

Intellectual Decline Predicts the Parietal Perfusion Deficit in Alzheimer's Disease

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The pathophysiology of Alzheimer's disease may be reflected more in an individual's decline from premorbid levels of functioning than in current measures of absolute severity. To test this hypothesis, we computed an index of intellectual decline for individual patients and examined its relationship to Alzheimer's disease-related functional brain abnormalities. **Methods:** We studied 27 patients with Alzheimer's disease diagnosed by AD/DA-NINCDS criteria. We used patient demographics and published formulas to construct estimates of premorbid Wechsler Adult Intelligence Scale (WAIS-R) IQs for each subject in the sample and used a current IQ assessment to estimate the decline in IQ that occurred during the disease for each subject. Cortical perfusion was quantified by the planar ^{133}Xe regional cerebral blood flow (rCBF) technique. The characteristic abnormality in parietal cortex was expressed by the parietal index (PI). **Results:** Over the estimated disease duration of 3.8 ± 2.2 yr, the full-scaled IQ declined by an estimated 28.0 ± 15.5 points. The current PI was in turn well correlated with the IQ decline ($r = 0.66$; $p < 0.001$). This association was linear and stronger than those with other, more common measures of current severity. A multiple stepwise regression analysis suggested that IQ decline alone accounted for the variance in PI related to clinical deterioration. Actual images showed a mild blood flow deficit in patients with the smallest estimated IQ declines but deep and extensive lesions in patients with large declines. **Conclusion:** These results suggest that the decline from the premorbid baseline, rather than current level of functioning, best predicts the extent of brain damage reflected in the rCBF abnormality, a finding independent of demographic variance.

Key Words: intelligence quotient; Alzheimer's disease; cerebral blood flow; functional imaging

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It is currently unclear whether the fundamental severity of Alzheimer's disease is best estimated by clinical examination (e.g., Clinical Dementia Rating) (1,2), detailed neuropsychological assessment or measures of cerebral func-

tion, such as regional cerebral blood flow (rCBF) or metabolism. Clinical and neuropsychological instruments assess dementia and can be used to track disease progression but are less accurate for establishing cross-sectional severity because they are influenced by individual subject characteristics, such as native intelligence, educational attainment and even personality characteristics (3-5).

It is possible that direct measures of cerebral pathophysiology, such as rCBF, can avoid such biases and provide a more reliable estimate of disease severity. For example, Moritz and Pettiti (6) recently reported that education appears to have a significant effect on the point at which individuals present with symptoms of Alzheimer's disease, with more educated individuals presenting at a point when the disease is less severe in terms of standard measures of functional impairment. We previously demonstrated, however, that at equivalent levels of functional impairment more educated individuals have a greater deficit in parietal perfusion (7). Thus, more educated individuals may present at a point where they are equally functionally impaired but actually be further along in the progression of their disease, with respect to both pathophysiologic severity and, especially, the degree of decline from their own premorbid baseline of functioning.

Katzman (8) has proposed that the true severity of Alzheimer's disease is reflected in such functional decline and not by current absolute levels of impairment. If direct measures of cerebral metabolism or perfusion are an accurate determination of underlying pathophysiology, in turn, they should be better correlated with measures of decline from premorbid baseline than with conventional clinical measures of severity because the latter only reflect current status.

To evaluate whether rCBF is truly an unbiased indicator of underlying disease severity, an independent behavioral measure of individual decline from premorbid level of functioning is necessary. Such information is rarely available in conventional dementia studies, since patients typically present after onset of symptomatology. Attempts have been made to use tests of crystallized intelligence to estimate premorbid abilities (9-11), but even these tests are subject to the influence of dementing processes and may only be useful in the very earliest stage of disease (12). One

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TABLE 1
Sample Characteristics (n = 27)

	Mean \pm s.d.	Range
Age (yr)	68.6 \pm 10.2	53–84
Education (yr)	11.2 \pm 3.9	4–20
Occupation rating	4.4 \pm 1.3	2–6
Age of onset (yr)	65.1 \pm 10.9	48–87
Duration of illness (yr)	3.8 \pm 2.2	1.25–10.25
Modified Mini-Mental State Exam	31.7 \pm 8.5	16–45
Blessed Functional Activity Scale	9.8 \pm 3.8	2.5–18.5
Gender percentage	74.1% female	
Racial composition	96.3% white	

promising approach capitalizes on the fact that patients with Alzheimer's disease usually present with a lifetime of achievement, which contains information regarding their premorbid levels of functioning. Both Wilson et al. (13,14) and Barona et al. (15) have demonstrated the potential value of this approach for constructing estimates of IQ derived from the Wechsler Adult Intelligence Scale (WAIS) and Revised Wechsler Adult Intelligence Scale (WAIS-R) using data from the standardization samples for each.

