# Premorbid Brain Size as a Determinant of Reserve Capacity Against Intellectual Decline in Alzheimer's Disease

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*Objective: Both the magnitude of brain atrophy and premorbid brain size determine the volume of the brain affected by Alzheimer's disease. To examine the possibility that premorbid brain volume is a determinant of cognitive reserve in patients with Alzheimer's disease, the relation between diffuse brain atrophy and cognitive decline and the impact of premorbid brain size on cognitive decline were studied in patients with Alzheimer's disease. Method: By measuring whole brain volume and intracranial volume in 60 patients with probable Alzheimer's disease, mild to moderate in severity, with the use of high-resolution magnetic resonance imaging and image processing, the authors studied the impact of premorbid brain volume and magnitude of diffuse brain atrophy on cognitive functions. On the basis of the normative brain-calvarium relationship derived from data an 28 healthy adults and the total intracranial volume measure of each patient, the magnitude of brain atrophy and premorbid brain volume were estimated. Results: After control for the effects of age, sex, and education as confounding factors, it was found that the Alzheimer's disease patients' intelligence was correlated both positively with premorbid brain volume and negatively with magnitude of brain atrophy, while impairments in language and memory were correlated with magnitude of brain atrophy but not with premorbid brain volume. Conclusions: These findings partially support the hypothesis that premorbid brain volume is a determinant of reserves against intellectual decline in Alzheimer's disease.*

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Diffuse brain atrophy, a main gross pathological feature of Alzheimer's disease, follows neuronal and synaptic loss (1, 2). Both the magnitude of atrophy and premorbid brain size determine the volume of the brain affected by Alzheimer's disease (3–9). If extra numbers of neurons and synaptic connectivities are included in a larger brain (10), the brain might maintain function after a part of them are lost through the disease process. Katzman et al. (11), on the basis of a pathology study, speculated that the larger brains of the cognitively intact subjects may have provided a functional reserve against the consequences of the pathological changes. More recently, investigators in a retrospective computerized tomography (CT) study (12), which demonstrated that onset of symptoms of Alzheimer's disease was delayed in proportion to premorbid brain size, hypothesized that premorbid brain volume is a determinant of cognitive reserve in patients with Alzheimer's disease. To examine this hypothesis, we studied the impact of premorbid brain volume on cognitive impairment in patients with Alzheimer's disease. Even after brain atrophy has developed, the total intracranial volume remains unchanged and thus is a good indicator of maximal mature brain size. Therefore, by measuring total intracranial volume, we can estimate the premorbid

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brain volume, as anthropologists estimate hominoid brain size from fossil skulls. In this study, using high-resolution magnetic resonance imaging (MRI) and a semiautomatic method of image analysis, we directly measured whole brain volume and intracranial volume, thereby estimating the magnitude of brain atrophy and the premorbid brain volume. Age, sex, and education, which may have an influence on both types of brain volume (3, 4, 13, 14) and neuropsychological test scores (15, 16), were also taken into consideration in this cross-sectional study.

## METHOD

The whole procedure of this study strictly followed the clinical study guidelines of the ethics committee of Hyogo Institute for Aging Brain and Cognitive Disorders, Himeji, Japan, in 1993 and was approved by the internal review board. After a complete description of the study to the subjects and their relatives, written informed consent was obtained.

According to the following criteria, 60 Japanese patients with mild to moderate Alzheimer's disease were recruited from those who were consecutively seen in our hospital between July 1993 and June 1995. All patients were examined by both neurologists and psychiatrists during their short-term hospital stays and underwent routine laboratory tests, standard neuropsychological examinations, EEG, MRI of the brain, magnetic resonance angiography of the neck and head, and cerebral perfusion/metabolism studies by positron emission tomography or single photon emission computed tomography. The inclusion criteria for the study were 1) meeting the criteria of the National Institute of Neurological Disease and Stroke/Alzheimer's Disease and Related Disorders Association for probable Alzheimer's disease (17), 2) mild to moderate severity of functional impairment (grades 0.5, 1, and 2 on the Clinical Dementia Rating [18]), and 3) no evidence of focal brain lesions on MRI. The exclusion criteria were 1) age greater than 80 years, 2) complications of other neurological diseases or physical illnesses, 3) any evidence of developmental abnormalities that may affect brain development, 4) a Mini-Mental State (19, 20) score less than 11, suggesting the presence of severe language, attention, and behavioral disorders that would make the neuropsychological assessment difficult, and 5) our inability to obtain informed consent from a patient and his or her relatives.

