Alzheimer Disease and Cognitive Reserve

Variation of Education Effect With Carbon 11–Labeled Pittsburgh Compound B Uptake

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Objective: To evaluate the cognitive reserve hypothesis by examining whether individuals of greater educational attainment have better cognitive function than individuals with less education in the presence of elevated fibrillar brain amyloid levels.

Design, Setting, and Participants: Uptake of carbon 11–labeled Pittsburgh Compound B ([11C]PiB) was measured for participants assessed between August 15, 2003, and January 8, 2008, at the Washington University Alzheimer’s Disease Research Center and diagnosed either as nondemented (n=161) or with dementia of the Alzheimer type (n=37). Multiple regression was used to determine whether [11C]PiB uptake interacted with level of educational attainment to predict cognitive function.

Main Outcome Measures: Scores on the Clinical Dementia Rating sum of boxes, Mini-Mental State Examination, and Short Blessed Test and individual measures from a psychometric battery.

Results: Uptake of [11C]PiB interacted with years of education in predicting scores on the Clinical Dementia Rating sum of boxes (P=.003), the Mini-Mental State Examination (P=.001), the Short Blessed Test (P=.03), and a measure of verbal abstract reasoning and conceptualization (P=.02) such that performance on these measures increased with increasing education for participants with elevated PiB uptake. Education was unrelated to global cognitive functioning scores among those with lower PiB uptake.

Conclusion: The results support the hypothesis that cognitive reserve influences the association between Alzheimer disease pathological burden and cognition.

Arch Neurol. 2008;65(11):1467-1471

The Cognitive Reserve Hypothesis states that persons with greater cognitive reserve are able to withstand more Alzheimer disease (AD) pathological burden without becoming demented by using cognitive processing approaches or compensatory brain networks. Education is a commonly used proxy of cognitive reserve. Adjusting for level of AD pathological burden determined at autopsy, greater education has been associated with better cognitive function during life. Education interacts with AD pathological burden such that a greater pathological burden is required to show an effect on cognition among persons with more education.

A recent advance in AD research is the development of positron emission tomographic (PET) radiotracers to image fibrillar β-amyloid (Aβ) pathology in vivo. In individuals diagnosed with mild dementia of the Alzheimer type (DAT), those with 15 or more years of education (n=12) were found to have higher uptake of carbon 11–labeled Pittsburgh Compound B ([11C]PiB) in the frontal cortex compared with [11C]PiB levels in 13 individuals with 6 years of education. These results suggest that more Aβ pathological burden was required among highly educated individuals than less educated individuals to manifest mild DAT, supporting the cognitive reserve hypothesis.

We used [11C]PiB imaging to further explore the cognitive reserve hypothesis by testing whether education and level of fibrillar brain Aβ interactively affect cognitive functioning in nondemented participants and those with DAT.

METHODS

Data were obtained from participants in longitudinal studies conducted by the Washington University Alzheimer’s Disease Research Center. Participants completing clinical and cognitive assessments and determined to either be nondemented or have DAT who also completed a PET scan to determine [11C]PiB uptake were included.
CLINICAL ASSESSMENT

Details regarding recruitment, enrollment, and clinical assessment in these studies were published previously. Briefly, experienced clinicians conduct a semistructured interview of the participant and a knowledgeable collateral source as well as a general physical and neurologic examination of the participant. Scores on the Mini-Mental State Examination (MMSE) and the Short Blessed Test (SBT), 2 objective measures commonly used to globally assess and rate dementia severity, can be derived from the clinical assessment, although the scores are not available to the clinicians. Without reference to cognitive test scores, clinicians assign a Clinical Dementia Rating (CDR) score based on the participant’s cognitive ability to function in each of 6 individually scored domains (or boxes): memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Absence of dementia is indicated by a CDR score of 0. A CDR score of 0.5 or higher indicates that the clinician believes the participant’s cognitive abilities have declined relative to his or her previous levels of performance (ie, the participant serves as his or her own control). Very mild, mild, moderate, and severe dementias are represented by CDR scores of 0.5, 1, 2, and 3, respectively. The CDR sum of boxes (CDR-SB) score is obtained by summing the scores from the individual domains. For this study, CDR-SB, MMSE, and SBT are considered measures of global cognitive function.

For participants with a CDR score of 0.5 or greater, a clinical diagnosis is assigned in accordance with standard criteria. Our clinical diagnostic criteria for DAT have been validated with 93% accuracy for histopathological AD, including individuals diagnosed with DAT at the CDR score of 0.5 who elsewhere may be considered to represent mild cognitive impairment.

