Association of Premorbid Intellectual Function With Cerebral Metabolism in Alzheimer's Disease: Implications for the Cognitive Reserve Hypothesis

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Objective: *Clinical heterogeneity in Alzheimer's disease has been widely observed. One factor that may influence the expression of dementia in Alzheimer's disease is premorbid intellectual ability. It has been hypothesized that premorbid ability, as measured by educational experience, reflects a cognitive reserve that can affect the clinical expression of Alzheimer's disease. The authors investigated the relation between estimates of premorbid intellectual function and cerebral glucose metabolism in patients with Alzheimer's disease to test the effect of differing levels of premorbid ability on neurophysiological dysfunction.* *Method:* *In a resting state with eyes closed and ears occluded, 46 patients with Alzheimer's disease were evaluated with positron emission tomography and [^{18}F]-2-fluoro-2-deoxy-D-glucose to determine cerebral metabolism. Premorbid intellectual ability was assessed by a demographics-based IQ estimate and performance on a measure of word-reading ability.* *Results:* *After the authors controlled for demographic characteristics and dementia severity, both estimates of premorbid intellectual ability were inversely correlated with cerebral metabolism in the prefrontal, premotor, and left superior parietal association regions. In addition, the performance-based estimate (i.e., reading ability) was inversely correlated with metabolism in the anterior cingulate, paracentral, right orbitofrontal, and left thalamic regions, after demographic and clinical variables were controlled for.* *Conclusions:* *The results suggest that higher levels of premorbid ability are associated with greater pathophysiological effects of Alzheimer's disease among patients of similar dementia severity levels. These findings provide support for a cognitive reserve that can alter the clinical expression of dementia and influence the neurophysiological heterogeneity observed in Alzheimer's disease.*

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Premorbid function, as measured by years of education, may influence the clinical expression of Alzheimer's disease (1, 2). In epidemiological studies (3–5), a lower level of education was associated with a higher prevalence and incidence of Alzheimer's disease. A high education level or its correlates may reflect a cognitive reserve such that the neuropathological effects of Alzheimer's disease must be more severe for the clinical symptoms of dementia to become evident (1). Stern et al. (6, 7) reported that high levels of premorbid educational and occupational attainment were associated with greater deficits in parietotemporal perfusion in a group of patients with Alzheimer's disease, after clinical dementia severity was controlled for. These studies provided initial physiological support for the cognitive reserve hypothesis, using cortical perfusion assessed with inhaled xenon-133 as a

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TABLE 1. Characteristics of 46 Patients With Alzheimer's Disease and 41 Matched Healthy Comparison Subjects

Characteristic	Comparison Subjects		Alzheimer's Disease		Two-Tailed t Test		
	Mean	SD	Mean	SD	t	df	p
Age (years)	65.6	12.7	67.8	10.6	0.90	85	n.s.
Education (years)	15.6	2.6	14.7	3.0	−1.46	85	n.s.
Age at onset (years)			62.7	10.0			
Duration of illness (years)			5.2	2.6			
Mini-Mental State score	29.6	0.6	17.8	6.4	−11.19	81	0.0001
Mattis Dementia Rating Scale total score	140.0	4.1	104.9	21.6	−10.27	85	0.0001
WAIS full-scale IQ	125.4	13.0	93.8	17.7	−9.32	83	0.0001
Demographic IQ estimate[a]	123.1	9.7	121.3	9.2	−0.87	85	n.s.
Wide Range Achievement Test reading subtest (level II)	15.4	2.8	12.6	3.9	−3.75	85	0.001
Global gray matter glucose metabolism (mg/100 g per minute)	8.2	1.0	6.6	1.0	−7.66	85	0.0001

[a]Demographics-based estimate of WAIS full-scale IQ calculated with the regression formula of Wilson et al. (21).

pathophysiological marker of disease severity. The use of high-resolution functional neuroimaging to study the association between premorbid intellectual function and neurophysiological dysfunction in Alzheimer's disease has yet to be investigated.