In this period, 99 patients were diagnosed as having probable Alzheimer's disease, 89 of whom met the inclusion criteria. Twenty-nine of these patients were excluded because of older age (N=16), lower Mini-Mental State score (N=7), complications (N=4), and inability to give informed consent (N=2). Consequently, 60 patients (37 women and 23 men) were included. Their mean age was 70.2 years (SD=7.1, range=44–79), their mean level of education was 8.9 years (SD=2.3, range=6–16), and their mean Mini-Mental State score was 18.8 (SD=3.9, range=11–26). According to information from informant interviews, the patients' mean age at symptom onset was 67.1 years (SD=7.5, range=42–77) and the mean duration of symptoms was 37.3 months (SD=28.8, range=3–120). The female and male patients did not differ significantly in age, education, age at first symptoms, duration of symptoms, and Mini-Mental State score.

To determine the normative relationship between the mature calvarium and brain volume in healthy Japanese subjects, 28 normal middle-aged volunteers (16 women and 12 men) whose mean age was 58.3 years (SD=4.1, range=47–64) were recruited from the community. They had no neurological signs, no substantial antecedent medical problems, and no abnormal findings on MRI. All of these subjects achieved scores of 29 or 30 on the Mini-Mental State examination.

### *MRI Studies*

All studies were performed on a 1.5-T MRI unit (Signa Advantage 5.x, General Electric) with the use of a circularly polarized head coil as both transmitter and receiver. Coronal three-dimensional spoiled gradient echo images (field of view=220 mm, matrix=256×256 pixels, 124×1.5-mm contiguous sections, TR=14 msec, TE=3 msec, flip angle=20°) perpendicular to the anterior-posterior commissure plane that covers the whole calvarium were used for the volumetric studies (21). Axial $T_2$-weighted, proton density, and $T_1$-weighted images were also obtained for diagnosis.

The MRI data sets of all images were directly transmitted to a personal computer (Power Macintosh 8100/100, Apple) from the MRI unit and analyzed with the public domain National Institutes of Health image program (22), version 1.58, with residential macro programs developed in our institute after an appropriate data conversion. Measurements were performed by one investigator (E.M.).

Whole brain volume and total intracranial volume were measured on coronal spoiled gradient echo sections. The slice volume of each structure was obtained by automatically counting the number of pixels within the segmented regions and then multiplying the number by voxel size ($0.859^2 \times 1.5 = 1.1068$ mm$^3$). Basically, we used a semiautomatic segmentation technique through density thresholding, thereby avoiding partial voluming and observer's bias (23). The cranial cavity was semiautomatically segmented and extracted by using a density threshold set above the minimum value of the CSF (the lateral ventricle). When density thresholding insufficiently segmented the object, outlining with a manually driven mouse cursor was supplemented along the inner table of the skull and along the margins of the cerebral hemispheres basally. Subsequently, the whole brain was automatically segmented on the extracted images by using a density threshold set at a range between minimum and maximum pixel values, where the maximum value was the largest pixel value of the cerebrum and the minimum value was half the value of the mean pixel value of the gray matter (the caudate head) and the mean value of the CSF, since the gray matter and CSF are predominant constituents of the brain-extrabrain interface.

The test-retest reliabilities, expressed as intraclass correlation coefficients, which were derived from three repeated measurements by a single rater (E.M.) under blind conditions in 10 randomly selected patients, were 0.990 for total intracranial volume and 0.987 for whole brain volume. In a validity experiment that used phantom constructions filled with copper sulfate solution, accuracies of 99.4% for a 2664-ml sphere and 98.3% (average) for 5-ml cylinders were achieved, which indicated that the equipment and measurement we used resulted in a slight underestimation of volume.

