Brain Volume Decline in Aging

Evidence for a Relation Between Socioeconomic Status, Preclinical Alzheimer Disease, and Reserve

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Objectives: To assess the relation between socioeconomic status (SES) and structural brain change in nondemented older adults and to ascertain the potential role of preclinical Alzheimer disease (AD).

Design: Cross-sectional and longitudinal observation.

Setting: Alzheimer’s Disease Research Center, St Louis, Missouri.

Participants: Volunteer sample of 362 nondemented adults aged 18 to 93 years. The main cohort of 100 was evaluated for dementia and SES; a Clinical Dementia Rating (CDR) of 0 (no dementia) and middle, high-middle, or high SES was required for eligibility. All 362 received magnetic resonance imaging; of the main 100, 91 received follow-up clinical assessment, and 33 received follow-up magnetic resonance imaging over at least a 3-year interval. A separate sample of 58 CDR 0 participants (aged 47 to 86 years) took part in amyloid imaging with Pittsburgh Compound B (PiB) labeled with radioactive carbon ($^{11}$C).

Main Outcome Measures: Whole-brain volume adjusted for head size (aWBV) and change per year.

Results: aWBV declined by 0.22% per year between the ages of 20 and 80 years with accelerated decline in advanced aging. Controlling for effects of age and sex in older adults (>65 years) with CDR 0, higher SES was associated with smaller aWBV (3.8% difference spanning the sample range from middle to high privilege, $P<.01$) and more rapid volume loss (0.39% per year to 0.68% per year from middle to high privilege, $P<.05$). aWBV was reduced by 2.5% in individuals positive for PiB binding ($n=9$) as compared with individuals negative for PiB binding ($n=49$, $P<.05$), supporting an influence of undetected preclinical AD. Follow-up clinical data revealed that brain volume reduction associated with SES was greater in those who later developed very mild dementia (preclinical CDR 0 group, $n=19$) compared with those who remained nondemented (stable CDR 0 group, $n=64$; group×SES interaction, $P<.05$).

Conclusions: Privileged nondemented older adults harbor more preclinical brain atrophy, consistent with their having greater reserve against the expression of AD.

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between SES and brain aging without any involvement of preclinical pathology. To explore the contribution of preclinical pathology, we supplemented our main analysis with subject stratification based on amyloid binding with Pittsburgh Compound B (PiB) labeled with radioactive carbon (¹¹C) and longitudinal clinical assessment. Support for a reserve explanation would come from finding that greater volume decline was accounted for by privileged individuals on the threshold of clinically detectable dementia.

### METHODS

#### PARTICIPANTS

Magnetic resonance imaging (MRI) scans were obtained from 362 individuals (aged 18 to 93 years) participating in the longitudinal studies of the Washington University Alzheimer’s Disease Research Center (ADRC) or other studies of younger adult aging and development. Detailed selection and attrition characteristics of this population have been described previously. All participants were scanned using identical procedures. The main cohort comprised 100 clinically screened ADRC participants aged 65 to 93 years. Of these 100, 33 were followed up with MRI for an extended interval to allow for longitudinal data analysis (mean, 4.4 years; range, 3.3-6.3 years). Participants were classified as initially nondemented if their Clinical Dementia Rating (CDR) nearest the time of baseline MRI was 0. Specialist clinicians determined the CDR, blind to the results of neuropsychological testing and prior clinical assessment, through examination of the participant and interview with an informant (usually a family member) who knew the participant well and could provide information regarding decline from the participant’s normal cognitive and functional abilities.

Estimation of Whole-Brain Volume

Our method of image acquisition and estimation of total intracranial volume (eTIV) and whole-brain volume (WBV) has been described previously. Head-size differences were corrected using a covariance procedure. The term adjusted whole-brain volume (aWBV) is used to denote covariance-adjusted volumes as distinct from proportionally normalized whole-brain volume (nWBV). aWBV was defined as

\[
aWBV = WBV - b(eTIV - \text{mean eTIV})
\]

where WBV is the uncorrected (native) whole-brain volume, b is the slope of the volume regression on eTIV, eTIV is the head-size estimate derived from atlas scaling, and mean eTIV is the sample mean. When the relations of multiple variables to WBV were being explored simultaneously, eTIV was always entered as a covariate, and the dependent variable is denoted as aWBV to reflect this adjustment.