It is widely accepted that cerebral metabolic dysfunction assessed with positron emission tomography (PET) and [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) reflects pathophysiological disease severity in Alzheimer's disease. The patterns of neocortical cerebral metabolic deficit are associated with clinical dementia severity (8, 9) and have been shown to correspond to distributions of Alzheimer's disease histopathology (10, 11). Although the patterns of cerebral dysfunction appear heterogeneous in Alzheimer's disease (9, 12, 13), the parietal, temporal, and frontal association areas are most consistently and severely affected (14–16).

Using only demographic characteristics, such as years of education, to estimate patient functioning before the onset of dementia may not fully reflect the degree of intellectual ability achieved during the life span. Performance-based measures of word-reading ability can remain relatively preserved in the early stages of dementia and offer an alternative to demographically based estimates of premorbid intellectual function in Alzheimer's disease (17, 18).

In the current study, the association of cerebral glucose metabolism, as shown by PET and FDG, with premorbid function was investigated in a group of patients with Alzheimer's disease. It was hypothesized that if premorbid intellectual function reflects a cognitive reserve that influences the expression of dementia, then cerebral metabolism in brain regions typically affected in Alzheimer's disease, i.e., the parietotemporal and frontal association cortices, would be inversely related to premorbid ability among patients with similar degrees of clinical dementia severity. By using high-resolution functional neuroimaging and estimates of premorbid ability derived from both demographic variables and word-reading performance, we sought to evaluate the relation between pathophysiological disease severity and premorbid function in Alzheimer's disease with methods that offer greater sensitivity than do methods previously applied to this question. Further, with the use of a tomographic imaging technique, we assessed the relation of premorbid function in Alzheimer's disease to metabolic activity in brain regions previously not assessed, including subcortical and limbic regions.

METHOD

Subjects

Forty-six patients meeting the DSM-III-R criteria for dementia and the research diagnostic criteria for probable Alzheimer's disease of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association guidelines (19) were included in the present study. Fifteen of the patients have since come to autopsy and shown histopathology consistent with Alzheimer's disease (20). The patients were enrolled as part of a longitudinal study of dementia in the Laboratory of Neurosciences, National Institute on Aging. Of the 46 patients, 26 were men, and 20 were women; 44 were right-handed, and two were left-handed. Healthy volunteers, recruited by newspaper advertisement, were matched to the Alzheimer's disease group on demographic characteristics, including means and distributions of age, education, gender, race, and handedness. Of the 41 comparison subjects, 20 were men, and 21 were women; 37 were right-handed, and four were left-handed. All of the subjects in both groups were white. Other characteristics of the two groups are given in table 1. The study of patient and comparison subjects was approved by the National Institute on Aging Institutional Review Board (National Institutes of Health protocols 80-AG-26 and 81-AG-10). Written consent was obtained from each subject (and the conservator, if appropriate) after a full explanation of the purpose, procedures, and risks of the study.

Procedures

Clinical screening. Each subject received a review of medical history, physical and neurological examinations, and a psychiatric evaluation. The medical screening included EEG, magnetic resonance imaging (MRI) study of the brain, chest X-ray, ECG, audiological assessments, the Mini-Mental State examination (22), the Hachinski Ischemia Scale (23), the Hamilton Depression Rating Scale (24), an assessment of extrapyramidal signs, and ratings of ability to perform daily living activities. Blood tests were performed to assess routine blood counts, sedimentation rate, clotting, and serum chemistry; thyroid, liver, and renal function; levels of cholesterol, high-density lipoproteins, triglycerides, rheumatoid factor, vitamin B12, and folate; presence of antinuclear antibodies and hepatitis B antigen; and VDRL and HIV status. A subject was excluded if he or she had a history of important medical, neurological, or psychiatric illness, including neoplastic disease, epilepsy, stroke, traumatic head injury, and alcohol or drug abuse. There was no evidence of major cerebrovascular disease, lacunar infarcts, or mass effects on MRI scans of the head. None of the subjects had taken over-the-counter medications for at least 2 weeks or psychotropic drugs for at least 4 weeks before entering the study. Estimates of age at onset and duration of dementia were obtained from patient and family reports.