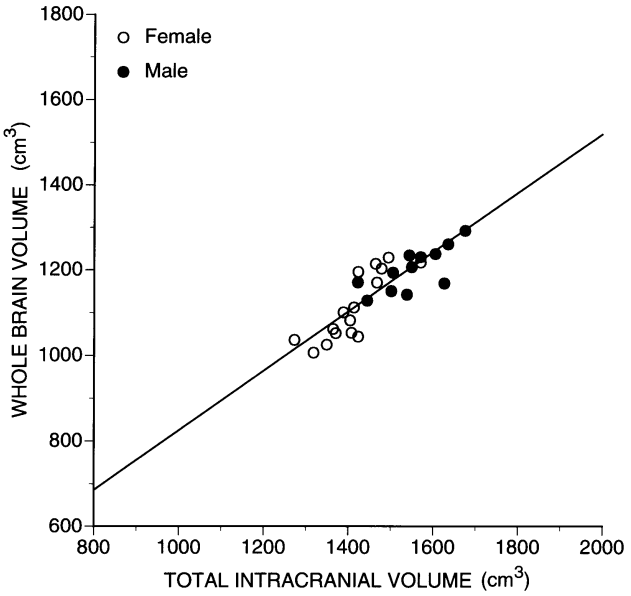
### *Neuropsychological Assessments*

MRI studies and neuropsychological evaluations were performed within a 1-month interval. To assess the cognitive dysfunction of the subjects, we administered the cognitive items of the Alzheimer's Disease Assessment Scale (24, 25), the Western Aphasia Battery (26, 27), and the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (28, 29). The Raven Coloured Progressive Matrices (30) was also administered as a part of the Western Aphasia Battery. Besides the total scores on the Mini-Mental State examination and the cognitive items of the Alzheimer's Disease Assessment Scale, the Western Aphasia Battery aphasia quotient, the score on the Raven Coloured Progressive Matrices, and the WAIS-R full-scale IQ, we analyzed separately the word recall score on the cognitive part of the Alzheimer's Disease Assessment Scale and the WAIS-R verbal IQ and performance IQ. The word recall subtest is inherently a verbal learning test, in which the retention of a written 10-word list is measured by free immediate recall after each of three learning trials. The score is expressed as the mean number of words recalled in three trials.

### *Statistical Analysis*

The normative calvarium-brain volume relationship in normal subjects was determined by using a simple regression analysis, which yielded the regression coefficient and a constant term. To examine the effects of age and sex on whole brain volume, a multiple regression analysis was applied, with whole brain volume as the dependent variable and age, sex, and total intracranial volume as the independent variables. Each patient's premorbid brain volume, which implies

**FIGURE 1. Relation Between Total Intracranial Volume and Whole Brain Volume in 28 Normal Subjects**




whole brain volume during the patient's middle age, when not yet affected by the disease, was estimated as follows: premorbid brain volume equals the regression coefficient multiplied by the total intracranial volume plus the constant term. The magnitude of brain atrophy in each patient was calculated by subtracting the observed brain volume from the premorbid brain volume. The patient's whole brain volume was normalized to total intracranial volume with the covariance method described by Jack et al. (31): normalized whole brain volume=observed brain volume – regression coefficient × (patient's total intracranial volume – mean total intracranial volume in normal subjects). Then the magnitude of brain atrophy can be alternatively expressed as the mean value of whole brain volume in the normal subjects minus the normalized whole brain volume.

The relation between each brain volume and each neuropsychological test score was evaluated by means of multiple linear regression, with each neuropsychological test score as the dependent variable, premorbid brain volume and magnitude of brain atrophy as the independent variables, and education, age, and sex as potential confounding variables that might be related both to each neuropsychological test score and to each brain volume. Multiple linear regression analysis was also used to test the relation between premorbid brain volume and age at onset of dementia, with age at onset as the dependent variable, premorbid brain volume as the independent variable, and education and sex as potential confounding variables. Analyses were repeated after entering body size (either height or weight) into the model as a confounding factor to test whether the relationships mentioned above were maintained after correction for body size.