In this study, we used the regression formula developed by Barona et al. (15) to construct an estimate of premorbid intelligence for a group of patients with Alzheimer's disease who had ^{133}Xe rCBF scans. Current intellectual functioning was then assessed with the WAIS-R. An estimate of decline in overall intellectual functioning was subsequently computed by subtracting the premorbid estimate from the results of the current assessment. These data were then compared to results from the rCBF assessment as well as to other current severity measures.

METHODS

Patients

The 27 patients were clinically diagnosed with probable Alzheimer's disease (NINCDS-ADRDA criteria) (16). Demographic data for these patients are provided in Table 1. Of these 27, 26 had been included in a previous report from this laboratory (17); only those who received all measures (clinical, neuropsychological and rCBF) during their first evaluation were used here. As part of the standard evaluation, the patients were tested with a modified version of the Mini-Mental State Exam (MMS) developed by Mayeux et al. (18), as well as the Blessed Dementia Rating Scale (BDRS) (19). Scores on the modified MMS (mMMS) may be converted to standard Folstein MMS (20) scores by linear regression. This equation, based on 124 administrations of both scales, is $\text{MMS} = (\text{mMMS} - 3)/1.8$ ($r = 0.97$; Prohovnik I, Keilp JG, and Huey E, unpublished data, 1994). Thus, in standard units, our patients had a mean MMS of 15.9 ± 4.7 , with a range of 7 to 23, or severe to very mild dementia.

Patients were initially diagnosed at the Memory Disorders Clinic of the New York State Psychiatric Institute as previously described (17,21) and then referred for participation in a longitu-

dinal rCBF study. After informed consent was obtained, the patients received a battery of neuropsychological tests that included a WAIS-R (22). Educational and premorbid occupational data were gathered from family members. Mean educational attainment was approximately 3 yr of high school, and more than half the sample (59.3%) had completed high school. Occupationally, 7.4% of these subjects had been semiskilled laborers; 22.2% housewives or volunteer workers; 7.4% skilled laborers or craftspersons; 44.4% managers, clerks or salespersons; and 18.5% professional or technical workers.

Regional Cerebral Blood Flow

Data reported here are from the initial scan in this series, conducted under resting conditions (subjects lying still with eyes closed in a darkened, quiet room) according to procedures that we have described previously (23). Cerebral blood flow was assessed by planar counts in 32 brain regions, with NaI (T1) scintillation detectors sampling 16 cortical regions in each hemisphere, using a commercial device (Cerebrograph 32c; Novo Diagnostic Systems, Hadsund, Denmark). The principal measure of perfusion was the initial slope index (ISI) calculated from the M2 four-compartment model (24,25). This ISI has previously been shown to be highly reliable in low-flow conditions. The results can be expressed in ml/100 g/min, if the blood/brain partition coefficient for the relevant tissue volume is assumed to be 1.0, and the flow values are relatively immune to atrophy.

End-tidal PCO_2 , blood pressure and respiratory rate were recorded using a fully computerized system. Blood pressure and P_eCO_2 values were all within normal ranges for this age group (systolic = 132.8 ± 15.7 ; diastolic = 75.8 ± 12.7 ; $\text{P}_e\text{CO}_2 = 35.8 \pm 4.2$). To minimize irrelevant noise, absolute perfusion estimates were conservatively corrected to a P_eCO_2 value of 37 mmHg by 2%/mmHg (26). Whole-cortex mean flow was computed as the average of the 32 adjusted regional cortical values. In addition, a parietal index (PI), which is computed by expressing flow to inferior parietal detectors (P1 and P3 bilaterally) as a percentage of flow to perirolandic (C1) and occipital (O2) detectors, was also calculated. Mean flow is included here as a measure of nonspecific cerebral pathology, since previous studies have shown that it is reduced in various cerebral diseases and loosely associated with the degree of functional impairment. The PI, in contrast, is a more specific measure of pathology that has been shown to reliably discriminate cases of probable Alzheimer's disease from normal function (17), major depression in the elderly (27) and vascular dementia (28).