Neuropsychological and premorbid measures. A series of neuro-

psychological tests was administered to each subject to assess general intellectual functions, memory, language, visuospatial skills, and attention. The tests included the WAIS (25), Mattis Dementia Rating Scale (26), Selective Reminding Test (nine items, eight trials) (27), Wechsler Memory Scale (logical memory subtest, form I) (28), Boston Naming Test (29), FAS (30), Extended Range Drawing Test (8), Block Tapping Test (31), and Trail Making Test (32).

Premorbid intellectual function was estimated by using years of education, a demographics-based IQ estimate, and performance on the reading subtest of the Wide Range Achievement Test (level II) (WRAT) (33). The demographics-based IQ estimate was computed from a regression formula described by Wilson et al. (21), which was used to predict IQs for the WAIS standardization sample by using age, gender, education, race, and occupational history. The equation for computing this demographic IQ estimate is as follows: (0.17)age − (1.53)sex − (11.33)race + (2.97)education + (1.01)occupation + 74.05. The validity of the three estimates of premorbid intellectual function was evaluated in the 41 healthy comparison subjects matched to the Alzheimer's disease group on demographic variables. Years of education ($F=17.22$, $df=1, 39$, $p<0.0003$), the demographics-based IQ estimate ($F=27.41$, $df=1, 39$, $p<0.0001$), and the WRAT reading score ($F=23.68$, $df=1, 39$, $p<0.0001$) each significantly predicted WAIS full-scale IQ in the comparison group. The combination of age, gender, and the WRAT reading score was the best predictor of intellectual function in the comparison subjects, accounting for 62% of the variance ($F=19.91$, $df=3, 37$, $p<0.0001$).

Although word-reading performance remains relatively preserved in the early stages of Alzheimer's disease, patients with moderate or severe dementia demonstrate poorer reading performance than healthy comparison subjects (18). In our study group, the patients with Alzheimer's disease did not differ from the comparison group in the demographic IQ estimate, but they did show significantly poorer reading performance (table 1). We used linear regression analysis to statistically adjust reading performance for cognitive decline in the Alzheimer's disease group (34), using the Mattis Dementia Rating Scale to produce WRAT reading scores adjusted for dementia severity as a performance-based estimate of premorbid ability.

PET. The PET scans were performed with a Scanditronix PC1024-7B tomograph (Uppsala, Sweden); seven slices with 6-mm transverse and 10-mm axial resolutions were acquired. All scans were performed in a resting state with the subjects' eyes covered and ears occluded. A thermoplastic mask was used to maintain head position during scanning. Transmission scans were obtained for attenuation correction before administration of a 5-mCi bolus of FDG, injected intravenously. Emission scans were performed after a 45-minute uptake period. Two interleaved scans were obtained parallel to, and 10–100 mm above, the inferior orbitomeatal line, producing a total of 14 slices for each subject. Arterial blood samples were drawn during the procedure to measure radioactivity and glucose concentration in plasma. Rates of glucose metabolism in specific cerebral regions were calculated by using the Brooks modification (35) of the equation by Sokoloff et al. (36).

The image analysis procedures have been described in detail elsewhere (37). Briefly, the PET data were analyzed by using a template containing circular regions of interest 8 mm in diameter. The regions of interest were spaced evenly throughout the cerebral cortical rim and were centered in the subcortical regions. Scan slices for each subject were individually adjusted to best fit the corresponding slice template. Metabolic rates for larger functional regions were obtained by averaging values in the small circular areas that are included in larger anatomical regions according to a standard neuroanatomical atlas (38). High interrater reliability for this method of image analysis across all regions has been previously reported (13). The raters were not blind to patient diagnosis, but they were unaware of patient premorbid status and severity of cognitive impairment.