### CROSS-SECTIONAL ANALYSIS

To explore differences in brain volume across the full life span, aWBV was plotted cross-sectionally vs age for the entire sample of 362 individuals, including the cohort of 100 clinically screened...
nondemented older participants (aged 65 to 93 years) and the young and middle-aged volunteers from the community (aged 18 to 64 years). Statistical analysis was conducted with both JMP and SAS software packages (SAS Institute, Cary, NC). Analysis of covariance and hierarchical polynomial regression were used to test for additional effects of age and sex. To test for a cross-sectional relation between SES and brain volume, analysis (including recomputation of aWBV) was restricted to the main, carefully screened older adult sample of 100, and SES was entered as the predictor variable with age and sex as covariates.

**LONGITUDINAL ANALYSIS**

To test for a longitudinal relation between SES and brain volume, we used multilevel modeling (SAS PROC MIXED, full maximum likelihood estimation) with aWBV as the dependent measure and the time × SES term as the predictor; covariates were baseline age, time (expressed as years from baseline), SES, and sex. For visualization, the most precise ordinary-least-squared regressions of aWBV against time were plotted per individual with individuals ranked by SES (via the Hollingshead index).

**PRECLINICAL AD**

Amyloid was visualized by positron emission tomography (PET) scanning with [11C]PiB, a radiotracer with high affinity for amyloid in β amyloid plaques.20,21 Pittsburgh Compound B was imaged with PET in a sample of 58 nondemented ADRC participants that partially overlapped with this study’s main MRI sample. Characteristics of the PiB sample are described in Table 2. Other articles describe PiB-PET image acquisition and analysis.22,23,26 Uptake of PiB in 4 cortical brain regions (prefrontal, lateral temporal, precuneus, and gyrus rectus) was obtained by manual drawing of regions of interest on the coregistered MRI and application to the dynamic PET data. Binding potential was calculated using Logan graphical analysis with a cerebellar reference region of interest (descriptions of regions of interest).

<table>
<thead>
<tr>
<th>Table 2. Pittsburgh Compound B Amyloid Imaging Sample</th>
<th>CDR 0 PiB−</th>
<th>CDR 0 PiB+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (cross-sectional)</td>
<td>49</td>
<td>9</td>
</tr>
<tr>
<td>Sex, F/M, No.</td>
<td>39/10</td>
<td>7/2</td>
</tr>
<tr>
<td>Sum box score 0/0.5, No.</td>
<td>46/3</td>
<td>9/0</td>
</tr>
<tr>
<td>Age, mean (SD) [range], y</td>
<td>69 (11) [47-86]</td>
<td>72 (7) [61-81]</td>
</tr>
<tr>
<td>Education, mean (SD) [range], y</td>
<td>16 (3) [11-20]</td>
<td>14 (3) [11-18]</td>
</tr>
<tr>
<td>MMSE score, mean (SD) [range]</td>
<td>29 (1) [26-30]</td>
<td>29 (1) [26-30]</td>
</tr>
<tr>
<td>Weight (sex-adjusted), mean (SD) [range], kg</td>
<td>72 (12) [51-107]</td>
<td>60 (12) [53-79]</td>
</tr>
</tbody>
</table>

Abbreviations: CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination (score range, 30 [best] to 0 [worst]); PiB, Pittsburgh Compound B.

*Preclinical Alzheimer disease, as suggested by imaging of PiB labeled with radioactive carbon (11C) in a separate sample, was explored for potential contributions to structural magnetic resonance imaging findings. Positive/negative groupings (PiB−/+...) were based on mean regional PiB uptake as described in the “Methods” section.

b Twenty-eight of those with PiB imaging also belonged to the main cohort described in Table 1. The rest were either younger, less privileged, or missing socioeconomic status data. The PiB+ group weighed less than the PiB− group after adjusting for sex ($t_{37} = 2.63, P < .05$). There were no other significant group differences, including for additional clinical variables in Table 1 (not shown).
Figure 2. Cross-sectional and longitudinal plots of brain volume as a function of socioeconomic status (SES). A, Cross-sectional whole-brain volume adjusted for head size (aWBV) is reduced in more privileged individuals. Each data point represents a nondemented older adult from the main sample of 100. B, Longitudinal aWBV from 33 of the 100 who participated in follow-up magnetic resonance imaging (MRI); here each data point represents an MRI with best-fit lines connecting each participant’s data. Lines are positioned according to participants’ Hollingshead ranking, and time is nested with 5 years scaled as shown. Hollingshead ranking does not vary per individual.
RESULTS

BRAIN VOLUME REDUCTIONS IN NONDEMENTED AGING

Cross-sectional brain volumes in nondemented individuals, aged 18 to 93 years, are illustrated in Figure 1 (using covariance-adjusted whole-brain volume; aWBV). Parameter estimates for age, age², sex, and age×sex were all significant in the model ($F_{1,309}=1394.14, P<.001, R^2=0.93$). Between ages 20 and 80 years, aWBV was estimated to decline from 1199 cm³ to 1025 cm³ (3.8% difference).