Estimation of Premorbid IQ

Estimates of premorbid WAIS-R IQs—full-scale, verbal and performance—were computed using the formulas developed by Barona et al. (15). These formulas generate an IQ estimate from the demographic factors of age, sex, race, education, occupation, region of residence and urban versus rural residence. The formulas used to compute IQ estimates are as follows:

$$\begin{aligned} \text{Full-Scale IQ} = & 54.96 + 0.47 (\text{age}) + 1.76 (\text{sex}) + 4.71 (\text{race}) \\ & + 5.02 (\text{education}) + 1.89 (\text{occupation}) \\ & + 0.59 (\text{region of residence}). \end{aligned}$$

$$\begin{aligned} \text{Verbal Scale IQ} = & 54.23 + 0.49 (\text{age}) + 1.92 (\text{sex}) + 4.24 (\text{race}) \\ & + 5.25 (\text{education}) + 1.89 (\text{occupation}) \\ & + 1.24 (\text{urban/rural residence}). \end{aligned}$$

$$\begin{aligned} \text{Performance Scale IQ} &= 61.58 + 0.31 (\text{age}) + 1.09 (\text{sex}) \\ &+ 4.95 (\text{race}) + 3.75 (\text{education}) \\ &+ 1.54 (\text{occupation}) \\ &+ 0.82 (\text{region of residence}). \end{aligned}$$

Scores on each variable are grouped and ranked according to demographic categories used in the original standardization sample of the WAIS-R (22). Details of the scores assigned to other categories of each of these demographic variables may be obtained from the authors' original publication (15). One modification of the procedures suggested by the Barona group were made in generating premorbid estimates here: because all of the subjects in this study were no longer working, lifetime occupational status rather than current status (not working, for all subjects) was used.

Following estimation of premorbid IQs, the estimate of IQ decline associated with the diagnosis of Alzheimer's disease was computed. This estimate was generated by subtracting estimated from currently assessed IQ.

RESULTS

Premorbid IQ Estimation, IQ Decline and Association with Blood Flow Parameters

Mean estimated premorbid IQs, currently assessed IQs and the estimated decline in IQ for the sample are presented in Table 2. Overall, premorbid IQs appear reasonable, given the educational and occupational attainment of the sample. The current IQs, in turn, appear to reflect a genuine, significant decline in functioning from premorbid levels. These current IQs fall within or near the Borderline Retarded range, at a level well below what would be expected for a sample in which more than half of the subjects are high school graduates. The mean estimated declines in the various IQ scales indicate a drop of nearly 2 s.d. on each scale. Although a single subject had current IQs that were slightly higher than her estimated premorbid scores, all other subjects in the sample showed a decline in IQ from estimated premorbid levels. Furthermore, the decline in performance IQ is greater than the decline in verbal IQ (paired $t[26] = 7.44; p < 0.0001$), as is expected in Alzheimer's disease (17).

Associations between all demographic and clinical severity measures and the rCBF indices are presented in Table 3. Education shows a moderate negative correlation with the PI, which is consistent with our previous report of this effect (7). The more educated patients have the greatest deficits in this index. Also, the occupation rating has a significant negative association to perfusion measures,

which is consistent with the education effect ($r = 0.66; p < 0.001$ between education and occupation ratings). Among standard severity measures, however, only the age at onset is significantly related to the PI, with earlier onset patients showing the most significant parietal perfusion deficits.

Among the IQ measures, the premorbid IQ estimates show a striking negative association to perfusion measures. Since this estimate is based largely on education and occupation, this association is not surprising. In essence, the most educated, occupationally fortunate and presumably brightest subjects in this sample exhibit the worst deficits on perfusion measures. Current IQs, in contrast, exhibited positive correlations with the perfusion measures. The current full-scale and performance IQs were significantly correlated with both the PI and mean flow, so that higher IQs were associated with higher perfusion. This association was strongest for the performance IQ and is consistent with expectations that the least deteriorated patients exhibit the least abnormal flows. The relationships among IQ measures and perfusion measures were maximized, however, when the premorbid estimate and current assessment were combined into an estimate of decline from premorbid functioning. All correlations between the IQ decline measures and the perfusion indices are >0.59 and highly significant.

