Executive functions	-3.44	0.04 *	-1.09	0.02 *	4.45	0.03 *
4 Learning	-2.39	0.13	-0.68	0.17	1.75	0.41
5 Memory	1.04	0.42	-0.83	0.04 *	-2.20	0.20

We adjusted the linear regression models for age, education, raloxifene versus placebo group, and baseline value of the outcome. Factors are in standard deviation units. A negative beta coefficient indicates that higher baseline values of a factor were associated with better global cognition, less severe dementia, and worse daily function at 1 year.

* Nominal $P < 0.05$.

[1] Rosen et al, 1984.

[2] Morris, 1993.

[3] Galasko et al, 1997.

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Table 6

Baseline Semantic Memory Test Scores as Predictors of 1-Year Outcomes

	Global Cognition (ADAS-cog[1])		Dementia Severity (CDR-SOB[2])		Daily Function (ADL Inventory[3])	
	β	*P*	β	*P*	β	*P*
Confrontation naming[4]	-0.45	0.09	-0.19	0.009*	0.08	0.78
Category fluency[5]	-0.55	0.10	-0.29	0.007*	0.34	0.41
Semantic recognition[6]	-1.16	0.001*	-0.20	0.13	0.09	0.86
Semantic naming[6]	-0.71	0.09	-0.15	0.30	0.40	0.45
Semantic density[7]	-0.17	0.62	-0.12	0.31	0.50	0.27
Semantic retrieval composite	-0.77	0.01*	-0.19	0.07	0.15	0.72

We conducted separate linear regression analyses for each baseline predictor and outcome. We adjusted the models for age, education, raloxifene versus placebo group, and baseline value of the outcome.A negative beta coefficient indicates that better semantic memory at baseline was associated with better global cognition, less severe dementia, and worse daily function at 1 year.

*Nominal $P < 0.05$.

[1]Rosen et al, 1984.

[2]Morris, 1993.

[3]Galasko et al, 1997.

[4]Mack et al, 1982.

[5]Troyer, 2000.

[6]Kraut et al, 2006, 2007.

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