The two-tailed t test and Pearson's correlation were used where appropriate. All statistical analyses were carried out with SAS Release 6.10 software (32). The level of significance was set at $<0.05$ for all statistical analyses.

## RESULTS

The mean total intracranial volume for the group of normal subjects was 1472 $cm^3$ (SD=101, range=1273–1675); the mean for the women was 1413 $cm^3$ (SD=73), and the mean for the men was 1551 $cm^3$ (SD=76). The mean whole brain volume for the normal subjects was 1150 $cm^3$ (SD=81, range=1006–1292); the mean for the women was 1113 $cm^3$ (SD=79), and the mean for the men was 1201 $cm^3$ (SD=51). A highly significant correlation was found between total intracranial volume and whole brain volume ($r=0.856$, $F=71.26$, $df=1, 26$, $p<0.001$, simple regression analysis). The relation between total intracranial volume and whole brain volume is expressed in the following regression equation: whole brain volume=0.685 × total intracranial volume + 143, where the regression coefficient is 0.685 and the constant term is 143 (figure 1). A multiple regression analysis with total intracranial volume partialed out revealed that whole brain volume was not correlated with either age (partial $r=–0.059$, $p=0.78$) or sex (partial $r=0.066$, $p=0.75$).

The mean scores of the patients with Alzheimer's disease on the neuropsychological tests are shown in table 1. A significant negative correlation was found between level of education and age ($r=–0.447$, $F=14.49$, $df=1, 58$, $p<0.001$, simple regression analysis). The women did not differ significantly from the men on each of the scores in table 1. There was no significant correlation between education and each score or between age and each score.

Table 2 shows the results of volume measurement in the patients with Alzheimer's disease. Total intracranial volume was significantly correlated with observed brain volume ($r=0.780$, $F=89.89$, $df=1, 58$, $p<0.001$, simple regression analysis). There was a significant difference between men and women in observed brain volume and in total intracranial volume. Age was not significantly correlated with observed brain volume or with total intracranial volume.

The mean premorbid brain volume and the mean magnitude of brain atrophy were 1140 $cm^3$ and 145 $cm^3$, respectively. The mean premorbid brain volume was significantly larger in the men than in the women. There was no difference in magnitude of brain atrophy between the women and the men (table 2). There was no correlation between brain atrophy magnitude and premorbid brain volume ($r=–0.066$, $F=0.25$, $df=1, 58$, $p=0.62$, simple regression analysis). Age and education were not significantly correlated with brain atrophy magnitude or premorbid brain volume. Although premorbid brain volume was significantly correlated with body height ($r=0.611$, $F=34.50$, $df=1, 58$, $p<0.001$, simple regression analysis) and body weight ($r=0.384$, $F=10.06$, $df=1, 58$, $p=0.002$, simple regression analysis), these correlations were no longer significant when the effect of sex was partialed out, which implies that an effect of sex accounts for a large part of the relation between body size and brain size.

Results of the regression analyses are shown in table 3. We found that both brain atrophy magnitude and premorbid brain volume were significantly correlated with some cognitive functions (figure 2 and table 3). The total score and the recall score on the cognitive part of the Alzheimer's Disease Assessment Scale, the Western Aphasia Battery aphasia quotient, the Raven matrices score, and the WAIS-R full-scale IQ, verbal IQ, and performance IQ were each significantly and appropri-