Scatter plots of the association between the estimated decline in full-scale IQ and both the PI and mean flow are presented in Figure 1. Although the correlation between full-scale IQ decline and the PI is robust, it is attenuated by an influential outlying value. With this value removed, this correlation increases from 0.66 to 0.79, and the regression appears strikingly linear. This outlier (Patient 60029) had the largest hemispheric difference in parietal perfusion, with deficits much greater in the right hemisphere than the left. He also had one of the largest differences in relative decline of performance versus verbal IQ with his performance IQ declining to a much greater degree. Thus, this subject appeared to have an extremely lateralized disease and appears as an outlying value when perfusion data are averaged across hemispheres.

Figure 2 illustrates the progression of perfusion deficits that accompany increasingly greater degrees of decline in IQ. For the sake of this illustration, subjects were divided into three groups of approximately equal size with: (a) greater than 35-point decline in IQ, (b) between 20- and 35-point decline and (c) with less than a 20-point decline. Perfusion data are averaged across subjects and hemi-

TABLE 2
Estimated Premorbid, Current and Decline in IQs

WAIS-R scale	Estimated premorbid IQ (range)	Current IQ (range)	Decline in IQ (range)
Full scale	103.5 ± 10.6 (86–120)	75.4 ± 11.6 (60–113)	–28.0 ± 15.5 (–57 to +6)
Verbal	102.7 ± 10.9 (84–120)	80.2 ± 11.4 (43–114)	–22.4 ± 14.3 (–50 to +8)
Performance	103.5 ± 8.2 (88–116)	71.2 ± 11.7 (59–109)	–32.3 ± 15.2 (–56 to +3)

TABLE 3
Correlations between rCBF Indices and Clinical Severity Indicators

	Parietal index	Mean flow
Age (yr)	0.34	0.02
Education	-0.41*	-0.38*
Occupation rating	-0.49†	-0.39*
Age of onset	0.45*	0.08
Duration of illness	-0.29	-0.07
Modified Mini-Mental State Exam	0.31	0.18
Blessed Functional Activity Scale	-0.29	-0.26
Estimated premorbid IQ		
Full-scale	-0.49†	-0.46*
Verbal	-0.49†	-0.46*
Performance	-0.51†	-0.46*
Current IQ		
Full-scale	0.43*	0.49†
Verbal	0.27	0.37
Performance	0.58†	0.56†
IQ decline		
Full-scale	0.66‡	0.68‡
Verbal scale	0.59†	0.65‡
Performance scale	0.71‡	0.68‡

*p < 0.05.

†p < 0.01.

‡p < 0.001.

spheres. The apparent enhancement of flow to frontal cortex in subjects with greater IQ declines is an artifact: Absolute frontal flow is lower in these subjects but not to the degree that mean flow is lower. Since all detector values presented here are normalized to mean flow, relative flow to frontal regions is relatively higher in subjects with the

greatest IQ decline and greatest parietal deficit. Parietal flows, however, dramatically worsen as the degree of IQ decline increases.

Specific Relationships to Blood Flow Abnormalities

Because IQ decline is associated with both the PI and mean flow, it is possible that, in the context of Alzheimer's disease, it represents nonspecific deterioration associated with general cerebral dysfunction. Associations between IQ decline and the PI remain strong and significant, even when mean flow is partialled out. Partial correlations between IQ decline measures and the PI, controlling for mean flow, are as follows: for decline in full-scale IQ $r_{\text{partial}} = 0.51$ ($p = 0.004$), for decline in verbal IQ $r_{\text{partial}} = 0.41$ ($p = 0.019$) and for decline in performance IQ $r_{\text{partial}} = 0.60$ ($p = 0.001$). Decline in IQ, then, appears to be specifically associated to this blood flow abnormality related to Alzheimer's disease.

The variability in IQ decline is not, however, associated solely with parietal blood flow deficits. Some residual variation is associated with mean flow, in that the correlation between IQ decline and mean flow remains significant after partialling out the effects of the PI. Partial correlations between IQ decline and mean flow, controlling for the PI, are as follows: for decline in full-scale IQ $r_{\text{partial}} = 0.55$ ($p = 0.002$), for verbal scale decline $r_{\text{partial}} = 0.51$ ($p = 0.004$) and for performance scale decline $r_{\text{partial}} = 0.54$ ($p = 0.002$).

