Relationship between lifetime occupation and parietal flow:

Implications for a reserve against Alzheimer's disease pathology

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Article abstract—We previously reported an inverse relation between parietal cerebral blood flow and years of education in Alzheimer's disease (AD) patients matched for clinical severity. This suggested that the clinical manifestation of advancing AD pathology is delayed in patients with higher educational attainment. Other aspects of life experience may also provide a reserve against the clinical expression of AD. To test this hypothesis, we classified the primary lifetime occupations of 51 AD patients using the *Dictionary of Occupational Titles*, published by the US Department of Labor, and derived six factor scores describing intellectual, interpersonal, and physical job demands. Regional cerebral blood flow was measured using the xenon-133 inhalation method. After controlling for age, clinical dementia severity, and education, there was less relative perfusion in the parietal region in subjects whose occupations were associated with higher interpersonal skills and physical demands factor scores. We conclude that independent of education, aspects of occupational experience may provide a reserve that delays the clinical manifestation of AD.

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There have been reports of increased prevalence of dementia in individuals with lower educational attainment, suggesting that life experience may play a role in the clinical manifestation of dementia.[1,2] In a previous study,[3] we hypothesized that education may provide some form of a reserve that must be depleted below a threshold level before dementia is clinically manifested. In that sense, education would protect against the emergence of the clinical features of AD. This hypothesis predicted that, given comparable clinical severity of dementia, patients with more years of education would have more advanced AD pathology. To test this hypothesis, we used the reduced perfusion in the parietal area that occurs in AD[4-7] as an indirect index of AD pathology. Parietal perfusion and metabolic deficit is specific to AD,[8-11] correlates with disease severity,[6] and is homologous with areas of AD pathology.[12] We found that, given comparable clinical severity, years of education correlated inversely with parietal perfusion in AD, supporting our hypothesis.

The cognitive reserve hypothesis suggests that aspects of life experience supply a set of skills or repertoires that allow an individual to cope for a longer time with the progressing AD pathology before the effects of the disease become clinically apparent. If this is the case, the relatively brief period of life spent in school might not be as important as the bulk of later life experiences. To that end, we wondered whether a person's occupational experiences might also play a role in cognitive reserve.

To investigate this concept, we evaluated disease severity and regional cerebral blood flow (rCBF) indices from the same patients as in our previous study,[3] incorporating new information about dimensions of each patient's primary lifetime occupation. Our a priori hypothesis was that occupations that are more cognitively or interpersonally demanding might be associated with reserve. We predicted that after controlling for indices of disease severity, there would be an inverse correlation between measures of pa-

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tients' lifetime occupations and parietal perfusion and that this relationship would be present even after controlling for the effect of education.

Methods. *Subjects.* Occupational data were available for 51 of the 58 patients from our original report.[3] Data from patients who did not have sufficiently detailed occupational information (N = 2) and from housewives who were never employed (N = 5) were not used. Clinical and rCBF evaluations are identical to those described previously.[3]

All subjects underwent extensive neurologic and neuropsychological evaluations and met DSM-III-R criteria for dementia[13] and NINCDS-ADRDA criteria for probable AD.[14] There was no a priori selection of patients based on education or occupation, and rCBF played no role in the diagnostic process.

Procedures. Clinical measures. Measures assessing clinical severity were administered separately from the neuropsychological battery that was used to confirm diagnosis. The modified Mini-Mental State Examination (mMMSE)[15,16] provided an estimate of general intellectual function. This brief, 57-point scale tests memory, orientation, attention, language, and constructional abilities and has established validity and reliability. Change in the ability to perform day-to-day activities of daily living (ADL) also occurs in AD, and the degree of impairment in ADL can be independent of intellectual dysfunction.[17] The Blessed Dementia Rating Scale–Part 1 (BDRS)[18] was used to rate ADL. Duration of clinical symptoms and age at onset were estimated from interviews with the patient and all available informants.

Occupational measures. The primary lifetime occupation of each patient was determined on the basis of chart records and interviews with the patient and family. We attempted to determine the occupation that each patient had for the longest period of his or her life. In all cases this constituted the occupation the subject engaged in for the majority of his or her working life. Follow-up questions clarified occupational duties and occupation-specific training, producing information sufficient to allow classification of occupations using the *Dictionary of Occupational Titles*, 4th ed, published by the US Department of Labor.[19] This document contains descriptions and definitions of more than 12,000 occupations. The Department of Labor also generated scores for 44 characteristics of each listed occupation based on extensive on-site observation of jobs as they were actually performed.[20] We summarized these scores using the factor structure described by Cain and Treiman,[20] as modified by Link et al,[21] which reduces the 44 scores to six factors: substantive complexity, motor skills, physical demands, management, interpersonal skills, and undesirable working conditions. Items loading on each of these factors are summarized in table 1. To derive factor scores, all item scores were standardized to a 0-to-1 scale and then scores for items in each factor were summed.