Statistical Analysis

Group differences in demographic and clinical measures were tested by using t tests and chi-square tests where appropriate. Multiple linear regression analysis was used to assess the prediction of intellectual function by the estimates of premorbid ability in the healthy comparison group. Pearson product-moment correlations were used to test the associations among the premorbid IQ estimates and their relation to neuropsychological performance in the Alzheimer's disease group. Spearman rank correlations were performed for the neuropsychological measures that were not normally distributed. The association of the premorbid IQ estimates with both global and regional cerebral glucose metabolic values in the patients with Alzheimer's disease was assessed by using partial correlations. Age, gender, and illness duration were used as initial covariates in the partial correlations for the adjusted WRAT reading score, whereas dementia severity (according to the Mattis Dementia Rating Scale) was included as an additional covariate in partial correlations with the demographics-based IQ estimate. Multiple linear regression analysis was used to identify the set of brain regions that explained the most variance in premorbid ability among the patients with Alzheimer's disease.

RESULTS

Relation of Premorbid IQ Estimates to Clinical and Demographic Characteristics

The IQ measures and global cerebral metabolic values of the two groups are given in table 1. In the Alzheimer's disease group, there was no significant correlation between the premorbid intellectual measures and age. Although the men had more years of education ($t=-3.33$, $df=44$, $p<0.002$) and a higher mean demographic IQ estimate ($t=-3.63$, $df=44$, $p<0.001$) than the women in our Alzheimer's disease group, there was no significant gender difference in WRAT reading performance among the patients with Alzheimer's disease. After adjustment of the WRAT reading scores for dementia severity with the Mattis Dementia Rating Scale, there was no significant correlation with any neuropsychological measure in the patients with Alzheimer's disease. Years of education and the demographic IQ estimate were highly correlated with each other ($r=0.97$, $df=44$, $p<0.0001$), whereas only the demographic IQ estimate was significantly correlated ($r=0.30$, $df=42$, $p<0.05$) with a measure of general intellectual function (WAIS full-scale IQ) in the Alzheimer's disease group. Additionally, the adjusted ($r=0.39$, $df=44$, $p<0.007$) and unadjusted ($r=0.40$, $df=44$, $p<0.006$) WRAT reading scores were equally correlated with years of education, indicating that the correction for dementia severity did not alter the association of WRAT reading performance with demographic measures of premorbid function. There was no relation between illness duration and the estimates of premorbid intellectual ability among the patients with Alzheimer's disease.

Association of Premorbid IQ Estimates With Cerebral Metabolism

We focused on the adjusted WRAT reading score and the demographic IQ estimate as performance- and demographics-based premorbid estimates for the primary analyses determining correlation with cerebral metabolism. There was no significant relation between the adjusted WRAT reading score and mean global cerebral metabolic rate for glucose when age, gender, and illness duration were controlled for (table 2). Similarly, there

TABLE 2. Partial Correlations Between Premorbid Intellectual Function and Cerebral Metabolism in 46 Patients With Alzheimer's Disease

Brain Region Assessed by PET for Glucose Metabolism[a]	Partial Correlation (r)[b]	
	Adjusted Score on WRAT Reading Subtest[c]	Demographic IQ Estimate[d]
Prefrontal		
Right	−0.55††	−0.31***
Left	−0.45†	−0.27**
Premotor		
Right	−0.51††	−0.30**
Left	−0.48†	−0.34***
Inferior, middle, and superior temporal		
Right	−0.01	−0.05
Left	0.10	−0.01
Anterior medial temporal		
Right	−0.08	−0.13
Left	0.11	−0.10
Posterior medial temporal		
Right	−0.08	−0.11
Left	−0.04	−0.20
Inferior and middle parietal		
Right	−0.05	−0.13
Left	0.01	−0.23
Superior parietal		
Right	−0.17	−0.26*
Left	−0.29**	−0.42†
Occipital		
Right	0.02	−0.15
Left	0.21	−0.05
Calcarine		
Right	0.05	−0.13
Left	0.18	−0.16
Orbitofrontal		
Right	−0.29**	−0.08
Left	−0.25*	−0.06
Basal ganglia		
Right	−0.06	0.10
Left	−0.10	−0.03
Thalamus		
Right	−0.11	0.06
Left	−0.28**	−0.01
Insula		
Right	−0.11	0.02
Left	−0.01	−0.03
Anterior cingulate		
Right	−0.36***	−0.15
Left	−0.31***	−0.13
Paracentral gray		
Right	−0.29**	−0.15
Left	−0.27**	−0.13
Posterior cingulate	−0.01	−0.12
Global gray matter	−0.18	−0.14

[a]Regional PET values were referenced to metabolism in the left sensorimotor cortex, as this region was least correlated with the premorbid estimates and remains relatively preserved in Alzheimer's disease.