Both of these characteristic AD-related deficits, specific and nonspecific, appear to be related to IQ decline.

Associations between IQ decline and cerebral perfusion

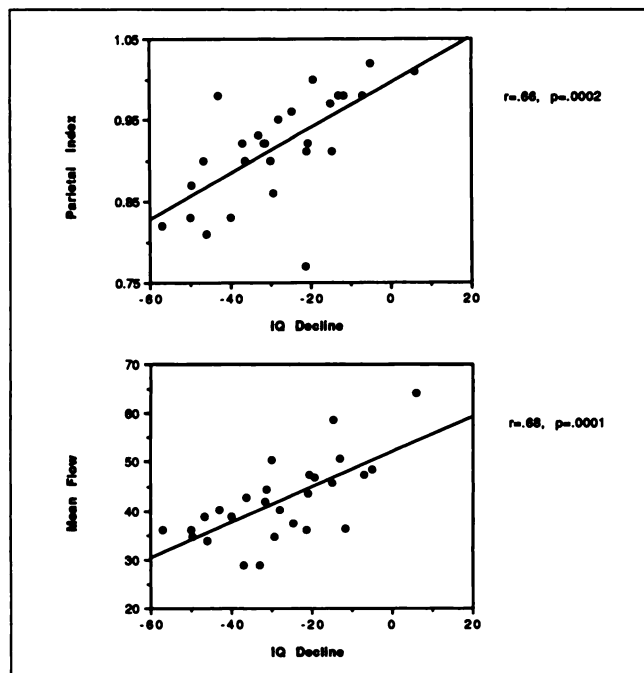


FIGURE 1. Scatter plots of the associations between the PI and IQ decline (top) and mean flow and IQ decline (bottom).

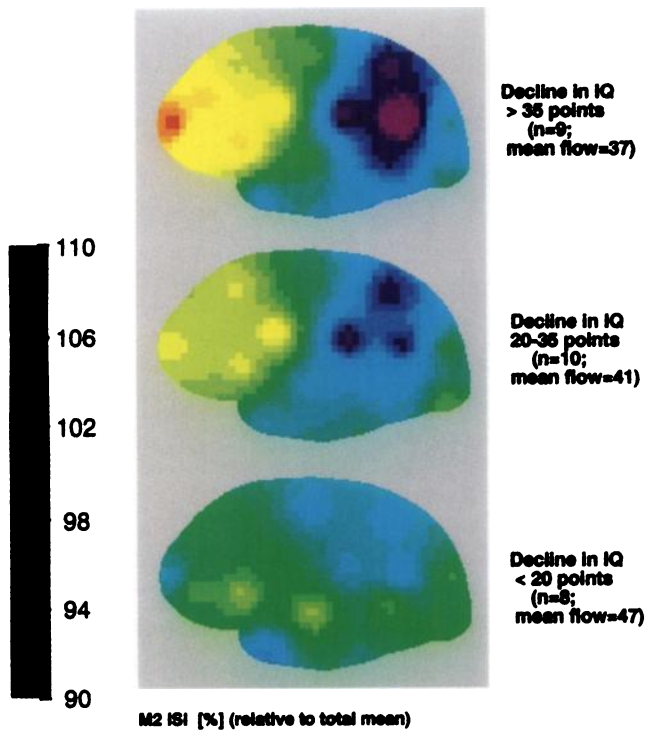


FIGURE 2. Relative perfusion in IQ decline subgroups averaged across hemispheres. All flow values (M2 ISI) are depicted as percentages relative to global means.

measures may be excessively influenced by the underlying association in this sample between high estimated premorbid IQ and poorer perfusion. If the variability in IQ decline related to estimated premorbid IQ is considered, however, by entering this variable into a regression equation first, both the PI and mean flow still contribute significantly and independently to the prediction of IQ decline. With all three variables in the equation predicting full-scale IQ decline, multiple $R = 0.83$ ($R^2 = 0.68$; $F = 16.41$; $p < 0.0001$). Partial correlations between IQ decline and the PI ($r_{\text{partial}} = 0.41$; $p = 0.022$) and mean flow ($r_{\text{partial}} = 0.48$; $p = 0.007$) are reduced but remain significant.

