Loss of basic lexical knowledge in old age

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ABSTRACT

Background Basic lexical skills are hypothesised to be relatively preserved in mild dementia, but clinical studies have reported inconsistent results.

Methods More than 400 older Catholic nuns, priests and brothers recruited from groups across the USA completed annual evaluations for up to 15 years, died and underwent brain autopsy. Each clinical evaluation included administration of a 20-item word reading test and a 15-item vocabulary test, which were combined to form a composite measure of word knowledge. In a uniform neuropathological examination, Alzheimer's disease pathology was quantified with a composite index of plaques and tangles, and the presence of gross and microscopic cerebral infarctions and Lewy bodies was recorded.

Results The post-mortem level of Alzheimer's disease neuropathology was linearly related to rate of decline in word knowledge. Decline was nearly fourfold faster at a relatively high level of pathology (75th percentile) compared with a relatively low level (25th percentile). Neocortical (but not nigral or limbic) Lewy bodies and gross (but not microscopic) cerebral infarction were also associated with a more rapid decline in word knowledge. Effects for word reading and vocabulary were similar, except that gross cerebral infarction was associated with accelerated decline in vocabulary, but not in word reading.

Conclusion Common neuropathological changes associated with late-life dementia impair word knowledge in old age, calling into question the use of word knowledge tests to estimate premorbid cognitive ability.

Word knowledge is thought to be relatively well maintained in late life,[1 2] especially when assessed with methods that minimise demands on other cognitive abilities.[3 4] Word knowledge tests of this sort, most notably the National Adult Reading Test,[5] are also hypothesised to be performed normally by persons with mild dementia[5 6] and therefore to provide an index of cognitive ability prior to dementia onset. Research examining this hypothesis has been inconclusive, however. One problem is that most longitudinal studies have had few subjects (ie, less than 100[7–13]) who have been tested on relatively few occasions (ie, two or three per subject[7 11–13]), making it difficult to characterise change in performance over time. In addition, the definition of mild dementia has varied from study to study.

The present study examines the relation of dementia to change in word knowledge. It differs from previous research, however, in that the outcome is defined by neuropathological rather than clinical manifestations. Participants were older Catholic nuns, priests and brothers from the Rush Religious Orders Study who had undergone annual testing of word knowledge and brain autopsy. In a uniform neuropathological examination, summary measures of plaques and tangles, gross and microscopic cerebral infarction, and Lewy bodies were obtained. We used mixed-effects models to characterise change in word knowledge and to test the hypothesis that decline in word knowledge is due in part to common brain lesions associated with late-life dementia.

METHODS

Participants

The subjects were older Catholic nuns, priests and brothers participating in the Rush Religious Orders Study.[14] They all agreed to annual clinical evaluations and brain autopsy at death. The study began data collection in 1994 and is ongoing. It was approved by the Institutional Review Board of Rush University Medical Center.

Eligibility for analyses required a brain autopsy plus longitudinal data on word knowledge. At the time of these analyses, 495 study participants had died, and 463 (93.5%) had undergone a brain autopsy, the results of which were pending in 14. Of the remaining 449 individuals, 34 died with only one valid word knowledge score, leaving 415 with pathological data and longitudinal clinical data. They had a mean age at baseline of 79.6 (SD=6.9) and a mean age at death of 87.1 (SD=7.0). They had a mean of 17.9 years of education (SD=3.4), and 61.7% were woman. They died a mean of 6.4 months after the last assessment of word knowledge (SD=3.9) with a mean post-mortem interval of 7.9 h (SD=8.0). All 415 had data on AD pathology, 395 had data on Lewy bodies, and 383 had data on cerebral infarction.

Assessment of word knowledge

At each annual clinical evaluation, two measures of word knowledge were administered. A 20-item reading test with items from the National Adult Reading test[5] and subsequent modifications[15 16] required reading aloud words with atypical spelling—sound correspondence (eg, epitome, impugn). A 15-item version[17] of Extended Range Vocabulary[18] required selecting the best synonym for each target word from five alternatives. Because the two tests loaded on a common factor in a previous factor analysis,[17] we used a composite measure based on both of them as the primary outcome to minimise floor and ceiling artefacts and other forms of measurement error. Raw scores on each test were converted to z scores, using the baseline mean and SD from the entire cohort, and averaged to yield the composite. Further information on each test and the derivation of the composite measure of word knowledge is published elsewhere.[17]