Within a few weeks of the clinical assessment, psychometricians administer to all participants a 1.3-hour psychometric battery without knowledge of the CDR score or clinical diagnosis. The battery includes tests measuring specific types of cognitive processes: animal naming, Trailling A and B tests, Free and Cued Selective Reminding Test, and the similarities subtest of the Wechsler Adult Intelligence Scale, third edition (WAIS-III).

PET IMAGING

Detailed information on the imaging procedures is available. In brief, PET imaging is conducted using a Siemens 961 HR ECAT PET scanner (Siemens/CTI, Knoxville, Tennessee) or a Siemens 962 HR+ ECAT PET scanner (Siemens/CTI) with [11C]PiB synthesized in accordance with a standard protocol. After a transmission scan to measure attenuation, [11C]PiB (range, 4.5-20.1 mCi; mean, 12.2 mCi) is administered intravenously with initiation of a 60-minute dynamic PET scan in 3-dimensional mode (septa retracted; 24 five-second frames; 9 twenty-second frames; 10 one-minute frames). The measured attenuation factors and a ramp filter are used to reconstruct the dynamic PET images. A fully 3-dimensional single-scatter simulation algorithm is used to correct scatter. In addition to PET imaging, all of the participants have anatomical magnetic resonance imaging performed using medium-resolution (1 × 1 × 1.25-mm) magnetization-prepared rapid-acquisition gradient-echo T1-weighted volume acquisitions. A high-resolution, low-noise anatomical image data set for region-of-interest (ROI) determination is created for each participant by aligning and averaging 3 magnetization-prepared rapid-acquisition gradient-echo sequences.

MEAN CORTICAL BINDING POTENTIAL

Each participant’s structural magnetic resonance image is registered to a standard atlas that minimizes bias due to atrophy. Alignment of PET and magnetic resonance images within a participant is accomplished via use of an in-house cross-modal registration algorithm, and ANALYZE software (Mayo Clinic, Rochester, Minnesota) is used to create 3-dimensional ROIs for each participant based on his or her individual magnetic resonance image. The ROIs are applied to unblurred images of the PET dynamic data, yielding high-resolution regional time-activity curves. Each time-activity curve is analyzed for PiB specific binding using the graphical analysis by Logan et al, taking the cerebellum ROI data as a reference tissue input function. The cerebellum was chosen as the reference region because there is little specific binding of PiB in postmortem samples of cerebellar cortex even among individuals with AD at autopsy. The slope produced by the graphical analysis by Logan and colleagues is equal to the tracer distribution volume in the tissue of interest when compared with the input function. A binding potential (BP) for each ROI is calculated using the equation BP = distribution volume–1 to express the regional binding values in a manner proportional to the number of binding sites. Mean BP values from the prefrontal cortex, gyrus rectus, lateral temporal cortex, and precuneus ROIs are used to calculate a mean cortical BP (MCBP) value based on brain regions known to have high PiB uptake among participants with DAT. An MCBP of 0.18 serves as a borderline value, as nearly all individuals with DAT have MCBPs greater than that value and all young healthy individuals have MCBPs less than that value. Participants were dichotomized into PiB-negative (MCBP < 0.18) or PiB-positive (MCBP ≥ 0.18) groups.

STATISTICAL ANALYSIS

Multiple linear regression analysis using PROC REG (SAS Institute, Inc, Cary, North Carolina) was used to test for a significant interaction between education and PiB group (PiB positive vs PiB negative) in predicting test scores. Better performance is indicated by lower scores for the CDR-SB, SBT, Traillaking A test, and Traillaking B test and by higher scores on the MMSE, animal naming, Free and Cued Selective Reminding Test, and WAIS-III similarities subtest.

Education in years, PiB group, and a term representing their interaction were included in all of the models. The stepwise selection procedure identified variables that improved the model fit using the default SAS criteria for model entry (P = .10) and exit (P = .15). Candidate variables for stepwise entry included sex, age group, the presence of at least 1 apolipoprotein E (APOE) ε4 allele (APOE ε4 positive vs APOE ε4 negative), and time between clinical assessment and PiB scan. Age (median, 67.7 years) and time between clinical assessment and PiB scan (median, 0.42 years) were dichotomized using median splits. Preliminary examination of the data suggested a potential interaction between age group and APOE ε4 status for the global tests such that older participants without an APOE ε4 allele did better on the cognitive tests than older participants with an APOE ε4 allele, but test scores were similar for the APOE ε4 groups among younger participants. Therefore, a term representing that interaction was also a candidate for stepwise entry. Because regression diagnostics indicated that the residuals were skewed, CDR-SB scores were log transformed after adding 0.5 to each value.