Educational Effects

Because education is negatively correlated with the PI in this sample, it is possible that the association between IQ decline and the PI is simply a restatement of this correlation. The partial correlation, however, between full-scale IQ decline and the PI, controlling for education, was 0.57 ($p = 0.001$). If the sample is divided into three educational “strata” composed of those with less than 12 yr of education ($n = 11$), 12 yr ($n = 9$) and more than 12 yr ($n = 7$), the correlations between IQ decline and the PI within each of these groups are, respectively, 0.45, 0.65 and 0.65 (Fig. 3). Inspection of this scatter plot reveals that the computed regression line in the two higher education groups is similar to that in the sample as a whole. The lowest education group, however, contains the single outlier. With this outlier removed, the correlation between IQ decline and the PI improves to 0.75 among those with the least education, and

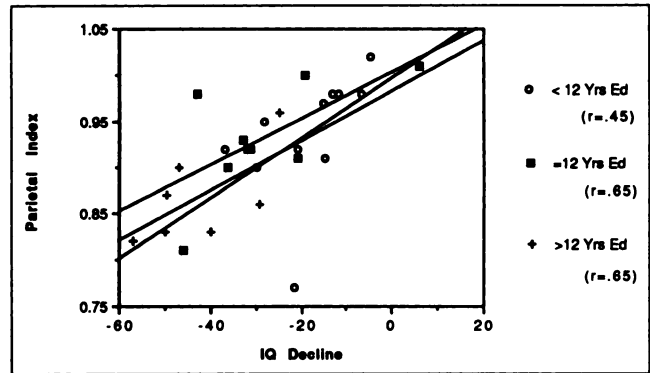


FIGURE 3. Scatter plot of the association between PI and IQ decline at different educational levels.

the slope of the regression line in this educational group becomes more equivalent to those in the other education groups.

For mean flow, the association with IQ decline also remains highly significant after controlling for education ($r_{\text{partial}} = 0.61$; $p < 0.001$).

Gender and Age at Onset Effects

A set of analyses was conducted to determine if subject gender or age at disease onset had any systematic effects on the association observed between IQ decline and the cerebral perfusion measures. Among women, who constituted nearly three-quarters of this sample ($n = 20$), full-scale IQ decline was highly correlated with both the PI ($r = 0.80$; $p < 0.001$) and mean flow ($r = 0.71$; $p < 0.001$). Men could not be separately analyzed due to the small sample size ($n = 7$, including the outlier described above).

As for the effect of age at onset, among subjects with presenile onset Alzheimer’s disease ($n = 14$), the correlations between IQ decline and the PI were weak when the outlying value was included ($r = 0.29$; $p = 0.300$) and much stronger after its removal ($r = 0.61$; $p = 0.026$). The correlation between IQ decline and mean flow, however, was strong and significant ($r = 0.72$; $p = 0.004$). Among senile onset subjects ($n = 13$), these associations are less equivocal. Correlations between IQ decline and the PI ($r = 0.83$; $p < 0.001$) and mean flow ($r = 0.86$; $p < 0.001$) are both highly significant. Overall, subsamples in this group of patient subjects are not heterogeneous enough for complete stratified analysis, but the available data suggest that the associations between IQ decline and perfusion measures are maintained across groups. More importantly, this association is found within senile onset subjects, even though the greatest degrees of both IQ decline and perfusion deficit are found among subjects with an earlier onset. The association between these variables does not appear to result from simply pooling these two subsamples.

Duration Effects

If subjects are divided into those with less than 3 yr duration of illness ($n = 13$) and those with more ($n = 14$), the association between estimated IQ decline and perfusion indices appears to be strongest among those with

shorter duration. Correlations with IQ decline were very robust for both the PI ($r = 0.86$; $p = 0.0002$) and mean flow ($r = 0.81$; $p = 0.0008$) in the short duration group. Correlation with IQ decline was lower in the long duration group ($r = 0.43$; $p = 0.124$ with PI; $r = 0.50$; $p = 0.072$ with mean flow), although, again, the influence of the outlying value affected these results ($r = 0.69$; $p = 0.009$ between IQ decline and PI with the outlier removed). Overall, the association between IQ decline and perfusion measures appears to be strongest in the earlier stages of illness.