Neuropathological assessment

A standard protocol was followed for brain removal (at Rush and 11 predetermined sites across the USA), tissue sectioning and preservation, and quantification of pathological findings, as described in more detail elsewhere.[19 20] AD pathology was summarised in a composite measure based on counts of neuritic plaques, diffuse plaques and neurofibrillar tangles in four brain regions (entorhinal cortex, midfrontal gyrus, middle temporal gyrus, inferior parietal gyrus) using a modified Bielschowsky silver stain. For each type of AD pathology, raw counts in each region were standardised and averaged to form composite measures. The mean of the three composites measure was used as an overall index of AD pathology, as previously described.[21] Lewy bodies in six brain regions (substantia nigra, cingulate cortex, entorhinal cortex, midfrontal gyrus, middle temporal gyrus, inferior parietal gyrus) were identified with antibodies to alpha-synuclein. In analyses, persons with no Lewy bodies were contrasted with two subgroups: those with Lewy bodies in neocortex and those with Lewy bodies confined to nigral or limbic regions. All cerebral infarctions visible to the naked eye were noted, and the age of each was estimated. The presence of chronic microscopic infarcts was determined using H&E stain. Gross and microscopic infarctions were each treated as present or absent in analyses.

Data analysis

We used mixed-effects models[22] to characterise change in lexical knowledge and to test the relation of each pathological index to rate of change. The primary outcome was a composite measure of word knowledge. The first and all subsequent models included terms for time (in years since baseline) and for the potentially confounding factors of age (at death), sex and education plus their interactions with time. The term for time indicates the mean change per year in word knowledge. In a second model, we added terms for AD pathology and its interaction with time to test the association of AD pathology with level of and rate of change in word knowledge. We repeated this analysis, first excluding those with dementia at baseline and then using individual tests as outcomes instead of the composite measure of word knowledge. We conducted similar analyses of the relation of Lewy bodies and cerebral infarction to change in the three measures of word knowledge. A final series of analyses included all pathological measures in the same model.

To better understand the relationship of AD pathology to change in word knowledge, each person's annual rate of change in word knowledge (estimated from the model without pathology) was plotted against AD pathological burden score (excluding one subject with an extreme burden score) and fitted with a function that uses robust locally linear fits.[23]

RESULTS

Change in word knowledge

At baseline, scores on the composite measure of word knowledge ranged from a low of −3.17 to a high of 1.43 (mean=−0.09, SD=0.97, skewness=−0.76). A higher word knowledge score was associated with younger age (r=−0.12, p=0.018), more education (r=0.47, p<0.001) and female gender (t (413)=5.6, p<0.001). Word knowledge was assessed annually from study entry to death, with up to 16 observations per individual (mean=7.2, SD=3.3). To assess change in word knowledge, we constructed a series of mixed-effects models. The initial analysis included terms to control for the potentially confounding effects of age at death, sex and education (as did all subsequent models) but did not include neuropathological variables. In this analysis (based on 415 subjects), there was a mean loss of 0.067 unit per year (SE=0.009, p<0.001) in the composite measure of word knowledge.

Alzheimer's disease pathology

To test the hypothesis that neuropathological lesions contribute to loss of word knowledge, we repeated the analysis of change in the word knowledge measure with terms added for neuropathological measures and their interaction with time. We began with the composite measure of AD pathological lesions which had a somewhat skewed distribution, with scores ranging from a low of 0 to a high of 4.38 (mean=0.62, SD=0.56, skewness=1.48). In the analysis (based on 415 subjects), word knowledge did not decline in the absence of post-mortem evidence of AD, as shown by the term for time (table 1). AD pathological burden was not related to level of word knowledge, but it was related to change. For each point on the composite measure of AD pathological burden, the annual decline in word knowledge score increased by 0.082 unit.

To visually examine these results, we used the model to predict 7-year paths of change in word knowledge in participants who had different levels of AD pathology but were

Table 1 Relation of post-mortem measures of neurodegeneration to change in word knowledge*

	Word knowledge			Reading			Vocabulary		
	Estimate	SE	p Value	Estimate	SE	p Value	Estimate	SE	p Value
Time	−0.011	0.012	0.363	0.097	0.046	0.033	−0.106	0.044	0.017
Alzheimer's disease pathology	0.025	0.073	0.740	0.375	0.358	0.295	−0.139	0.269	0.606
Time×Alzheimer's disease pathology	−0.082	0.012	<0.001	−0.366	0.050	<0.001	−0.262	0.045	<0.001
Time	−0.060	0.010	<0.001	−0.137	0.039	<0.001	−0.270	0.037	<0.001
Neocortical Lewy bodies	−0.038	0.139	0.782	−0.445	0.639	0.487	−0.119	0.505	0.814
Time×neocortical Lewy bodies	−0.125	0.024	<0.001	−0.283	0.101	0.005	−0.399	0.091	<0.001
Subcortical Lewy bodies	−0.065	0.134	0.625	0.174	0.618	0.778	−0.495	0.485	0.308
Time×subcortical Lewy bodies	−0.001	0.023	0.966	0.000	0.088	0.998	0.042	0.083	0.609
Time	−0.057	0.011	<0.001	−0.154	0.043	<0.001	−0.248	0.041	<0.001
Gross infarction	0.021	0.088	0.808	0.093	0.410	0.820	0.062	0.320	0.846
Time×gross infarction	−0.046	0.016	0.003	−0.039	0.062	0.528	−0.167	0.057	0.003
Time	−0.064	0.011	<0.001	−0.137	0.043	0.001	−0.274	0.041	<0.001
Microscopic infarction	−0.131	0.091	0.151	−0.448	0.421	0.288	−0.574	0.329	0.087
Time×microscopic infarction	−0.024	0.017	0.140	−0.100	0.064	0.119	−0.092	0.061	0.130