Since substantive complexity was viewed a priori as a potentially important aspect of occupational experience, we also used a different measure of substantive complexity, one derived by Kohn and Schooler[22] from the *Dictionary of Occupational Titles* codes. They used the dictionary ratings of complexity in dealing with data, people, and things to predict their own survey-based measure of substantive complexity in a multiple-regression analysis. We used the scoring scheme they derived from this analysis to construct a second measure of substantive complexity.

Regional cerebral blood flow. rCBF procedures are described in detail elsewhere.[23] A commercial system (Novo Cerebrograph 32c) with 32 scintillation detectors was used.

Table 1. Individual items constituting the occupational factors

Substantive complexity	**Management**
General educational development	Talking
Intelligence	Dealing with people
Specific vocational preparation	Scientific, technical
Complexity of functioning with data	Activities versus business contact
Verbal aptitude	Direction, control, planning
Numeric aptitude	Complexity of function in relation to people
Motor skills	**Interpersonal skills**
Finger dexterity	Sensory or judgmental criteria
Motor coordination	Feeling, information, facts
Complexity of functioning with things	Influencing people
Manual dexterity	Activities involving processes and machines versus social welfare
Form perception	
Seeing	**Undesirable working conditions**
Physical demands	Fumes, dust, odors, poor ventilation
Climbing, balancing	Hazardous conditions
Eye-hand-foot coordination	Extreme heat, cold, noise, humidity
Outside working conditions	
Stooping, kneeling, crouching, crawling	
Lifting, carrying, pulling, pushing	

All measurements were made with patients in resting, supine conditions. Extensive quality control standards were used.[24] Clearance curves were analyzed with a six-unknown model (M2) that provides greater sensitivity and accuracy under low flow conditions.[25] We used the initial slope index derived from the model as the dependent variable, since this index showed the best discrimination of AD and controls in a previous study.[23] Global perfusion was examined by using whole-cortex mean values. When examining regional flows at specific detectors, we eliminated general flow effects by computing a relative distribution value for each region consisting of normalization by the global mean flow for each subject. We also calculated a parietal perfusion index (PI), which consisted of the sum of two detectors reflecting parietal flow (P1 and P3) divided by the sum of two reference detectors reflecting occipital and perirolandic flow (O2 and C1). This index is typically reduced in AD patients but not in controls or patients with other dementing illnesses.[22,26]

Statistical analysis. The relation between occupational demands and demographic/clinical variables was investigated using correlational analyses. To address our study hypotheses, partial correlations were subsequently performed to assess the relationship between the occupational factors and cortical perfusion, while controlling for the effects of relevant demographic and clinical characteristics. This was followed by multiple-regression analyses to provide an estimate of the unique contribution of the occupational factor scores over and above education in predicting the cortical perfusion deficit characteristic of AD. To control for type I error in the multiple-correlation analyses, we differentiated between a priori and exploratory analyses. An alpha value of 0.05 was required for correlations involving the substantive complexity and interpersonal skill factors, since they were included in our a priori hypotheses. Analyses involving other factors were considered exploratory, and an alpha value of 0.01 was required.

We next attempted to identify differences in the pattern

of regional flows associated with the occupational factors identified by the preceding analyses. Patients were stratified into high and low groups on the basis of the factor scores, and regional flow data were analyzed using MANCOVAs controlling for demographic and clinical variables. These analyses involved multiple comparisons and must be considered exploratory.

Results. Mean (±SD) patient age was 67.3 ± 9.6 years; mean duration of education was 13.4 ± 4.4 years. Average age at onset was 63.2 ± 9.8 years, and mean disease duration 4.2 ± 6.6 years. The mean mMMSE score was 30.9 ± 10.6, and the mean BDRS score 9.8 ± 4.2.

The mean occupational factor scores were as follows: substantive complexity, 3.33 ± 1.29; motor skills, 2.43 ± 1.30; physical demands, 0.51 ± 0.61; management, 2.82 ± 1.47; interpersonal skills, 1.22 ± 1.07; and undesirable working conditions, 0.12 ± 0.38.