[b]For the adjusted Wide Range Achievement Test reading score, partial correlations controlled for age, gender, and illness duration. Total score on the Mattis Dementia Rating Scale was included as an additional covariate for partial correlations with the demographic IQ estimate.

[c]Standardized reading scores were adjusted for dementia severity with the Mattis Dementia Rating Scale.

[d]Demographics-based estimate of WAIS full-scale IQ calculated with the regression formula of Wilson et al. (21).

*p=0.06. **p<0.05. ***p<0.025. †p<0.005. ††p<0.0001.

was no association between the demographic IQ estimate and global cerebral metabolic rate when age, gender, dementia severity (Mattis Dementia Rating Scale), and illness duration were used as initial covariates. In the analyses for regional glucose metabolic values, similar partial correlations with absolute cerebral metabolic rates and with values referenced to the left sensorimotor cortex were performed. The left sensorimotor region was selected as a reference value for the regional analyses to reduce intersubject variability in glucose metabolic rate. This region remains relatively preserved in Alzheimer's disease (8, 13–15, 37) and, among typically used reference values (e.g., those for global gray matter, calcarine cortex, and sensorimotor regions), was the least correlated ($0.01 \leq r \leq 0.04$, df=44, n.s.) with the premorbid intellectual measures in the Alzheimer's disease group.

Table 2 shows the results of partial correlations between the estimates of premorbid intellectual function and regional metabolism relative to the left sensorimotor cortex. After we controlled for demographic and clinical characteristics, both premorbid measures were significantly inversely correlated with cerebral activity in the prefrontal, premotor, and left superior parietal association regions. The adjusted WRAT reading score was additionally inversely correlated with metabolism in the anterior cingulate and paracentral gray areas, bilaterally, and with the right orbitofrontal and left thalamic regions. No significant associations between other brain regions and the estimates of premorbid ability for the Alzheimer's disease group were observed.

We repeated the partial correlation analyses by using absolute regional PET values (milligrams of glucose per 100 g of tissue per minute) to determine whether the significant associations with premorbid function were also observed without the use of ratio normalization. The inverse correlations remained significant for several regions, despite the greater variability in the absolute cerebral metabolic data. With controls for the same clinical and demographic variables, the adjusted WRAT reading score was significantly inversely correlated with absolute glucose metabolic rate in the right ($r=-0.36$, df=41, $p<0.009$) and left ($r=-0.28$, df=41, $p<0.04$) prefrontal, right ($r=-0.31$, df=41, $p<0.02$) and left ($r=-0.26$, df=41, $p<0.05$) premotor, and right anterior cingulate ($r=-0.25$, df=41, $p<0.05$) regions. The demographic IQ estimate was significantly correlated with the left superior parietal association area ($r=-0.34$, df=39, $p<0.02$).

Relation of Education to Cerebral Metabolism in Alzheimer's Disease

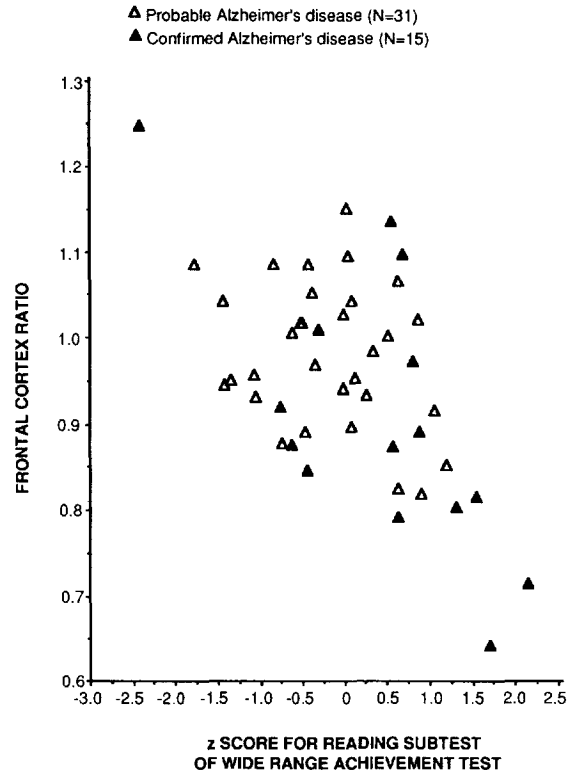
Although years of education was highly correlated with the demographic IQ estimate, we specifically tested the relation between education and regional cerebral metabolism to allow for a direct comparison with the previously reported association of education with regional cerebral blood flow (CBF) in Alzheimer's disease (6). Partial correlations, with controls for age, gender, dementia severity, and illness duration, showed sig-

