Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study

Kathryn P. Riley a,b,c, David A. Snowdon b,c, Mark F. Desrosiers b, William R. Markesbery b,c,d

a Department of Preventive Medicine, University of Kentucky, Lexington, KY 40536, USA
b Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA
c Department of Neurology, University of Kentucky, Lexington, KY 40536, USA
d Department of Pathology, University of Kentucky, Lexington, KY 40536, USA

Received 22 December 2003; received in revised form 2 June 2004; accepted 16 June 2004

Abstract

The relationships between early life variables, cognitive function, and neuropathology were examined in participants in the Nun Study who were between the ages of 75 and 95. Our early life variable was idea density, which is a measure of linguistic ability, derived from autobiographies written at a mean age of 22 years. Six discrete categories of cognitive function, including mild cognitive impairments, were evaluated, using the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) battery of cognitive tests. Neuropathologic data included Braak staging, neurofibrillary tangle and senile plaque counts, brain weight, degree of cerebral atrophy, severity of atherosclerosis, and the presence of brain infarcts. Early-life idea density was significantly related to the categories of late-life cognitive function, including mild cognitive impairments: low idea density was associated with greater impairment. Low idea density also was significantly associated with lower brain weight, higher degree of cerebral atrophy, more severe neurofibrillary pathology, and the likelihood of meeting neuropathologic criteria for Alzheimer’s disease.

Keywords: Cognitive ability; Early life function; Linguistic ability; Neuropathology; Alzheimer’s disease; Braak staging; Mild cognitive impairments; Dementia

1. Introduction

It is becoming increasingly clear that the clinical symptoms and neuropathology of Alzheimer’s disease develop over the course of decades [2,6,14,29]. An important question is whether there are experiences or risk factors in early life that affect these key outcomes in late life. Previous findings from the Nun Study have shown that low linguistic ability measured in early life is strongly related to dementia and to the presence and severity of Alzheimer’s neuropathology in late life. However, little is known about the relationship of early life variables to the full spectrum of cognitive ability, including mild cognitive impairments [4,9,15–17,19,22].

The present study builds on previous work with the early-life linguistic ability measure of idea density [25,27,29,31]. We examined the extent to which idea density, a measure of linguistic ability, was related to the late life expression of cognitive function in participants in the Nun Study, a longitudinal study of aging and Alzheimer’s disease. We used six discrete categories of cognitive function [20] to examine the full range of cognition ranging from intact status to dementia. In addition, we examined the relationships among idea density and late life neuropathology, including the Braak method of staging neurofibrillary pathology of Alzheimer’s disease as well as diffuse and neuritic plaques, stroke, atherosclerosis, cerebral atrophy, and brain weight.

2. Methods

2.1. Study population

Women included in the present analysis were participants in the Nun Study, a longitudinal study of aging and...
Alzheimer’s disease. The design of this longitudinal study has been described in detail elsewhere [3,25,26,28,29] and will only briefly be described here. Participants in the Nun Study are members of the School Sisters of Notre Dame religious congregation and live in communities in the Midwestern, Eastern and Southeastern United States. At the first exam in 1991–1993, the 678 participants were 75–102 years old (mean = 83). Cognitive and physical functions were assessed annually and all participants agreed to brain donation at death. Attained educational levels among the participants ranged from grade school through the doctoral level.

The study population for the present analyses was restricted to participants who had handwritten autobiographies that were written when they were 18–32 years old. This group of 180 participants has been included in previous Nun Study publications [5,27]. Analyses of neuropathologic findings were based on a subset of 90 participants who had died as of April 2003 and had complete neuropathologic data.

2.2. Linguistic ability measure

Details about idea density, our measure of linguistic ability, may be found in previous publications [25,27,29]. Briefly, idea density measures were derived from handwritten autobiographies that were found in the convent archives for 180 US born sisters who took their religious vows during 1931–1943. The autobiographies were written within two years before the sisters formally joined the congregation. All of the autobiographies were written by sisters who entered either the Milwaukee, Wisconsin or the Baltimore, Maryland convents. Each participant wrote an autobiography some time between the age of 18 and 32 (mean age = 22). At that time, 18% had less than a high school education, 76% had earned a high school diploma, and 6% had earned a bachelor’s or master’s degree. An average of 58 years after writing the autobiographies, when the participants were 75–91 years old (mean = 80), they began to participate in the Nun Study. By that time, 91% of the 180 participants had earned bachelor’s degrees.