*From separate mixed-effects models adjusted for age at death, sex, education and their interactions with time.

otherwise typical. As shown in figure 1, the decline in word knowledge was nearly four times faster in those with relatively high AD pathological burden (75th percentile, score=0.92, dashed line) compared with those with a relatively low burden (25th percentile, score=0.13, solid line).

To further examine the contribution of AD to decline in word knowledge, we plotted the model-based estimate of each person's annual rate of change in word knowledge (ie, slope) against AD pathological burden fitted with a locally reweighted linear smooth function (figure 2). The figure suggests an approximately linear relationship of AD pathological burden with rate of decline in word knowledge.

At baseline, 55 subjects met criteria for dementia. Exclusion of these individuals did not substantially affect results (estimate of interaction of time with AD pathology=−0.060, SE=0.011, p<0.001).

To see if differences between the components of the word knowledge measure affected results, we repeated the analysis, first with the word reading test (based on 409 subjects) and then with the vocabulary test (based on 414 subjects). A higher level of AD neuropathology was associated with a more rapid decline in both word reading and vocabulary, as shown by the interaction terms in each model in table 1.

Other forms of neuropathology

Data on Lewy bodies were available in 395 persons: Lewy bodies were present in neocortex in 40 (10.1%) and confined to nigral or limbic regions in 44 (11.1%). As shown in table 1, neocortical Lewy bodies were associated with an approximate threefold increase in rate of word knowledge decline with no effect for nigral-limbic Lewy bodies.

Infarction data were available in 383 persons: 140 (36.6%) had one or more gross cerebral infarctions, and 118 (30.8%) had one or more microscopic infarctions. Gross cerebral infarction was associated with an 81% increase in rate of decline in word knowledge with no effect for microscopic infarction (table 1).

When all pathological measures were included in a single model (based on 383 subjects), results were similar. In this analysis, AD pathology (estimate for interaction with time=−0.094, SE=0.013, p<0.001), neocortical Lewy bodies (estimate for interaction with time=−0.112, SE=0.023, p<0.001) and gross cerebral infarction (estimate for interaction
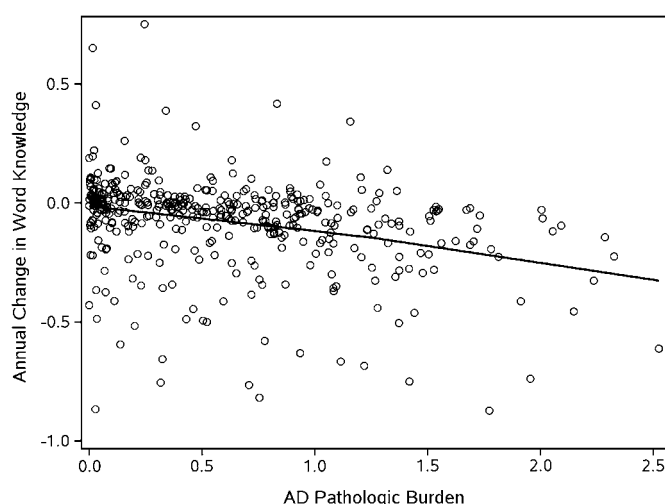
Figure 2 Relation of Alzheimer's disease (AD) pathological burden to decline in word knowledge, using predicted annual rate of decline in word knowledge (from mixed-effects model adjusted for age, sex, and education) as a function of AD pathological burden fitted with a locally reweighted linear smooth function.

with time=−0.039, SE=0.014, p=0.007) were each associated with more rapid decline in word knowledge. In the absence of these lesions, there was no change in word knowledge (estimate for time=0.020, SE=0.014, p=0.141).

We repeated these mixed-effects analyses using individual tests as outcomes in place of the composite measure of word knowledge. Neocortical Lewy bodies were associated with decline in both reading (based on 390 subjects) and vocabulary (based on 394 subjects), whereas gross infarction was related to decline in vocabulary (based on 382 subjects) but not reading (based on 379 subjects) (table 1). When pathological measures were simultaneously analysed, results were comparable, and in the absence of these lesions, reading score increased (estimate for time=0.132, SE=0.058, p=0.023) and vocabulary score did not change (estimate for time=0.000, SE=0.051, p=0.996).