Correlation of occupational factors and demographic/clinical variables. We first investigated the relation between the occupational factors and demographic/clinical variables, including age, education, mMMSE score, BDRS score, and duration of illness. Significant positive correlations were found between years of education and the substantive complexity ($r = 0.73$, $p < 0.01$), interpersonal skills ($r = 0.47$, $p < 0.01$), and management ($r = 0.31$, $p < 0.05$) factor scores. Negative correlations were obtained between age and work environment ($r = -0.34$, $p < 0.05$) and between the BDRS score and interpersonal skills ($r = -0.32$, $p < 0.05$). No other significant correlations were observed between the demographic/clinical variables and the occupational scores.

Relation of occupation to global mean flow. The relationship between the occupational factors and global mean flow was assessed with a series of partial correlations controlling for disease severity (mMMSE score, BDRS score, and duration of illness), age, and pCO_2. Significant negative correlations were observed between global mean flow and the substantive complexity ($r = -0.28$, $p < 0.05$), interpersonal skills ($r = -0.26$, $p < 0.04$), and motor skills scores ($r = -0.28$, $p < 0.05$). However, after education was included as an additional covariate, these effects were reduced to nonsignificance.

Relation of occupational factors to parietal flow. Similar partial correlations, controlling for the same covariates, were used to investigate the relationship of occupational factor scores to the PI. There were significant negative partial correlations between the PI and two factors, substantive complexity ($r = -0.30$, $p < 0.05$) and interpersonal skills ($r = -0.36$, $p < 0.01$). The correlation between the PI and the physical demands factor was of borderline significance ($r = -0.21$, $p = 0.08$). When education was included as an additional covariate, the association between the PI and substantive complexity was reduced to nonsignificance, the correlation with interpersonal skills remained significant ($r = -0.27$, $p < 0.04$), and the correlation with physical demands approached significance ($r = -0.29$, $p < 0.03$).

Similar analyses were conducted using the substantive complexity factor derived by Kohn and Schooler.[22] This factor correlated strongly with education ($r = 0.71$), as well as with the other substantive complexity factor ($r = 0.86$). When substituted for the other substantive complexity factor, it yielded similar results in all analyses.

Multiple-regression models for occupational effects. We used a stepwise multiple-regression analysis to model the differential contribution of the occupational factors and education in predicting the PI. Age, disease severity indicators (mMMSE score, BDRS score, and illness duration), and education accounted for 23.8% of the variance in the PI. Adding the interpersonal factor to the model explained an additional 7.5% of the variance, a significant increase ($F = 4.69$, $p < 0.05$). Subsequently adding the physical demands factor accounted for an additional 11.5% of the variance, again a significant increase ($F = 8.41$, $p < 0.01$). No other occupational factors accounted for additional significant variance in the PI. Thus, after accounting for demographic/clinical variables and education, the interpersonal skills and physical demands factors accounted for an additional 19% of the variance of the PI.

Subgrouping patients using occupational factors. To investigate the implications of subgrouping AD patients by occupational demands for the pattern of rCBF across the entire cortex, we divided our patient sample into low and high groups for the substantive complexity and interpersonal factors using median cutoff scores for these two occupational variables. For both occupational factors, the low and high groups differed in years of education but did not differ significantly on other demographic or dementia severity variables (table 2), although a strong trend was observed for a difference in gender distribution between the low and high substantive complexity groups. Group (low versus high)-by-gender MANCOVAs with right and left hemisphere flow as a repeated-measure factor were initially used to investigate potential interactions between hemisphere and occupational demands. Because no significant interactions were observed, regional flow values were averaged across hemispheres to simplify the analyses. Analyses controlled for age, mMMSE score, BDRS score, and duration of illness. A similar analysis was done for the physical demands factor, but neither the omnibus test nor any of the subsequent univariate tests was significant. For the comparison of high and low substantive complexity, the omnibus test did not reach significance (Hotelling's $T^2 = 0.56$ [NS]). In the subsequent univariate comparisons, patients in the high substantive complexity group had significantly lower flows at one parietal and two occipital detectors compared with the low substantive complexity group. Flow was relatively elevated at one frontal detector in the high complexity group. The omnibus test for the MANCOVA comparison of the high and low interpersonal skills factor reached significance (Hotelling's $T^2 = 1.19$, $p < 0.05$). In the subsequent univariate comparisons, the high interpersonal patients had relatively

Table 2. Summary of demographic and clinical measures for the low and high substantive complexity groups and the low and high interpersonal skills groups