**TABLE 1. Results of Neuropsychological Tests of Patients With Alzheimer's Disease**

| Measure | All Patients (N=60) Mean | SD | Range | Female Patients (N=37) Mean | SD | Male Patients (N=23) Mean | SD | Difference Between Female and Male Patients (p)[a] |
|---|---|---|---|---|---|---|---|---|
| Alzheimer's Disease Assessment Scale cognitive items | | | | | | | | |
| Total score | 22.4 | 8.4 | 10–47 | 24.0 | 9.2 | 19.8 | 6.2 | 0.06 |
| Recall score | 6.5 | 1.3 | 3–10 | 6.6 | 1.4 | 6.2 | 1.2 | 0.21 |
| WAIS-R | | | | | | | | |
| Full-scale IQ | 75.4 | 12.5 | 55–112 | 74.3 | 10.3 | 77.1 | 15.5 | 0.40 |
| Verbal IQ | 79.0 | 11.6 | 59–120 | 77.9 | 9.0 | 80.7 | 15.0 | 0.37 |
| Performance IQ | 74.6 | 14.0 | 49–108 | 73.7 | 12.4 | 76.1 | 16.4 | 0.51 |
| Western Aphasia Battery aphasia quotient | 83.1 | 8.5 | 59–97 | 82.5 | 9.1 | 84.1 | 7.4 | 0.48 |
| Raven Coloured Progressive Matrices score | 19.0 | 6.1 | 6–33 | 17.8 | 5.6 | 20.5 | 6.5 | 0.09 |

[a]By t test (df=58).

**TABLE 2. Brain Volume Measurements of Patients With Alzheimer's Disease**

| Measure | All Patients (N=60) Mean | SD | Range | Female Patients (N=37) Mean | SD | Male Patients (N=23) Mean | SD | Difference Between Female and Male Patients (p)[a] |
|---|---|---|---|---|---|---|---|---|
| Total intracranial volume ($cm^3$) | 1455 | 111 | 1276–1703 | 1396 | 68 | 1552 | 100 | <0.001 |
| Observed brain volume ($cm^3$) | 995 | 93 | 809–1179 | 952 | 62 | 1063 | 95 | <0.001 |
| Brain atrophy magnitude ($cm^3$) | 145 | 58 | 33–311 | 146 | 57 | 142 | 62 | 0.80 |
| Premorbid brain volume ($cm^3$) | 1140 | 76 | 1016–1310 | 1099 | 46 | 1206 | 69 | <0.001 |

[a]By t test (df=58).

ately correlated with magnitude of brain atrophy. The WAIS-R full-scale IQ, verbal IQ, and performance IQ and the Raven matrices score were significantly correlated with premorbid brain volume. For instance, the regression model for full-scale IQ predicted an IQ decline of 1 point that occurs for each 14.3-$cm^3$ increase (95% confidence interval=8.3–50 $cm^3$) in brain atrophy will be canceled by each 11.9-$cm^3$ increase (95% confidence interval=7.3–31.3 $cm^3$) in premorbid brain volume. When the effect of body size (height or weight) was partialed out, partial correlation coefficients were not altered very much. Results of the analyses with correction for height are also presented in table 3. When subjects were divided according to sex, both female and male patients showed a pattern of correlations similar to that in the overall analysis with or without corrections for body size, although dividing the number of subjects affected the power of the statistics; the performance IQ of the women and the verbal IQ of the men were not significantly correlated with premorbid brain volume or with brain atrophy magnitude, and a significant correlation with the Raven matrices score was observed only for the brain atrophy magnitude of the men.

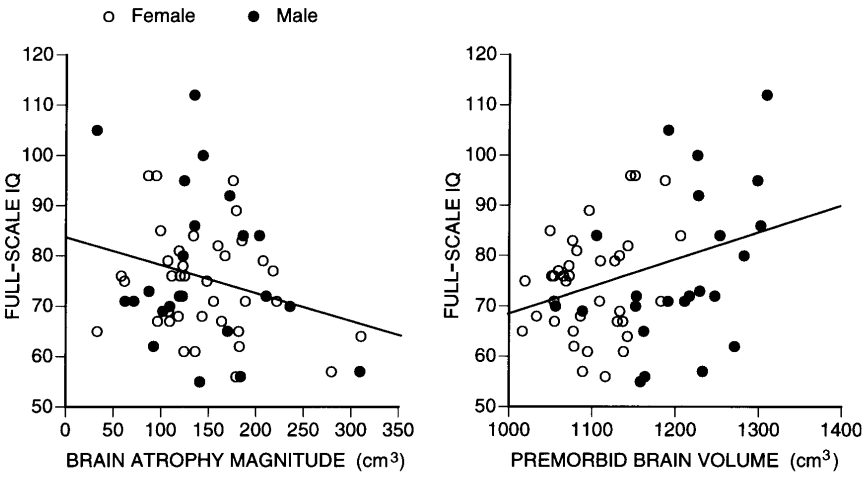
**TABLE 3. Partial Correlations of Neuropsychological Test Scores With Brain Atrophy Magnitude and Premorbid Brain Volume in 60 Patients With Alzheimer's Disease[a]**