nificant inverse correlations between years of education and the right prefrontal ($r=-0.30$, $df=40$, $p<0.03$), right ($r=-0.29$, $df=40$, $p<0.03$) and left ($r=-0.33$, $df=40$, $p<0.02$) premotor, left inferior and middle parietal ($r=-0.27$, $df=40$, $p<0.05$), and left superior parietal ($r=-0.42$, $df=39$, $p<0.003$) association regions referenced to the left sensorimotor cortex. Years of education was also associated with absolute metabolic rate in the left superior parietal association region ($r=-0.31$, $df=39$, $p<0.03$).

Regression Model of Premorbid Function in Alzheimer's Disease

We used multiple linear regression analyses to identify which set of brain regions was the best predictor of premorbid intellectual function in the patients with Alzheimer's disease. The standardized residuals from a multiple linear regression analysis predicting WRAT reading performance with age, gender, dementia severity (Mattis Dementia Rating Scale), and illness duration were computed to create a premorbid IQ variable uncorrelated with these demographic and clinical characteristics. Multiple regression analyses were subsequently performed to predict the residual WRAT reading scores with brain regions referenced to the metabolic rate in the left sensorimotor cortex. The combination of right and left prefrontal and premotor association regions was the best predictor ($F=4.96$, $df=4, 41$, $p<0.003$), explaining 33% of the variance in WRAT reading performance when demographic and clinical variables were removed statistically. The association between WRAT reading performance and the mean rate of glucose metabolism for the right and left prefrontal and premotor regions relative to the left sensorimotor cortex is shown in figure 1.

FIGURE 1. Correlation Between Premorbid Intellectual Ability and Cerebral Metabolism in the Frontal Association Cortex, Referenced to the Left Sensorimotor Region, for 46 Patients With Alzheimer's Disease[a]



[a]Premorbid intellectual function was measured by using standardized residuals (z scores) of reading performance on the Wide Range Achievement Test, after statistical removal of the effects of age, gender, illness duration, and dementia severity (measured with the Mattis Dementia Rating Scale). The diagnoses of probable Alzheimer's disease were based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (19), and the confirmed diagnoses were based on autopsies. The frontal cortex ratio is the mean of the values for the right and left prefrontal and premotor association regions divided by the value for the left sensorimotor cortex.

DISCUSSION

The results demonstrate an association between the pathophysiological effects of Alzheimer's disease and premorbid intellectual function. Specifically, higher levels of premorbid intellectual ability were associated with greater cerebral metabolic deficits in several areas of association cortex in our group of patients with Alzheimer's disease, after we controlled for clinical and demographic characteristics. The negative association with the left superior parietal cortex is consistent with previously found (6, 7) inverse correlations between educational or occupational attainment and parietal perfusion shown by using the planar xenon-133 technique to measure regional CBF. Consistent with our hypothesis were the negative correlations we found in broader areas of association cortex known to be affected in Alzheimer's disease, including the prefrontal and premotor regions. That the association of premorbid ability with cerebral metabolic deficits was strongest for the prefrontal and premotor association regions in our study may be related to the higher spatial resolution of our imaging method and the greater educational attainment by our patients with Alzheimer's disease than those in the previous studies of regional CBF. Although individual variability in patterns of cerebral dysfunction is often observed in Alzheimer's disease (9, 12, 13), metabolic activity in the parietotemporal association areas is most consistently affected early in the clinical course and is often followed by declines in frontal and other association areas (9, 13–16). A broader range of individual differences in the pathophysiological effects of Alzheimer's disease may be seen in the frontal cortex than in the parietotemporal association areas among highly educated patients with Alzheimer's disease.