	Low complexity (N = 25)	High complexity (N = 26)	Low interpersonal (N = 27)	High interpersonal (N = 24)
Age (yr)	66.7 (10.3)	68.0 (9.0)	66.5 (10.0)	68.3 (9.6)
Education (yr)	10.4 (2.6)	16.2 (3.9)*	11.6 (3.1)	15.4 (4.7)*
Age at onset (yr)	62.7 (9.7)	63.6 (9.9)	61.8 (10.3)	64.7 (8.9)
Duration (yr)	3.9 (2.6)	4.6 (2.5)	4.7 (2.9)	3.8 (2.1)
mMMSE	29.4 (12.3)	32.4 (8.5)	29.0 (12.1)	33.0 (8.3)
BDRS	10.1 (4.6)	9.4 (3.9)	10.8 (4.5)	8.6 (3.6)
BP systolic (mm Hg)	134.6 (18.7)	133.5 (16.1)	131.3 (15.1)	137.2 (19.4)
BP diastolic (mm Hg)	76.8 (12.9)	74.9 (11.9)	75.9 (12.5)	75.8 (12.4)
% Nonwhite	12.0	7.7	7.4	12.5
% Right-handed	91.3	92.0	95.8	87.5
% English 1st language	72.0	88.5	70.4	91.7
% Female	72.0	42.3	63.0	50.0

Values are mean (SD) unless otherwise indicated.

* $p < 0.05$; p values are for t test or chi-square test comparisons of high and low groups for each factor.
mMMSE Modified Mini-Mental State Examination.
BDRS Blessed Dementia Rating Scale.

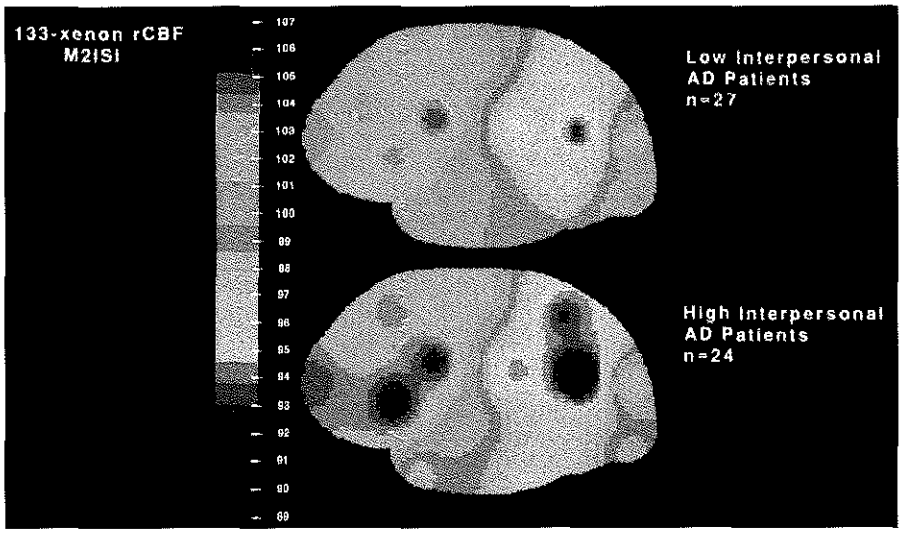

Figure. Comparison of relative rCBF in AD patients with low and high scores on the interpersonal skills occupational factor. rCBF at each detector is expressed relative to global flow, averaged across the right and left hemispheres. The red end of the color scale indicates relatively higher cortical perfusion values, while the blue end represents lower flows relative to global mean perfusion. Note the relative reductions of perfusion in the parietal region for both AD groups, with a markedly greater parietal deficit among patients with high scores on the interpersonal factor.

lower flows at one parietal lobe detector and relatively higher flows in two frontal detectors compared with the low interpersonal group. No significant group-by-gender interactions were observed throughout. Differences in regional perfusion between the low and high interpersonal skills groups are illustrated in the figure.

Discussion. Our findings confirm the prediction that a major aspect of life experience, occupational experience, may influence the clinical expression of AD. Among patients matched for clinical disease severity, those who had had occupations involving more substantive complexity, more interpersonal skills, and higher physical demands had greater deficits of parietal blood flow, suggesting that the underlying disease process was more advanced. In that sense, these life activities provide a reserve against the clinical expression of AD.