For tests showing a significant education × PiB interaction, least square mean scores and 95% confidence intervals for PiB-positive and PiB-negative participants within 3 education categories were calculated to illustrate the form of the interac-
RESULTS

One hundred ninety-eight participants, including 161 who were nondemented and 37 with DAT (26 with a CDR score of 0.5, 9 with a CDR score of 1, and 2 with a CDR score of 2), met inclusion criteria (Table 1 and Table 2). No significant differences between the PiB-positive and PiB-negative groups were found for history of heart disease (P = .35), the Free and Cued Selective Reminding Test (free recall subtest, P = .50; total, P = .19). After repeating the analyses without the interaction term, better cognitive functioning on all of the tests was significantly associated with PiB-negative status and was associated with more years of education for animal naming, Free and Cued Selective Reminding Test free recall subtest, and the Trailmaking B test (Table 3). Similar results were found when PiB uptake was treated as a continuous variable, with significant interactions between education and MCBP found for the global tests (CDR-SB, P = .004; MMSE, P < .001; and SBT, P = .01) and the WAIS-III similarities subtest (P = .04).

These results provide support for the cognitive reserve hypothesis. On each of 3 measures of global cognitive functioning, education interacted with PiB status to predict cognitive function such that persons with greater education maintain better global cognitive functioning in the presence of Aβ pathology. In both nondemented individuals and those with DAT, the interaction between education and Aβ pathology takes the form of a floor effect such that differences between individuals with and without Aβ pathology increase with increasing years of education. Based on autopsy data, there may be a ceiling effect when extensive Aβ pathological burden is present as in late-stage DAT. Presumably, as the AD pathological burden increases, a greater proportion of highly educated participants reaches the threshold for dementia and the initial advantage provided by cognitive reserve decreases. Longitudinal imaging of Aβ pathology in vivo will soon allow us to determine whether these inferences from cross-sectional studies are accurate.

Correlations between educational attainment and scores on global cognitive functioning tests such as the MMSE may indicate test bias. We found no difference in global test scores between the education groups among participants who were PiB negative, but did find differences among those who were PiB positive, suggesting that some education-based differences in scores on global cognitive tests may reflect cognitive reserve differences that mitigate the presence of Aβ pathology.

Education interacted with Aβ uptake to predict scores on the WAIS-III similarities subtest, a measure of verbal abstract reasoning and conceptualization, but not on tests assessing category fluency, controlled word list learning and verbal/visual memory, attention, visual searching, and mental processing speed. Abstract reasoning may be one of the first types of cognitive processes to be affected in early DAT. Among multiple neuropsychologi-

### Table 1. Demographic Characteristics of 198 Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>67.4 (12.1)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>131 (66.2)</td>
</tr>
<tr>
<td>≥1 Apolipoprotein E4 allele, No. (%)</td>
<td>76 (38.4)</td>
</tr>
<tr>
<td>Time between clinical assessment and PET scan, mean (SD), y</td>
<td>0.6 (0.5)</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>15.5 (2.7)</td>
</tr>
<tr>
<td>Mean cortical binding potential, mean (SD)</td>
<td>0.20 (0.35)</td>
</tr>
<tr>
<td>CDR-SB score, mean (SD)</td>
<td>0.74 (1.85)</td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>28.4 (2.6)</td>
</tr>
<tr>
<td>SBT score, mean (SD)</td>
<td>2.8 (5.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomographic; SBT, Short Blessed Test.
a Indicates a mean cortical binding potential less than 0.18.
b Indicates a mean cortical binding potential of 0.18 or greater.

### Table 2. Participants With Negative and Positive Pittsburgh Compound B Status in Each Education Group

<table>
<thead>
<tr>
<th>Educationa</th>
<th>PiB Negativeb (n=139)</th>
<th>PiB Positivex (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High school or less</td>
<td>22 (15.8)</td>
<td>16 (27.1)</td>
</tr>
<tr>
<td>Some college or college graduate</td>
<td>69 (49.6)</td>
<td>29 (49.2)</td>
</tr>
<tr>
<td>Postcollege</td>
<td>48 (34.5)</td>
<td>14 (23.7)</td>
</tr>
</tbody>
</table>