Idea density [11,32] is defined as the average number of ideas expressed per ten words, computed for the last ten sentences of each autobiography. Ideas corresponded to elementary propositions, typically a verb, adjective, adverb, or prepositional phrase. Complex propositions that stated or inferred causal, temporal, or other relationships between ideas also were counted. Idea density is associated with educational level, vocabulary, and general knowledge.

Idea density scores were calculated separately for each convent (Milwaukee or Baltimore) due to differences in the distribution of this measure between the two convents (participants from Milwaukee had a slightly higher mean idea density score than those from Baltimore) [27]. Low idea density was defined by scores that fall in the lowest third (33.3%) for each convent; high idea density scores constitute the top two-thirds.

2.3. Cognitive function

The cognitive test battery used in the Nun Study [29] includes measures compiled by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD), [13] which assesses memory, language, visuospatial ability, concentration, and orientation. We use four of the measures from the CERAD battery to determine dementia and cognitive status classification: [20,28] delayed word recall [23], Boston naming [10], verbal fluency [1] and constructional praxis [23]. This set of measures includes assessment of memory, crucial to the determination of dementia, as well as cognitive functions known to decline in dementia. The Mini-Mental State Exam [7] also was used as one component in the determination of the cognitive states described below.

2.3.1. Definition of cognitive outcomes

Previous work in the Nun Study [20] has defined a set of mutually exclusive cognitive states that captures the full range of cognitive function from intact status through dementia. In addition to a category for intact function, three categories of cognitive and functional decline have been used: mild cognitive impairments, global impairments, and dementia. Persons classified as intact had scores that were within normal limits on all four tests of cognitive function [33]. In addition, the intact group was required to have unimpaired global cognitive function as measured by the Mini-Mental State Exam (score of 24 or greater) and intact daily living ability as measured by the activities of daily living measure [12,18]. This measure uses self-report data in participants who live independently, and nurses’ reports for those under nursing care.

Participants who meet our criteria for mild cognitive impairments must have at least one specific area of impaired cognitive function, such as memory or naming ability. However, they must have intact global cognitive ability (MMSE) and intact daily living ability. Participants who meet our criteria for global impairment must have impaired global cognitive ability and/or impaired daily living ability, and they may also have other impairments in a specific area of cognitive function. As seen in the tables, the mild and global impairment groups were subdivided according to whether or not the participants had impaired memory as measured by the delayed word recall test. None of the participants in the mild or global impairment groups meet our criteria for dementia.

Individuals who had dementia had each of the following conditions: [28] (1) impairment in memory; (2) impairment in at least one other area of cognition; (3) impairment in social or daily function, i.e., inability to use a phone, handle money, or dress oneself; and (4) decline in function from a previous level (observed during our study for the incident dementia cases, and inferred for the dementia cases prevalent at the first exam). The determination of dementia was based on quantitative measures from the CERAD battery of neuropsychological tests and the activities of daily living measure. The cut points for the neuropsychological tests were higher for the determination of mild cognitive impairments than for
lobe, i.e., 16 or more senile plaques per mm², (b) abundant senile plaques in the frontal, temporal, or parietal Alzheimer's disease, participants were required to have: (a) Gallyas stains. Sections were cut at 8-micron thickness including those for the temporal gyrus (area 21), and the CA1 and subiculum of the mamm area 9), inferior parietal lobule (areas 39/40), middle invovled microscopic fields of the middle frontal gyrus (Brod-mann area 9), inferior parietal lobule (areas 39/40), middle temporal gyrus (area 21), and the CA1 and subiculum of the hippocampus using the modified Bielschowsky stain. All sections were cut at 8-micron thickness including those for the Gallyas stains.