IQ Decline as a Measure of General Functional Impairment

The estimated decline in full-scale IQ was strongly correlated with a number of other demographic and clinical severity measures. It was positively associated with age ($r = 0.44$; $p = 0.023$) and age at onset ($r = 0.52$; $p = 0.006$) and negatively associated with education ($r = -0.59$; $p = 0.001$), indicating that the largest declines were found for younger, well-educated, early-onset subjects. Estimated decline in IQ was not significantly associated with duration of illness ($r = -0.31$; $p = 0.119$). In relation to other measures of dementia severity, the estimated decline in IQ was correlated with both the mMMS ($r = 0.51$; $p = 0.007$) and BDRS ($r = 0.44$; $p = 0.020$).

With regard to using these demographic and clinical severity measures to predict deficits in rCBF related to Alzheimer's disease, the estimated decline in IQ was found to be the only significant predictor of the PI. When all demographic and severity measures (age, education, age at onset, duration of illness, mMMS, BDRS and decline in full-scale IQ) were entered into a stepwise multiple regression in an attempt to predict the PI, only the decline in IQ entered and remained in the equation ($R^2 = 0.43$; $F = 19.03$; $p = 0.0002$). The remaining six predictors in turn accounted for only a nonsignificant increase of 5.7% in total variance accounted for ($F_{\text{change}} = 0.36$; $p = 0.90$), suggesting that the decline in IQ alone accounts for that portion of the variance in the PI that is related to global intellectual deterioration.

For mean flow, IQ decline also initially enters a stepwise equation but is accompanied on the second step by age at onset ($R^2 = 0.57$; $F = 15.71$; $p < 0.0001$). Age at onset, however, is weighted negatively, even though most of our previous data suggest that blood flow deficits are greatest among younger onset subjects. This negative weighting suggests in fact that the contribution by this variable is actually a function of its positive association with age ($r = 0.96$; $p < 0.001$), which is known to be related to reduced mean flow. The partial correlation of age with mean flow, after controlling for IQ decline, is -0.41 ; the partial correlation of age at onset with mean flow is very similar at -0.43 . If age is entered into the regression equation with IQ decline, the total variance accounted for is essentially the same as with age at onset ($R^2 = 0.55$; $F = 14.96$; $p = 0.0001$). It appears then that the largest proportion of vari-

ability in mean flow can be accounted for by some combination of the effects of both IQ decline and aging.

Relationship to the Fuld Profile

In an earlier article (17), we demonstrated the effectiveness of the "Fuld Profile" of WAIS-R subtest scores (29) for detecting individuals with severe perfusion deficits. In the sample used here, one-third ($n = 9$) was Fuld-positive and two-thirds ($n = 18$) Fuld-negative. Fuld-negative subjects had marked deficits in both the PI ($t[25] = 3.00$; $p = 0.006$) and mean flow ($t[25] = 2.32$; $p = 0.029$). Subjects who were Fuld-positive also showed significantly larger declines in IQ than those who were Fuld-negative (-37.5 ± 10.0 versus -23.3 ± 15.8 ; $t[25] = 2.45$; $p = 0.022$). There was significant overlap in the distribution of IQ decline in the two groups, however, with Fuld-positive subjects ranging between -50 and -21 points and Fuld-negative subjects ranging between -57 and $+6$ points. This overlap appears to reflect the low sensitivity/high specificity of the profile, in that it accurately detects a subset of those with marked deficits but misses others. The continuous IQ decline score would appear to be more informative regarding pathophysiological severity because of its apparent linear association to perfusion measures.

DISCUSSION

The diagnostic accuracy of parietal deficits for detecting Alzheimer's disease is reasonably well established (21,30-32). Our results suggest that the extent of these deficits carries important information about functional severity. Moreover, perfusion measures carry information about the extent of individual deterioration in a straightforward way that appears to be uncontaminated by demographic confounds. Thus, our findings strengthen the hypothesis that severity is best indexed by the individual's decline from premorbid levels and support the use of functional neuroimaging for the quantification of such severity.