Metabolism in the frontal and parietal association regions was consistently related to each of the three measures of premorbid ability. However, the WRAT reading

score adjusted for dementia severity appeared to be more sensitive to the neurophysiological effects of Alzheimer's disease than was either the demographics-based IQ estimate or years of education. Although the adjusted WRAT reading score was not associated with other measures of cognitive performance in the Alzheimer's disease group, it typically showed higher negative correlations over more extensive brain regions than did both other estimates of premorbid ability. Together, these findings suggest that reading performance, when adjusted for overall dementia severity, is a more useful measure of premorbid intellectual function in Alzheimer's disease than are demographics-based estimates, as it appears to reflect the neurophysiological heterogeneity related to premorbid function in Alzheimer's disease better than do demographics alone.

The current results support premorbid function as an important factor affecting the neurophysiological heterogeneity observed in Alzheimer's disease. Although the degree of brain atrophy was not assessed in our subjects, the current findings indicate an association between premorbid function and neurophysiological severity of Alzheimer's disease as measured with PET. Hypometabolism shown by PET reflects decreased synaptic activity associated with loss or dysfunction of brain synapses, and PET therefore offers greater sensitivity to the effects of neurodegenerative disease than do structural imaging methods (39). The greater neurophysiological deficits among patients with high compared to low levels of premorbid ability represent either predominant cerebral metabolic dysfunction or a combination of hypometabolism and the effects of atrophy. Partial volume effects in regional cerebral glucose metabolism can be enhanced by atrophy due to aging and dementia. However, the use of large regions of interest and a high-resolution PET scanner tends to minimize partial volume effects (40). Further, the effects of age and dementia severity were controlled in the correlations between premorbid function and cerebral metabolism in our study.

We used a template-based region-of-interest approach in analyzing the PET images of regional glucose metabolism. In contrast to pixelated methods, in which the entire brain is sampled by using semiautomated spatial normalization techniques to average scan data among subjects, the template-based method relies on sampling far fewer regions and manually adjusting the placement to best fit each scan. The values for the small regions of interest are averaged, producing metabolic values for large areas of cerebral cortex and subcortical regions, thereby providing potentially less regional specificity than in pixelated methods. Further, there is potential for greater intersubject regional variability due to small individual differences in the placement of regions of interest. However, we previously showed this method to be specifically useful in assessing cerebral dysfunction in Alzheimer's disease (8, 9, 11, 37) and demonstrated high levels of interrater reliability for the placement of regions of interest with this approach (13).

Our findings are consistent with the hypothesis that premorbid intellectual ability reflects a cognitive reserve that can alter the clinical expression of dementia in Alzheimer's disease. That greater cerebral dysfunction in areas typically affected in Alzheimer's disease was associated with greater premorbid intellectual function, after we controlled for dementia severity, suggests that a person's premorbid intellectual ability may delay or diminish the clinical features of dementia while the neuropathological effects of Alzheimer's disease progress. Threshold theories have been proposed to explain heterogeneity in the onset and progression of dementia, suggesting that an interaction of genetic and environmental factors can alter the course of dementia among individuals at risk for Alzheimer's disease (1, 2).