To meet the study’s neuropathological criteria for Alzheimer’s disease, participants were required to have: (a) abundant senile plaques in the frontal, temporal, or parietal lobe, i.e., 16 or more senile plaques per mm², (b) abundant neuritic plaques in at least one lobe, (c) neurofibrillary tangles in at least one lobe, and (d) abundant neurofibrillary tangles in entorhinal cortex and hippocampus. These criteria were as good as or better than other established neuropathologic criteria in distinguishing demented from non-demented participants [8].

2.4. Braak staging

The severity of Alzheimer’s disease neurofibrillary pathology was determined using the staging method of Braak and Braak [2]. This method postulates that the neurofibrillary pathology of Alzheimer’s disease evolves in a relatively pre-dictable sequence across the medial temporal lobe structures, subcortical nuclei, and neocortical areas of the brain in six stages. A seventh (stage 0) includes cases without any corti-cal neurofibrillary tangles or only extremely rare tangles in the entorhinal and hippocampal regions [2, 14]. Gallyas and Bielschowsky stained sections of the entorhinal cortex, hip-pocampus and amygdala, and Bielschowsky stained sections of the neocortex were used to determine Braak staging.

2.4.2. Atrophy of the neocortex and apolipoprotein E genotyping

Following formalin fixation, the intact brain was examined by the neuropathologist who rated the degree of atrophy of the neocortex prior to sectioning. The degree of atrophy was based on the extent of widening of the sulci and narrowing of the gyri in the frontal, temporal and parietal lobes. A detailed description of the measure of atrophy, which was validated by postmortem magnetic resonance imaging, is available else-where [30]. The present analyses used a dichotomous variable that classified the atrophy scores as moderate to severe versus mild or none.

Our procedures for apolipoprotein E (APOE) genotyping have been described in detail elsewhere [21, 24]. Those who performed the genotyping were unaware of the participants’ cognitive test scores. We used a dichotomous variable coded as presence or absence of at least one APOE ε-4 allele.

2.4.3. Atherosclerosis

The neuropathologist classified the degree of atheroscle-rosis of the major arteries at the base of the brain (circle of Willis) [30]. Mild/minimal atherosclerosis was defined as atherosclerotic plaques present in less than 25% of the vessel wall; moderate was defined as atherosclerotic plaques present in 25–50% and severe was defined as greater than 50%.

2.5. Statistical measures

Significance levels were set at a minimum P-value of less than 0.05 for all analyses. Logistic regression was used in the analysis of prevalence data. The comparison of distributions was done using Wilcoxon rank sums. Analysis of variance was done using the SAS statistical software package (SAS Institute, Cary, NC).

3. Results

3.1. Descriptive data

At the first exam, the mean age of the 180 participants was 80 (range, 75–91); at the last exam, mean age was 86 (range = 76–95). For participants who died, the last annual exam before death was used; for participants who were still living as of the cut-off date of April 2003, the seventh exam was used as their last. A total of 9% of the participants were in Braak stage, stage 0; 46% were in stages I and II (trans-en-torhinal); 13% were in stages III and IV (limbic); and 32% were in stages V or VI (neocortical). A total of 39 (56%) of the participants who had complete neuropathologic data met our neuropathologic criteria for Alzheimer’s disease. Of these 39 participants, 59% met our clinical criteria for dementia; 13% had global impairments; 25% had mild cognitive im-pairments; and 3% had intact cognitive status.