DISCUSSION

For up to 15 years, word knowledge was assessed annually in more than 400 older persons who subsequently died and underwent brain autopsy. Post-mortem measures of plaques, tangles, cerebral infarction and Lewy bodies were robustly related to the rate of decline in word knowledge during the observation period. The results indicate that word knowledge declines in old age largely due to common neuropathological lesions associated with late-life dementia.

The fate of lexical knowledge in old age and mild dementia has been difficult to establish. Word knowledge tests that minimise response demands have not been widely used in epidemiological studies of older people without dementia.[17] [24] Case−control studies of the effect of dementia on word knowledge are hard to interpret because lower premorbid cognitive ability is a risk factor for late-life dementia.[25] Longitudinal studies of persons with clinically diagnosed dementia have, with some exceptions,[7] [13] suggested that word reading does decline in affected individuals,[8-12] although the change has been minimal in some cases.[8] [11] The present study differs from prior research in using pathological rather than clinical measures of disease. We found that neuropathological measures of the lesions traditionally associated with late-life dementia were robustly related to rate of decline in word knowledge.
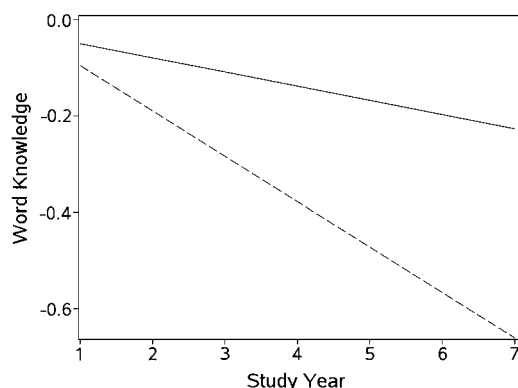

Figure 1 Decline in word knowledge with low and high Alzheimer's disease pathological burden, using predicted 7-year course of change in word knowledge in persons with relatively low (25th percentile, solid line) and high (75th percentile, dashed line) Alzheimer's disease pathological burden, from mixed-effects model adjusted for age, sex, and education.

Because basic lexical knowledge is widely believed to be relatively impervious to advancing age and mild dementia, word-knowledge assessment has long been used to estimate premorbid cognitive ability in persons suspected of cognitive decline.[5][26] Contrary to this assumption, however, decline in word knowledge in the present study was linearly related to level of AD pathology, indicating that the accumulation of common dementia-related neuropathology impairs word knowledge. Therefore, there is little justification for using performance on tests of word knowledge such as the National Adult Reading Test to estimate the premorbid level of cognitive ability in older persons. Determination of decline in cognitive ability is best based on repeated assessment of cognitive function over time or, when this is not feasible, on indicators of premorbid cognitive ability, such as the level of educational attainment, that are unaffected by dementia.[27-29]

Results were consistent across two measures of lexical knowledge with one exception. Gross cerebral infarction was associated with decline in vocabulary but not in word reading, suggesting that the response demands of the former (choosing synonym from five options) may exceed those of the latter (reading words aloud).

This study has several notable strengths. We used previously established neuropathological and psychometric measures in analyses. The availability of a mean of more than 7 years of evenly spaced observations enhanced our ability to reliably capture individual differences in change in word knowledge. The high participation in follow-up and brain autopsy reduces the likelihood that attrition affected results. An important limitation is the selected cohort; replication of these findings in other groups will be important.

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Information for patients from JNNP

Reading and vocabulary decline with brain changes

Changes to the brain from Alzheimer's disease or stroke may cause a drop in people's reading abilities and vocabulary, even in people who haven't actually been diagnosed with dementia.

What do we know already?

In advanced dementia, people may lose the ability to read or remember the meaning of words. But in early dementia, many people seem to retain their vocabulary and reading ability. For this reason, simple reading and vocabulary tests are sometimes used in the early stages of dementia as a 'baseline' to establish people's usual level of mental ability.

However, this assumption has never been properly tested. Now a study has looked at more than 400 elderly men and women (all monks or nuns) who had regular tests of their reading and vocabulary every year until their death, and who were then given a post-mortem examination to assess whether their brain showed signs of damage from Alzheimer's disease or stroke.

What does the new study say?

The people whose brains showed the most damage after their death also had the biggest and fastest decline in vocabulary and reading ability.

How reliable are the findings?

Each person in the study had at least two checks on their vocabulary and reading, and some had as many as 15. The post-mortem examinations were all carried out to the same process. This means the results should be fairly reliable.

What does this mean for me?

This study suggests that reading and vocabulary is affected by early dementia, so may not be the best test to demonstrate the usual mental abilities of people when they are being investigated for dementia.