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 $\times$ 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 (C) 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, 3.1 times over a 3.1- to 6.5-year interval; mean time, 4.3 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 WBV were being explored simultaneously, eTIV was allowed to enter as a covariate, and the dependent variable is denoted as aWBV to reflect this adjustment.

At the participant’s initial clinical evaluation, SES was assessed using the Hollingshead 2-factor index of social position. The Hollingshead index represents a linear combination of educational and household occupational attainment with occupation almost doubly weighted. The highest attained occupation was used for indexing. The index ranges from 11 to 77 grouped into 5 SES categories (I-V). To control for potential health confounds related to deprivation in the underprivileged, and because the cohort from which data were drawn contains too few low-SES individuals to disentangle these effects, this study focused on variation of the Hollingshead index within the range of the high-privilege to middle-SES groups (I-III). Neither participation in follow-up MRI nor any of the measured health variables differed between these groups (Table 1).

### 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

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non-demented 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 non-demented 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 interest24 (descriptions of regions of inter-

Table 2. Pittsburgh Compound B Amyloid Imaging Sample

<table>
<thead>
<tr>
<th>CDR 0 PiB−</th>
<th>CDR 0 PiB+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (cross-sectional)</td>
<td>49</td>
</tr>
<tr>
<td>Sex, F/M, No.</td>
<td>39/10</td>
</tr>
<tr>
<td>Sum box score 0/0.5, No.</td>
<td>46/3</td>
</tr>
<tr>
<td>Age, mean (SD) [range], y</td>
<td>69 (11) [47–86]</td>
</tr>
<tr>
<td>Education, mean (SD) [range], y</td>
<td>16 (3) [11–20]</td>
</tr>
<tr>
<td>MMSE score, mean (SD) [range]</td>
<td>29 (1) [26–30]</td>
</tr>
<tr>
<td>Weight (sex-adjusted), mean (SD) [range], kg</td>
<td>72 (12) [51–107]</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 (t3 = 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.
est and regional distribution of binding potential values appear elsewhere. A mean binding potential for these 4 regions greater than 0.2 was used to classify individuals with higher relative cortical binding as PiB+ based on the demonstrated association between CDR, cerebrospinal fluid β amyloid 42, and quantitative PiB uptake. Baseline MRIs from individuals classified as PiB+ were then compared against PiB− MRIs in a separate analysis of the PiB sample using aWBV as the dependent measure. Age and sex were covariates.

Later development of dementia was assessed by examining the longitudinal history of clinical examinations. A large overlapping clinical sample (in contrast to the limited PiB sample) allowed us to explore interactions with SES. Specifically, 91 of the 100 participants characterized in Table 1 as CDR 0 around the time of baseline MRI received at least 1 subsequent clinical follow-up. Participants were classified relative to their initial MRI as preclinical if they progressed to CDR 0.5 at any subsequent clinical examination. Group status (preclinical vs stable CDR 0) was added as an additional term in the cross-sectional analysis of SES described here.

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 \( F_{3,356} = 1394.14, P < .001, R^2 = 0.93 \). Between ages 20 and 80 years, aWBV was estimated to decline from 1199 cm³ to 1025 cm³ in men and from 1195 cm³ to 1050 cm³ in women (decline in annualized percentage terms, 0.24% per year and 0.20% per year, respectively). Initial aWBV is similar in men and women, reflecting the adjustment’s ability to accommodate head-size differences. The quadratic age term reflects acceleration of volume decline in advanced aging. Within the age range between 65 and 80 years, estimated declines were 0.40% per year (men) and 0.35% per year (women).

PRIVILEGED OLDER ADULTS AND REDUCED BRAIN VOLUME

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).

PRIVILEGED OLDER ADULTS AND ACCELERATED LONGITUDINAL VOLUME LOSS

To determine whether cross-sectional differences associated with SES relate to aging, volume change was estimated within participants using longitudinal MRI (Figure 2B and Table 3). More privileged individuals exhibited accelerated loss of aWBV (time × SES β = 0.11 cm³ per year per Hollingshead, \( P < .05 \)), controlling for sex × time and main effects of SES and time within the multilevel model (\( \gamma^2 = 191.96, P < .001 \); adding baseline age did not contribute). Spanning the longitudinal sample range from middle privilege (Hollingshead 40) to highest privilege (Hollingshead 11), model estimates of aWBV loss increased from 4.3 cm³ per year to 7.4 cm³ per year (0.39% per year to 0.68% per year, relative to model intercept).

EVIDENCE THAT RESERVE MAY BE AN IMPORTANT FACTOR IN AD

Figure 3 and Figure 4 display 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 \((P \leq 0.05)\) of positive PiB binding on brain volume: aWBV was estimated to decline 27 cm\(^3\) (2.5%, from 1066 cm\(^3\) to 1039 cm\(^3\)) in the CDR 0 PiB+ group after adjusting for effects of age and sex (model \(F_{3,54} = 151.62, P < 0.001, R^2 = 0.89\)). 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 \(F_{7,83} = 151.38, P < 0.001, R^2 = 0.93\) revealed a group × privilege interaction \((B = 2.2 \text{ cm}^3 \text{ per Hollingshead unit clinical conversion}, P < 0.05)\). The magnitude of the interaction predicts that the cross-sectional decline in aWBV with privilege \((B = 1.3 \text{ cm}^3 \text{ per Hollingshead unit overall})\) will increase by 2.2 cm\(^3\) 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.
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 nondemented 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, or 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. 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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REFERENCES