3.2. Findings

The findings presented here were not materially changed after adjustments were made for age at the time of cognitive
At the first exam, increased likelihood of low idea density approximately five times that of the cognitively intact group. That the likelihood of low idea density in this group was approximately five times that of the cognitively intact group in analyses reported here. For example, the odds ratio of 5.3 intact cognitive function served as the reference group in the analyses. Participants with increased prevalence of low idea density. It should be noted that the sample sizes for the two globally impaired groups at Exam 1 are very small, and the findings on these groups must be viewed in light of these small samples. The prevalence of low idea density increased as the severity of cognitive impairment increased. Among those with mild cognitive impairments, the prevalence of an impaired score on a delayed memory test was significantly associated with increased prevalence of low idea density. It should be noted that the sample sizes for the two globally impaired groups at Exam 1 are very small, and the findings on these groups must be viewed in light of these small samples. Table 2 shows the likelihood of low idea density in each of the late-life cognitive states. Participants with intact cognitive function served as the reference group in the analyses reported here. For example, the odds ratio of 5.3 for mild cognitive impairments (memory impaired) indicates that the likelihood of low idea density in this group was approximately five times that of the cognitively intact group. At the first exam, increased likelihood of low idea density reached statistical significance only among the three groups of participants who had impaired memory performance. As expected, there was a very strong relationship between the likelihood of low idea density and the presence of dementia. While our new findings replicate those from our prior studies on persons who met all of our criteria for dementia, the data presented here are the first to examine and demonstrate a significant relationship between low idea density and mild cognitive impairments. In addition to the primary analyses examining the relationship between idea density and the cognitive states described above, we determined the correlations between idea density in early life and late life scores (at Exam 1) on the five cognitive tests and the activities of daily living measure. Spearman-ranked correlation values were as follows: Mini-Mental State Examination, $r = 0.65$; delayed word recall, $r = 0.48$; constructional praxis, $r = 0.36$; verbal fluency, $r = 0.32$; Boston naming, $r = 0.29$; activities of daily living, $r = 0.41$. All correlations were significant at the $P < 0.001$ level. Regression modeling techniques showed the Mini-Mental State Exam and delayed word recall to be the best predictors of low idea density. These data show the relationship between individual measures of cognitive function as well as the categories of cognitive and functional ability. Results for the participants’ last cognitive exam showed significantly greater likelihood of low idea density in the same three groups of memory-impaired participants observed at Exam 1. The finding for the group that was globally impaired (intact memory) was weaker, although statistically significant. The same pattern of significant results was repeated when a non-parametric test (Wilcoxon rank sum test) was used.

### Table 1

<table>
<thead>
<tr>
<th>Cognitive State</th>
<th>Percent prevalence of low idea density (95% CI)</th>
<th>First exam</th>
<th>Last exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory intact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>17 (0–28; 11/66)</td>
<td>10 (3–22; 5/50)</td>
<td></td>
</tr>
<tr>
<td>Mild impairment</td>
<td>21 (11–34; 11/53)</td>
<td>23 (11–39; 9/39)</td>
<td></td>
</tr>
<tr>
<td>Global impairment</td>
<td>50 (7–93; 24)</td>
<td>36 (11–69; 4/11)</td>
<td></td>
</tr>
<tr>
<td>Memory impaired</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild impairment</td>
<td>52 (33–70; 16/31)</td>
<td>45 (23–68; 9/20)</td>
<td></td>
</tr>
<tr>
<td>Global impairment</td>
<td>83 (66–99; 18/20)</td>
<td>50 (19–81; 5/10)</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>90 (66–99; 18/20)</td>
<td>62 (47–75; 13/50)</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval.

When a non-parametric test (Wilcoxon rank sum test) was used, the adjusted results shown. Comparisons to intact group: $^{**}P < 0.005$; $^{*}P < 0.01$; $^{*}P < 0.001$. Table 2 shows the odds ratios of low idea density in early life autobiographies by late life cognitive state at the first and last examination for 180 participants in the Nun Study.

### Table 2

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<tr>
<td>Intact</td>
<td>1.0</td>
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<tr>
<td>Mild impairment</td>
<td>1.6 (0.5–3.3)</td>
<td>2.0 (0.8–5.8)</td>
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<tr>
<td>Global impairment</td>
<td>5.0 (0.6–39.4)</td>
<td>5.1 (1.1–23.9)</td>
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<tr>
<td>Memory impaired</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild impairment</td>
<td>5.2 (2.0–13.9)</td>
<td>7.4 (1.7–26.4)</td>
<td></td>
</tr>
<tr>
<td>Global impairment</td>
<td>25.0 (2.7–235.4)</td>
<td>9.0 (1.9–42.2)</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>45.0 (1.1–222.4)</td>
<td>14.7 (0.3–63.5)</td>
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Table 2 shows the likelihood of low idea density in early life autobiographies by late life cognitive state at the first and last examination for 180 participants in the Nun Study.