Abbreviation: PiB, Pittsburgh Compound B.
a High school or less indicates 12 or fewer years of education; some college or college graduate, 13 to 16 years of education; and postcollege, more than 16 years of education.
b Indicates a mean cortical binding potential less than 0.18.
x Indicates a mean cortical binding potential of 0.18 or greater.
cal tests, performances on tests of abstract reasoning along with memory were found to best differentiate individu-
als with mild DAT from those with normal cognition.26 Performance on the abstract reasoning task used here has also been found to be strongly related to education.27 Cognitive reserve, as reflected in education, may have a stron-
ger or earlier effect on specific cognitive processes com-
pared with other cognitive processes. However, greater

Table 3. Results of the Multiple Regression Modelsa

<table>
<thead>
<tr>
<th>Variable</th>
<th>CDR-SB (n=198)</th>
<th>MMSE (n=198)</th>
<th>SBT (n=194)</th>
<th>Animal Naming Subtest (n=190)</th>
<th>SRT Free Recall Subtest (n=184)</th>
<th>SRT Total (n=184)</th>
<th>Trailmaking A Test (n=190)</th>
<th>Trailmaking B Test (n=190)</th>
<th>WAIS-III Similarities Subtest (n=189)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIB positive</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.003</td>
</tr>
<tr>
<td>Education, y</td>
<td>.55</td>
<td>.32</td>
<td>.86</td>
<td>.003</td>
<td>.02</td>
<td>.50</td>
<td>.24</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.02</td>
</tr>
<tr>
<td>PIB positive × education</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Older age</td>
<td>.81</td>
<td>.96</td>
<td>.04</td>
<td>&lt;.001</td>
<td>.01</td>
<td>.003</td>
<td>&lt;.001</td>
<td>.91</td>
<td></td>
<td>.45</td>
</tr>
<tr>
<td>Older age × PIB positive apolipoprotein E ε4</td>
<td>.48</td>
<td>.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.09</td>
</tr>
<tr>
<td>Male</td>
<td>.03</td>
<td>.02</td>
<td>.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.14</td>
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<tr>
<td>Longer time between clinical assessment and scan</td>
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</table>

Abbreviations: CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination; PiB, Pittsburgh Compound B; SBT, Short Blessed Test; SRT, Free and Cued Selective Reminding Test; WAIS-III, Wechsler Adult Intelligence Scale, third edition.

a Empty cells indicate that the corresponding variable or interaction term did not meet stepwise entry and exit criteria for a particular model.

Figure. Least square mean scores on the Clinical Dementia Rating sum of boxes (CDR-SB) (A), the Mini-Mental State Examination (MMSE) (B), the Short Blessed Test (SBT) (C), and the Wechsler Adult Intelligence Scale, third edition (WAIS-III) similarities subtest (D) by education group for participants with negative and positive Pittsburgh Compound B (PiB) status. Error bars indicate 95% confidence intervals; P values, the significance of t tests between the means. High school or less indicates 12 or fewer years of education; some college or college graduate, 13 to 16 years of education; and postcollege, more than 16 years of education.
AB deposition was related to worse performance on all of the tests examined here, either as part of an interaction effect or by itself.

This study has several strengths, including a large sample comprising both demented and nondemented individuals and multiple measures of cognitive function. There also are limitations, including the high mean educational level of the sample. We also conducted multiple statistical tests, so some statistically significant differences reported here may be due to chance. Nonetheless, the findings extend the examination of the cognitive reserve hypothesis by indicating that persons who are PiB positive and have the highest education are clinically rated as less impaired and perform better on cognitive tests than PiB-positive individuals with less education.

Accepted for Publication: June 10, 2008.
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Author Contributions: Dr Roe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Roe, Mintun, D'Angelo, and Morris. Acquisition of data: Roe, Mintun, and Morris. Analysis and interpretation of data: Roe, Mintun, Xiong, and Grant. Drafting of the manuscript: Roe. Critical revision of the manuscript for important intellectual content: Roe, Mintun, D'Angelo, Xiong, Grant, and Morris. Statistical analysis: Roe, D'Angelo, and Xiong. Obtained funding: Mintun and Morris. Administrative, technical, and material support: Mintun, Grant, and Morris. Study supervision: Morris.

Financial Disclosure: None reported.

Funding/Support: This work was supported by grants P50-AG05681, P01-AG03991, and P01-AG26276 from the National Institute on Aging and P30-NS048056 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, and by the Charles and Joanne Knight Alzheimer’s Research Initiative of the Washington University Alzheimer’s Disease Research Center.

Additional Contributions: Martha Storandt, PhD, provided data, Denise Maue-Dreyfus, MA, and Monique Williams, MD, provided helpful comments, and the Genetics Core of the Washington University Alzheimer’s Disease Research Center provided APOE genotyping.

REFERENCES