| Measure | Correlation (r) Uncorrected for Body Size[b] Brain Atrophy Magnitude | Premorbid Brain Volume | Correlation (r) Corrected for Body Height[c] Brain Atrophy Magnitude | Premorbid Brain Volume |
|---|---|---|---|---|
| Alzheimer's Disease Assessment Scale cognitive items | | | | |
| Total score | 0.377** | –0.123 | 0.378** | –0.114 |
| Recall score | –0.305* | 0.096 | –0.305* | 0.124 |
| WAIS-R | | | | |
| Full-scale IQ | –0.359** | 0.399** | –0.359** | 0.396** |
| Verbal IQ | –0.353** | 0.365** | –0.354** | 0.360** |
| Performance IQ | –0.325* | 0.365** | –0.325* | 0.362** |
| Western Aphasia Battery aphasia quotient | –0.278* | 0.140 | –0.278* | 0.139 |
| Raven Coloured Progressive Matrices score | –0.354** | 0.284* | –0.352** | 0.289* |

[a]Effects of age, sex, and education as confounding factors were partialed out in all analyses.
[b]Multiple linear regression analysis (df=5, 54).
[c]Multiple linear regression analysis (df=6, 53).
*p<0.05. **p<0.01.

There was no significant correlation between premorbid brain volume and age at first symptom of dementia (partial r=0.004, p=0.97, multiple regression analysis). The results were similar when height was partialed out.

**FIGURE 2. Relation Between Magnitude of Brain Atrophy and Full-Scale IQ and Between Premorbid Brain Volume and Full-Scale IQ in 60 Patients With Alzheimer's Disease[a]**




[a]Simple linear regression analyses showed significant correlations between brain atrophy magnitude and full-scale IQ (r=0.279, F=3.83, df=1, 58, p=0.03) and between premorbid brain volume and full-scale IQ (r=0.327, F=6.93, df=1, 58, p=0.01). These correlations were significant in a multiple linear regression analysis with education, age, and sex partialed out.

## DISCUSSION

In this study, we used MRI to measure directly whole brain volumes and intracranial volumes in normal subjects and patients with probable Alzheimer's disease. The analysis of the relation of brain volume to intracranial volume in the normal subjects confirmed an extremely high correlation, indicating that the estimation of premorbid brain volume from intracranial volume was highly reasonable and could be done with fair confidence. This rationalizes the estimation of premorbid brain volume in each patient with Alzheimer's disease. Progressive decline in brain weight, an average of 2 g per year, begins at about 45–50 years of age (4, 5). Although a significant correlation between age and brain volume was not demonstrated in this study, probably because of the restricted age range of the normative group as well as its small size, premorbid brain volume and brain atrophy magnitude would be somewhat underestimated by a smaller constant term than that derived from younger normative subjects. Thus, each patient's premorbid brain volume should be regarded as the volume of the brain in the patient's middle age (late 50s) when he or she was not affected by the disease but was already involved in age-associated atrophy, and the magnitude of each patient's brain atrophy should be regarded as the reduction in volume from the brain size at his or her middle age. This underestimation of premorbid brain volume is not important in the correlational analyses and is unlikely to have affected the results.