### Table 3

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Examination, and for education at the time the autobiographies were written. Therefore, all findings presented here refer to the unadjusted results. Table 1 shows the percent prevalence of low idea density measured by early life autobiographies, classified by cognitive state measured at the first and last exams. The prevalence of low idea density increased as the severity of cognitive impairment increased. Among those with mild cognitive impairments, the prevalence of an impaired score on a delayed memory test was significantly associated with increased prevalence of low idea density. It should be noted that the sample sizes for the two globally impaired groups at Exam 1 are very small, and the findings on these groups must be viewed in light of these small samples. Table 2 shows the likelihood of low idea density in each of the late-life cognitive states. Participants with intact cognitive function served as the reference group in the analyses reported here. For example, the odds ratio of 5.3 for mild cognitive impairments (memory impaired) indicates that the likelihood of low idea density in this group was approximately five times that of the cognitively intact group. At the first exam, increased likelihood of low idea density reached statistical significance only among the three groups of participants who had impaired memory performance. As expected, there was a very strong relationship between the likelihood of low idea density and the presence of dementia. While our new findings replicate those from our prior studies on persons who met all of our criteria for dementia, the data presented here are the first to examine and demonstrate a significant relationship between low idea density and mild cognitive impairments. In addition to the primary analyses examining the relationship between idea density and the cognitive states described above, we determined the correlations between idea density in early life and late life scores (at Exam 1) on the five cognitive tests and the activities of daily living measure. Spearman-ranked correlation values were as follows: Mini-Mental State Examination, $r = 0.65$; delayed word recall, $r = 0.48$; constructional praxis, $r = 0.36$; verbal fluency, $r = 0.32$; Boston naming, $r = 0.29$; activities of daily living, $r = 0.41$. All correlations were significant at the $P < 0.001$ level. Regression modeling techniques showed the Mini-Mental State Exam and delayed word recall to be the best predictors of low idea density. These data show the relationship between individual measures of cognitive function as well as the categories of cognitive and functional ability. Results for the participants’ last cognitive exam showed significantly greater likelihood of low idea density in the same three groups of memory-impaired participants observed at Exam 1. The finding for the group that was globally impaired (intact memory) was weaker, although statistically significant. The same pattern of significant results was repeated when a non-parametric test (Wilcoxon rank sum test) was used.

### 3.2.1. Neuropathologic findings

Inspection of the relationship between cognitive state and neuropathologic findings revealed the following: 85% of those who met clinical criteria for dementia also met neuropathologic criteria for Alzheimer’s disease, compared to 50% of those with mild cognitive impairments, 50% of those with global impairments, and 12% of those with intact cognitive function. Table 3 shows the results for low and high idea density for a set of key neuropathologic variables, in the full sample of participants who had complete neuropathologic data. Participants with low idea density had significantly lower brain weight than those with high idea density. In addition, low idea density was significantly associated with greater severity of neurofibrillary pathology measured by Braak staging, and greater number of neurofibrillary tangles in the neocortex and in the hippocampus. The low and high idea density groups did not significantly differ on measures of neuritic plaques or combined counts of diffuse and neuritic plaques. Logistic regression analyses of an additional set of neuropathologic variables revealed significant increases in the likelihood of low idea density among those whose brain weight was less than 1000 grams (OR = 12.2; 95%
CI = 2.6–58.5), those who met our neuropathologic criteria for Alzheimer’s disease (OR = 3.7; 95% CI = 1.4–10.3), and those who had moderate or severe cerebral atrophy (OR = 4.7; 95% CI = 1.1–20.0).