We had predicted that substantive complexity would relate to parietal perfusion, since the cognitive demands of an occupation would be expected to provide experiences or behavioral repertoires that might aid in coping with AD pathology. However, individuals with more education typically achieved occupations with higher substantive complexity, so this factor added no significant predictive value over education. Although scores on the interpersonal skills factor also correlated with education, this factor appears to measure occupational requirements that are less likely to require specific training or advanced education. After controlling for education, interpersonal skills still accounted for a significant and unique proportion of the variance in parietal perfusion. Thus,

this aspect of occupational experience is not simply an alternate metric for education but appears to capture an aspect of life experience that may contribute to a reserve against AD above that provided by education.

Less expected was our finding regarding the physical demands factor. This factor had no apparent relation to the cognitive demands of an occupation (table 1), and it was not significantly related to the PI until the analyses controlled for education. One tentative explanation for this finding is that the physical demands of an occupation do not alone provide a reserve, in the way that education, substantive complexity, or interpersonal skills do. However, among persons of a certain level of educational or occupational attainment, those with occupations that are more physically demanding are more likely to tolerate the advancing AD pathology longer. Alternately, this finding is consistent with reports suggesting that strenuous activity might actually be protective against cognitive decline in normal aging.[27]

The mechanism by which occupational experience might contribute to reserve against AD is unclear. This reserve could be the result of increased synaptic density in the neocortical association cortex acquired on the basis of stimulation,[28] or an acquired set of skills or repertoires.[2,3,29] The latter possibility is more compatible with our present data, since it might explain how occupations with increased physical demands might contribute to reserve. Presumably, aspects of life experience could modify the paradigms used by the brain to mediate a task in a way that would make the paradigms more efficient or resilient in the face of AD pathology.

Interpretation of the present data relies on the assumption that rCBF is an effective measure of the AD disease process. The sensitivity and specificity of the rCBF changes in AD have already been discussed above. The cause of the flow defect is still unknown, but the distribution has considerable overlap with those cortical areas having the greatest density of histopathologic abnormalities, including loss of large neurons, neuritic plaques, and neurofibrillary tangles.[30-32] Further, nicotinic receptor blockade in normal subjects models the parietal perfusion deficit, suggesting it might be related to a cholinergic deficit.[33] Because the metabolic coupling of local perfusion is known to be intact in AD,[34] rCBF may be considered to reflect neuronal integrity and synaptic activity of the cortex. In addition, indices of local degeneration correlate well with rCBF in their topographic distribution.[35] It is therefore reasonable to assume that the flow reduction is an index of the physiologic changes of AD.

This perfusion pattern has also been reported in a patient with Parkinson's disease and dementia and is therefore not unique to AD.[36] However, we did not use the flow deficit as a diagnostic marker in this study; all patients were diagnosed with probable AD on the basis of the best existing clinical criteria. Rather, we used the degree of flow deficit as a marker of the pathophysiologic severity of AD.

A more basic issue is the extent to which the apparent reserve against the clinical expression of AD that is provided by education and occupational attainment is actually a function of these life experiences. If these aspects of life experience truly contribute to the reserve, then they represent a potentially modifiable factor that could reduce the expression of AD. On the other hand, education and occupation might simply be markers or surrogates for other, less modifiable or more innate, factors. An extreme example of the latter position would be that people are born with a certain intellectual potential and that later accomplishments are generally a reflection of this innate potential. The factors considered here may also reflect perinatal and lifetime medical care, other socioeconomic variables, or environmental exposures. While our data cannot be considered conclusive in this regard, they do suggest that the reserve can be influenced by some aspects of life experience. This supposition is based on our finding that various aspects of occupational experience that appear unrelated to innate intellectual or cognitive capacity make differential contributions to observed parietal flow deficit. Because there is no definitive diagnostic marker for AD, the concept of reserve must be weighed against the alternate possibility of a detection bias. Standard diagnostic tests may misrepresent the severity of dementia in individuals with lower educational or occupational attainment, resulting in earlier diagnosis and longer estimated durations of illness. Similarly, education might affect scores on the mMMSE and BDRS and bias results that rely on matching patients on these measures. The present study approached this issue in several ways. First, we controlled for several different severity indices, including measures of cognitive change, measures of function, and duration of illness, to minimize bias in any one measure. More important, in the present study we controlled for clinical severity and education and still found a relation between occupational indices and parietal rCBF. Further, physical demands predicted parietal flow after controlling for both education and occupational factors that might have some cognitive component. This argues strongly that the present findings do not simply reflect a systematic bias in assessing dementia severity.

Our findings are compatible with the results of several studies that suggest that prevalence of AD is increased in individuals with lower educational attainment.[1,37-41] Although education and occupation were not related to incidence in one study,[42] another study[48] found that incidence of dementia was increased in individuals with lower educational or occupational attainment, again suggesting a protective effect.

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