The results of a correlational analysis for patients with Alzheimer's disease demonstrated that some cognitive functions were correlated modestly but significantly with not only the magnitude of brain atrophy but also premorbid brain volume. The former relationship was consistent with findings in previous quantitative CT or MRI studies (33–35). Intelligence, as measured by the WAIS-R and the Raven Coloured Progressive Matrices, was correlated with both the magnitude of brain atrophy and premorbid brain volume. Aphasic disorder, as measured by the Western Aphasia Battery aphasia quotient, and dementia-related dysfunction, including memory impairment, as measured by the Alzheimer's Disease Assessment Scale cognitive items total score and word recall score, were correlated significantly with magnitude of brain atrophy. These associations were independent of the effects of age, sex, and education. There is a positive relationship between brain weight and body dimensions (36). However, there is disagreement about whether brain size should be corrected for body size—in other words, whether relative or absolute brain size should be used (37). In either case, these associations remained unchanged when brain size was controlled for body size. However, the modest degree of the relationships must be emphasized. Since correlations from 0.284 to 0.399 imply that premorbid brain volume accounts for only 8.1%–15.9% of the variance, many other factors must be involved in the cognitive decline in Alzheimer's disease.

Our findings on the relation between premorbid brain volume and intelligence at least partially support the hypothesis that premorbid brain volume is an important determinant of reserves against cognitive decline in Alzheimer's disease and are compatible with the findings of Schofield et al. (12). In a retrospective planimetric CT study in which the intracranial area in 28 female patients with probable Alzheimer's disease was measured, these authors demonstrated that age at onset of Alzheimer's disease was positively correlated with premorbid brain size. If cognitive functions stay within the range of the reserve capacity of normal brain performance even after the Alzheimer pathology starts to affect the brain, onset of dementia might be delayed. However, an unexpected finding was that the effect of premorbid brain volume was limited to psychometrically determined intelligence, a composite of multiple cognitive domains. The lack of influence of premorbid brain volume on fundamental functions such as memory and language might be attributable to the discreteness of those functions, which are hardly compensated for by other functions. The memory and language functions that are organized in specific brain regions might be influenced more by damage to those regions, possibly in proportion to the magnitude of brain atrophy. We also failed to find a significant correlation between

age at the first symptom of dementia and premorbid brain volume. This accords with the finding of little effect of premorbid brain volume on memory impairment, since a problem with memory is the initial symptom reported in most patients (38). The validity of using families' reports for determining age at onset of dementia is also disputable. Further studies, especially longitudinal studies, are required to confirm these unexpected findings.

The most likely interpretation of our findings is that the larger brain has a greater neural reserve capacity, which may underlie a greater functional reserve capacity. If extra numbers of neurons and synaptic connectivities relevant to cognitive functions are included in a larger brain, the brain might maintain the functions after a part of these neural components is lost through the disease process. This assumption would be supported only if among individuals the density of neurons and synapses is comparable and the quantity of myelin is proportional. Although estimations of this kind are few and may be subject to great error, Haug (10) showed that small increases in brain volume could translate into millions of excess neurons.

There is a considerable amount of evidence supporting the association between psychometrically determined intelligence and brain size in humans (37, 39–42), although there is much debate on this issue (43–45). In several MRI studies (41, 42), mature brain volume was shown to be positively correlated with intelligence in normal individuals. Other MRI studies (46, 47) demonstrated that level of education, which is expected to be correlated with intelligence (15), was correlated with brain size. On the other hand, the risk of dementia was reportedly reduced in highly educated subjects, either through decreasing the ease of clinical detection of Alzheimer's disease or through imparting a reserve that delays the onset of clinical manifestations (48, 49). Therefore, an alternative explanation for our findings is that the relation between brain volume and intelligence in the general population, if any, reflects the relation between premorbid brain volume and cognitive function in this study: those who have a larger brain would have higher premorbid intelligence and might achieve higher scores on some tests even after being affected by Alzheimer's disease. However, in this study, the relationship was independent of the effects of education, and no significant correlation was shown between the test scores and level of education. Longitudinal studies would be needed to determine the effects of premorbid level of cognitive function.

In conclusion, our findings partially support the hypothesis that premorbid brain volume is a determinant of reserves against cognitive decline that is linked to the magnitude of brain atrophy, and they suggest a threshold concept that dementia emerges after the exhaustion of the functional reserve capacity. Premorbid brain volume had an apparent effect on psychometrically determined intelligence but not on fundamental cognitive functions, including memory and language, or on age at onset of dementia. The roles of premorbid brain volume and premorbid cognitive function in neuronal and functional reserves against structural damage are to be determined in further longitudinal studies.

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