Analyses of the presence of brain infarcts showed that while there was a higher prevalence of large infarcts among participants with low idea density, these results were not statistically significant. Similarly, although the data suggest increased prevalence of lacunar infarcts and moderate to severe atherosclerosis in the circle of Willis among those with low idea density, neither finding was statistically significant. Finally, the likelihood of having low idea density was not significantly higher in those participants who had at least one APOE ε4 allele; for low idea density, 26/91 (29%) participants had at least one ε4 allele; for high idea density, 28/91 (29%) participants had at least one ε4 allele.

4. Discussion

4.1. Linguistic ability and cognition

Our findings support a strong inverse relationship between early-life linguistic ability and late-life cognitive function, including mild cognitive impairments. Low idea density in autobiographies, written at an average age of 22 years, was significantly associated with poorer cognitive function measured an average of 58–64 years later. Overall, our findings suggest that only cognitive states that involved impaired memory function were related to low idea density. The consistency of these findings at the first and last exams, as well as correlational data for idea density and our measure of delayed word recall, suggest that the presence of impaired memory was a particularly strong factor in the relationship between early-life linguistic ability and late-life cognition.

While we have previously published findings on the relationship between linguistic ability and dementia, [29] this is the first investigation of idea density with respect to the full spectrum of cognitive function. These data document a relationship between low idea density and mild cognitive impairments, when memory is impaired. No such relationship was seen in participants whose mild cognitive impairment was in an area other than memory (i.e., the Boston naming test). The question of whether mild cognitive impairments represent a different construct or disease entity from Alzheimer’s disease is a matter of great, but as yet unresolved, debate. While we do not address this larger issue here, our own previous work suggests that Alzheimer’s disease is an important underlying neuropathologic substrate for cognitive impairments that fall short of fully-developed dementia [20]. The extent to which the mild cognitive impairments observed in our population represent a very early form of Alzheimer’s disease, or another construct altogether, cannot be determined on the basis of the present data. Our current findings do demonstrate, for the first time, a relationship between an early life measure of cognitive function and indications of mild cognitive dysfunction in very late life.

4.2. Linguistic ability and neuropathology

The present findings extend previously reported findings on neuropathology and early-life linguistic ability. Using Braak staging, as well as lesion counts, we showed that neurofibrillary lesions of Alzheimer’s disease were significantly associated with low idea density. No such associations were found for plaques. The present findings were the first to document a significant relationship between low idea density and brain weight, and cerebral atrophy.

Idea density was not significantly related to the presence of large or lacunar infarcts or cerebral atherosclerosis. However, the trends we observed in these data suggest that our planned analyses with more refined and detailed measures of cerebrovascular disease, and a larger autopsy series in the future, may reveal meaningful relationship between these neuropathologic conditions and linguistic ability.

4.3. Concluding remarks

Throughout their adult lives, participants in the Nun Study had the same reproductive and marital histories; had similar
social activities and support; did not smoke, or drink excessive amounts of alcohol; had similar occupations, income, and socio-economic status; lived in similar houses and ate food prepared in similar kitchens; and had comparable access to preventive and medical care services. The relative homogeneity of the sisters’ adult lifestyles and environments suggests that sisters with low linguistic ability in early life brought risk factors with them when they joined the religious congregation at an early age.

Our findings suggest that it is possible to identify persons who are at risk for developing late-life cognitive impairment by measuring linguistic ability (idea density) in early adulthood, a measure which is associated with general knowledge and vocabulary. For the first time, low idea density measured decades earlier has now been shown to be related to mild cognitive impairments found in Nun Study participants more than 60 years later. In addition, previous findings linking idea density with more severe impairments associated with the diagnosis of dementia were replicated in a larger sample. Analyses that included age and education did not materially affect any of the findings reported here.

Finally, the link between low idea density and increased severity of neurofibrillary pathology, lower brain weight, and cerebral atrophy further supports the idea that both Alzheimer’s disease and other forms of neuropathology are related to factors that are present in early life. The question that remains to be answered is whether neuropathologic changes were already operating in early life, resulting in low idea density scores in participants, or whether the linguistic ability measure simply marks those who are susceptible to the development of Alzheimer’s disease pathology later in life.

References