By using the planar, low-resolution ^{133}Xe technique, the concordance between individual IQ decline and cortical perfusion appears to be restricted at present to global deterioration rather than the decline in any specific neuropsychological function. This can be illustrated in the case of Patient 60013 who showed no apparent decline in her IQ and very mild perfusion deficits. Her mMMS and BDRS scores suggested only mild impairment, although she presented with marked focal deficits in memory and some word-finding difficulty and was diagnosed with Alzheimer's disease. Over a 2-yr follow-up period, this woman maintained an IQ in the high average range, was Fuld-negative, maintained relatively normal cortical perfusion and showed only minimal evidence of clinical decline—a course that is atypical for Alzheimer's disease. After an accidental death, however, the diagnosis of Alzheimer's disease was confirmed at autopsy by conventional neuropathological criteria. This case, of course, is interesting in itself, because it may represent a divergence between the neuropathological definition (i.e., plaques and tangles) and

the manifestations in behavior and cerebral perfusion of Alzheimer's disease. Although it confirms the tight association between IQ decline and parietal perfusion deficits, it also suggests the existence of a minority of patients who fulfill neuropathological criteria but have neither. Clearly, more research is necessary in this area.

In addition to what they suggest about perfusion measures, findings here also help to validate the procedures used to estimate premorbid ability on the basis of demographic and achievement data. Even if the premorbid IQ estimate is not completely accurate, these procedures have the effect of "tailoring" deterioration norms for each specific patient, based on the performance of those who are demographically similar. This improvement in finding an appropriate baseline level of functioning for most patients results in what appears to be a much more sensitive index of functional decline. The effectiveness of this strategy can also be illustrated using the estimated Folstein MMS scores available for the patients in this sample and the recently published norms for various age and education groups on this test (33). If we use these norms to generate the expected MMS score for each patient at the time of disease onset and then compute an MMS decline score, the correlation of this score with the PI is higher ($r = 0.48$; $p = 0.012$) than for the MMS alone ($r = 0.31$; $p = 0.116$). With consideration of our outlying subject, this correlation increases even more ($r = 0.58$; $p = 0.002$). Correlations between the PI and WAIS-R IQ decline most likely run higher because of the superior psychometric qualities of the WAIS-R, but the strategy of correcting for estimated premorbid levels of functioning works in both cases.

It is important, on the other hand, to note some of the limitations of these procedures. The formula developed by Barona only estimates IQs within a range of 69 and 121 (from approximately -2.0 to $+1.5$ s.d. from the mean IQ of 100 ± 15). For those with true IQs above or below this range—approximately 11% of the population—these estimation procedures will produce an attenuated baseline estimate. The estimation procedures developed by Wilson et al. (13, 14), not used in this study, produce a wider range of scores but were validated on the WAIS rather than the more recent WAIS-R.

In addition, because this estimate is based solely on demographic factors, it does not take into account individual differences within various demographic subclassifications. As a result, the standard error of the estimate is relatively high (12.14 points for full-scale IQ or 0.81 s.d.). For these reasons, this estimation procedure may be limited in individual cases, although in larger research samples, it can only serve to enhance the information value of a current intellectual assessment. The premorbid IQ estimate may also be used to adjust more easily obtained ratings of dementia severity, such as the MMS or Blessed scales and may work well to remove demographic confounds. These research samples need to be sufficiently diverse, however, to offset the systematic sources of error in the estimation procedure.

The robust correlations observed between estimated IQ decline and perfusion measures in this study may have been enhanced somewhat by the nature of the sample, in that many of the subjects with the worst perfusion deficits also had higher estimated IQs. Reduced sensitivity of the WAIS-R at its lower extreme (10), for example, may attenuate the estimate of decline for lower IQ subjects and make it more likely that the more educated, occupationally fortunate subjects who have the worst perfusion deficits in this sample will also have the greatest estimated decline in IQ. The striking linearity of the relationship between estimated IQ decline and perfusion measures makes this less likely. If there were discontinuities in the assessment of decline, they should be apparent in the scatter plots versus the perfusion measures. Also, this effect is very robust among senile onset subjects, a subgroup that does not include many of those with the largest IQ declines and poorest perfusion.

CONCLUSION

These limitations notwithstanding, this study lends substantial support to the validity of cerebral perfusion measures as an index of fundamental pathophysiological processes in Alzheimer's disease. Our findings need to be extended, however, to other functional imaging methods. The planar ^{133}Xe rCBF method used here is sensitive to cortical phenomena, relatively immune to atrophy and provides full quantification. On the other hand, it provides no information about subcortical structures and its spatial resolution is low. This unique combination of strengths and weaknesses may have biased our results in unpredictable directions and suggests the need for replication with more conventional PET or SPECT methods.

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