The mechanism by which a cognitive reserve may influence expression of dementia is unclear. A high level of premorbid ability may indicate more cognitive resources, which allow for greater compensatory skills in response to advancing disease. It is also possible that premorbid experience directly influences brain function at the neuronal level. Increasing levels of mental stimulation during life can lead to alterations in brain physiology, such as production of greater synaptic interconnectivity among neurons (41, 42). It is widely accepted that cognition and behavior are related to regionally distributed networks or systems of neural activity (43–46) and that these systems may be specifically altered in disease states (47–49). A high level of premorbid intellectual function may reflect greater availability or efficiency of functional brain systems that are recruited when the performance of a task requires greater mental effort. This may be particularly relevant to the effects of neurodegenerative disease on brain function, whereby compromised neuronal activity may cause the same cognitive task to require increasing mental effort as the pathophysiology of the disease progresses. The inverse associations of cerebral metabolism in the frontal association, anterior limbic, and subcortical regions with premorbid function are compatible with this hypothesis. Moreover, the relation between the adjusted WRAT reading score and metabolism in the frontal association cortex was significant after we controlled for left parietal association metabolism as well as clinical and demographic variables, suggesting that the frontal association cortex is more sensitive to the effects of differences in this premorbid measure than are the parietal regions among Alzheimer's disease patients with similar degrees of dementia severity. Although these latter findings should be viewed as preliminary, they suggest that the greater pathophysiological severity seen among the patients with greater premorbid intellectual function may involve specific functional brain systems associated with compensatory cognitive functions.

A neurophysiological model of attentional processing including orbitofrontal, prefrontal, anterior cingulate, thalamic, and parietal brain regions has been described (50). Further, metabolic activity in these regions has been correlated with measures of visuospatial attention in patients with Alzheimer's disease (51). The anterior limbic and frontal association areas have been specifi-

cally implicated as brain regions that may be important for the "executive" allocation of cognitive resources when tasks require greater attentional demands (50). It may be that brain systems involved in allocating attentional resources and increasing mental processing need to be depleted before dementia is clinically observed among individuals at risk for Alzheimer's disease who have high levels of premorbid ability. Studies of Alzheimer's disease patients by means of PET performed during cognitive stimulation with parametrically increasing difficulty are needed to directly address this question.

The possibility that the current findings may be related to an ascertainment bias should also be considered. That is, individuals with greater premorbid intellectual function may be less likely to receive a diagnosis of dementia because of the limited sensitivity of the available clinical measures for diagnosing Alzheimer's disease. In our study, all patients met the DSM-III-R criteria for dementia, and we controlled for dementia severity in the patient group by using the Mattis Dementia Rating Scale. Performance on the Mattis scale was not correlated with years of education in our Alzheimer's disease group and is a sensitive measure of cognitive decline in dementia (18). Further, previous studies have suggested that a diagnostic requirement of impaired function in more than one cognitive domain that disrupts social or occupational functioning reduces the likelihood of an ascertainment bias, explaining the greater prevalence and incidence of Alzheimer's disease among individuals with low education levels (1, 5). Moreover, in the study of the association between premorbid occupational functioning and regional CBF measured with xenon-133 in Alzheimer's disease (7), even occupational factors that were not strongly related to education, such as interpersonal and physical job demands, were inversely correlated with cortical perfusion deficits in the Alzheimer's disease group.

In summary, our findings demonstrate that patients with Alzheimer's disease who have high levels of premorbid intellectual ability show greater pathophysiological effects of Alzheimer's disease than do patients with low levels of premorbid function but similar levels of clinical dementia severity. These results indicate that premorbid intellectual ability is an important factor affecting the neurophysiological heterogeneity observed in Alzheimer's disease. Further, the findings are consistent with the hypothesis that premorbid function reflects a cognitive reserve that may delay or diminish the clinical expression of dementia in Alzheimer's disease. By using high-resolution tomographic imaging, we identified inverse correlations not only in brain regions that are typically affected in Alzheimer's disease, but also in regions that have been implicated in models of cognition and brain systems that may be important for functional compensation as the pathological effects of Alzheimer's disease progress. Further studies are needed to directly investigate the cognitive reserve hypothesis by relating premorbid intellectual ability to the neurophysiological response to cognitive stimulation in Alzheimer's disease. One implication of a cognitive reserve is that early and perhaps even lifelong levels of intellectual activity will offer some protection against the clinical effects of dementia among individuals at risk for Alzheimer's disease. Understanding the specific role of premorbid function in the clinical and neurophysiological expression of Alzheimer's disease may be important for enhancing early diagnosis and developing behavioral and pharmacological interventions that may assist in delaying the onset and progression of dementia in Alzheimer's disease.

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