Table 3. Summary Data

<table>
<thead>
<tr>
<th>SES</th>
<th>Adjusted Whole-Brain Volume, Mean (SD), cm³</th>
<th>Change, Mean (SD), cm³/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=100)</td>
<td>Stable CDR 0 (n=64)</td>
</tr>
<tr>
<td>Middle</td>
<td>1058 (59)</td>
<td>1057 (54)</td>
</tr>
<tr>
<td>[n=31]</td>
<td>[n=20]</td>
<td>[n=5]</td>
</tr>
<tr>
<td>High</td>
<td>1038 (42)</td>
<td>1041 (44)</td>
</tr>
<tr>
<td>middle</td>
<td>[n=40]</td>
<td>[n=26]</td>
</tr>
<tr>
<td>High</td>
<td>1029 (40)</td>
<td>1025 (42)</td>
</tr>
<tr>
<td>[n=29]</td>
<td>[n=18]</td>
<td>[n=6]</td>
</tr>
</tbody>
</table>

Abbreviation: aWBV, whole-brain volume adjusted for head size; CDR, Clinical Dementia Rating; SES, socioeconomic status.

A whole-brain volume adjusted for head size (aWBV) is reduced in nondemented participants with high uptake of Pittsburgh Compound B (PiB), which binds to β amyloid in plaques. CDR indicates Clinical Dementia Rating. Asterisk indicates a statistically significant difference ($P<.05$).

Figure 2A shows the relation between SES and brain volume in nondemented older adults. After accounting for effects of age, sex, and age×sex on aWBV (model $F_{3,29}=218.74, P<.001, R^2=0.92$), more privileged individuals were associated with lower volume estimates ($β=1.3$ cm³ per Hollingshead unit, $P<.01$). Spanning the sample range from middle privilege (Hollingshead 43) to highest privilege (Hollingshead 11), aWBV was estimated to decrease from 1066 cm³ to 1026 cm³ (3.8% difference).

Figure 3. Whole-brain volume adjusted for head size (aWBV) is reduced in nondemented older adults with high uptake of Pittsburgh Compound B (PiB), which binds to β amyloid in plaques. CDR indicates Clinical Dementia Rating. Asterisk indicates a statistically significant difference ($P<.05$).

Figure 4 shows results that explore aWBV in relation to amyloid imaging with PiB and follow-up clinical assessments. Nine of 58 individuals (16%) within the separate CDR 0 PiB sample (aged 47 to 86 years) were pos-
tive for PiB binding. Figure 3 shows that there was a main effect (P < .05) of positive PiB binding on brain volume: aWBV was estimated to decline 27 cm³ (2.5%, from 1066 cm³ to 1039 cm³) in the CDR 0 PiB+ group after adjusting for effects of age and sex (model F₃,₅₄ = 151.62, P < .001, R² = 0.89). Figure 4 suggests that preclinical status contributes to the effect of SES. Participants were grouped as preclinical if subsequent clinical evaluation indicated very mild dementia (CDR 0.5). Adding group status to the cross-sectional model (F₇,₈₃ = 151.38, P < .001, R² = 0.93) revealed a group × privilege interaction (β = 2.2 cm³ per Hollingshead per clinical conversion, P < .05). The magnitude of the interaction predicts that the cross-sectional decline in aWBV with privilege (β = 1.3 cm³ per Hollingshead unit overall) will increase by 2.2 cm³ per Hollingshead unit in individuals with subsequent dementia.

**COMMENT**

Nondemented participants with high SES (the most privileged individuals) were found to have reduced brain volume (cross-sectional analysis) and accelerated volume loss (longitudinal analysis). The capacity for more privileged individuals to cope longer with brain pathology before manifesting dementia may contribute to this association.

**SES AND BRAIN VOLUME REDUCTION IN NONDEMENTED AGING**

This study's main result is that high SES is associated with lower aWBV in nondemented older adults (Figure 2). It is worth emphasizing that, by design, this study concerns individual differences in long-term structural change (Figure 1), not early established differences such as in head size. This focus on change is most clear in the longitudinal result that shows accelerated volume loss in more privileged individuals. Moreover, in the present sample, we did not find significant head-size differences attributable to SES.

Our main cross-sectional result (Figure 2A) extends and strengthens the findings of the study by Coffey and colleagues. The longitudinal finding illustrated in Figure 2B confirms the direction of the cross-sectional association between volume and privilege and provides novel evidence that this association is related to aging and present in older age.

Figure 4. The relation between adjusted whole-brain volume (aWBV) (as shown in Figure 2A) and socioeconomic status (SES) is stronger in nondemented participants who subsequently develop dementia. Each data point represents the same nondemented older adult as shown in Figure 2A for the 91 participants who had clinical follow-up subsequent to magnetic resonance imaging (MRI). Lines extending from each point represent the duration of clinical follow-up with 5 years nested and scaled as shown. Vertical ticks mark when certain participants received a Clinical Dementia Rating (CDR) of 0.5, indicating very mild dementia. These participants are classified as preclinical with respect to MRI acquired when all were nondemented (CDR 0); preclinical participants are shown in gray and stable CDR 0 participants are shown in black.

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ROLE OF PRECLINICAL AD AND COGNITIVE RESERVE

To explore whether the observed relation between brain aging and SES was associated with preclinical pathology, we conducted supplementary analyses on available amyloid imaging and clinical follow-up data. At least 3 results implicate preclinical AD as a possible factor. First, 16% of our non-demented PiB sample showed high levels of binding indicative of amyloid plaque presence, suggesting a number of individuals may harbor preclinical pathology. Second, high PiB binding was associated with reduced aWBV (Figure 3), suggesting that preclinical pathology is already having an influence on brain volume in some individuals. Third, in the full sample with follow-up clinical data, a group × SES interaction was observed with reduced aWBV associated with more privileged individuals who subsequently showed signs of very mild dementia (Figure 4). Together, these results suggest individuals with high SES are more likely to remain clinically nondemented in the early stages of AD relative to their less privileged peers even though AD is causing brain atrophy.

Preclinical neurodegeneration might affect more privileged individuals less because of relations between SES and AD pathology, between SES and the structural response to pathology, or between SES and the clinical response to pathology. The latter reserve explanation is supported by studies that reveal similar plaque burden leads to lessened cognitive decline in the most educated individuals. The recent observation that more educated individuals decline more rapidly on neuropsychological tests several years prior to AD diagnosis has also been interpreted in terms of cognitive susceptibility and reserve. The present data thus are consistent with SES influencing the ability to detect cognitive impairment in the presence of pathology. It is unclear whether there is any modification of underlying structural or disease processes by life experiences associated with SES. Education and occupational attainment may protect against AD through a “use it and hide it” mechanism in comparison with the more traditionally assumed “use it or lose it” explanation.

LIMITATIONS AND CAVEATS

Limitations of this study highlight open questions and may help guide future research. For example, the “use it and hide it” interpretation of our results implies that CDR 0 status is insensitive to some degree to AD pathology and associated cognitive variation, particularly in individuals with high SES. Development of sensitive neuropsychological markers to capture this cognitive variance is an active area of research at our ADRC. Future research should also aim to increase the precision of the presently characterized relation between SES and brain volume, both in terms of regional anatomy and analysis of the multiple factors that contribute to SES.

The present study explored SES between the middle and high range in older ADRC volunteers. This range is higher than most, but not all, epidemiological studies that have found protective demographic factors against AD and favors a gradient over threshold model of SES. Our sample was not randomly assigned from the population and not all participants were followed up longitudinally. Thus, broader and more prospective sampling could help establish the generality of these findings.

A final point to raise is that a reserve explanation for the present findings does not exclude the possibility that additional factors are at work. Specifically, it remains difficult to account fully for the magnitude of the SES-related volume difference unless SES-related protection against AD is greater and/or CDR 0 pathology more burdensome than recent research suggests. We thus conclude that reserve likely explains some, but perhaps not all, of the novel association reported here between SES and structural brain aging.

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Author Contributions: Study concept and design: Fotenos and Buckner. Acquisition of data: Mintun, Morris, and Buckner. Analysis and interpretation of data: Fotenos, Mintun, Snyder, Morris, and Buckner. Drafting of the manuscript: Fotenos. Critical revision of the manuscript for important intellectual content: Fotenos, Mintun, Snyder, Morris, and Buckner. Statistical analysis: Fotenos. Obtained funding: Mintun, Morris, and Buckner. Administrative, technical, and material support: Fotenos, Mintun, Snyder, Morris, and Buckner. Study supervision: Fotenos, Morris, and Buckner.

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REFERENCES


