Age at onset of Alzheimer's disease:

Relation to pattern of cognitive dysfunction and rate of decline

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Article abstract—We examined the pattern of cognitive impairment and rate of cognitive and functional decline as a function of age at symptom onset in 127 patients with probable Alzheimer's disease (AD). At baseline, early-onset (before age 65) and late-onset groups were mildly and comparably impaired on the modified Mini-Mental State Examination (mMMS) and the Blessed Dementia Rating Scale-Part 1 (BDRS). Repeated-measures analysis of variance revealed significantly more rapid decline in early-onset subjects over a 2-year follow-up period. Multivariate linear regression analyses indicated that age at symptom onset strongly predicted rate of decline on the mMMS and the BDRS, even after controlling for symptom duration, gender, family history of dementia, and baseline mMMS and BDRS scores. Early- and late-onset AD subjects also differed in terms of pattern of performance on the mMMS. Early-onset subjects scored significantly lower than late-onset subjects on attentional items of the mMMS at baseline and follow-up. Conversely, late-onset subjects scored significantly lower than early-onset subjects on memory and naming items at baseline, and the two groups were comparable on these tasks at follow-up. Results provide longitudinal evidence of more rapid cognitive and functional decline in subjects with early-onset AD and suggest that early-onset AD may be characterized by predominant impairment of attentional skills.

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Cross-sectional studies have suggested that early-onset Alzheimer's disease (AD) is characterized by faster clinical progression,[1,2] and actuarial analyses have revealed significantly decreased relative survival in early-onset patients.[3] Nevertheless, confirmation of more rapid cognitive decline in early-onset AD from prospective longitudinal neuropsychological studies has been lacking. Previous longitudinal studies[4-6] have been limited by inadequate statistical power or short or variable duration of longitudinal follow-up.

Cross-sectional studies also have suggested that the *pattern* of cognitive impairment differs in early- versus late-onset AD. Several reports indicate that disturbances of language function are more prevalent and more severe in patients with early-onset AD.[7] Other investigators, however, have reported that early-onset subjects perform *better* on formal tests of language than do late-onset subjects.[8,9] Brandt et al[10] concluded that the rates of decline of specific language skills differ between early- and late-onset patients. Although the reasons for these discrepancies in the literature are not entirely clear, they may be due to differences among studies in duration of illness, severity of dementia at baseline, or other as yet unidentified variables.

The current study compared cognitive and functional decline over 2 years in mildly demented AD patients with either early or late onset of symptoms. We examined rate of change and pattern of cognitive impairment as a function of age at symptom onset.

Methods. *Subjects.* All subjects were participants in the Predictors Study, a prospective multicenter study of predictors of disease course in AD. Study design, cohort characteristics, and intersite comparisons have been described previously.[11] Briefly, all subjects were recruited from outpatient dementia clinics at Columbia University, Johns Hopkins University, and Massachusetts General Hospital. All subjects met NINCDS-ADRDA criteria for probable AD.[12] Baseline evaluations have been completed on 236 subjects: 95 at Columbia University, 80 at Johns Hopkins University, and 61 at Massachusetts General Hospital. Neurologic, neuropsychological, psychiatric, and functional assessments were performed at the baseline visit and are repeated at 6-month intervals.

To be consistent with previous studies of presenile and senile AD, the conventional dividing line of 65 years was used to classify subjects into early- and late-onset groups. Age at symptom onset was estimated using infor-

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Table 1. Characteristics of early- and late-onset subject groups

	N	Sex (% female)	Age at onset*†	Age at baseline*†	Symptom duration*	Years of education*	Baseline mMMS total score*	Baseline BDRS total score*
Early-onset	44	59.1	58.77 (4.21)	63.55 (4.95)	4.77 (3.44)	14.16 (3.77)	38.00 (5.89)	7.63 (3.03)
Late-onset	83	63.9	74.10 (6.51)	78.17 (6.50)	4.07 (2.29)	12.82 (3.77)	38.30 (5.78)	7.91 (3.47)

* Values represent group mean (SD).
† Significant between-group difference ($p < 0.05$).

mMMS Modified Mini-Mental State Examination.
BDRS Blessed Dementia Rating Scale–Part 1.

mation provided by a family member or caregiver. Based on these data, subjects were divided into two groups: 44 subjects who had symptom onset prior to age 65, and 83 subjects who were 65 or older at the time of symptom onset. Medical and psychological histories of early- and late-onset subjects were compared to determine whether or not differences between groups on these variables may have contributed to differences in performance.

Procedures. A semistructured interview[13] that was administered to family members or caregivers at baseline was examined to determine the chronology of disease symptoms in early- and late-onset patients. The interview classifies symptoms into eight categories: memory, performance, language, disorientation, personality, depressed mood, behavior, and psychosis.

Dementia severity was assessed with a modified version[14] of the standard Mini-Mental State Examination (MMSE).[15] In addition to the 30 items from the standard MMSE, the 57-item modified MMSE (mMMS) includes digit span forward and backward,[16] two additional calculation items, recall of the current and four previous presidents of the United States, confrontation naming of 10 items from the Boston Naming Test,[17] one additional sentence to repeat, and one additional figure to copy. The mMMS has been shown to be a valid and reliable instrument for monitoring cognitive changes.[18]

A principal components analysis of mMMS subscale scores for the entire Predictors Study cohort (N = 236) at baseline suggested that the mMMS has two primary factors: an attentional factor, consisting of digit span forward and backward, mental calculations, sentence repetition, and figure copy; and a recall/naming factor, consisting of orientation, item recall, president recall, and confrontation naming. Initial registration of three memory items loaded separately on a third factor.

Day-to-day functioning was assessed with the Blessed Dementia Rating Scale-Part 1 (BDRS).[19] The reliability and validity of this instrument have been established, and it has proved to be useful in evaluating longitudinal changes in function. A principal components analysis of the BDRS suggested that it assesses four separate domains of function: instrumental activities of daily living (IADL; eg, doing chores, handling money); personality change (eg, egocentrism, aggressiveness); apathy (eg, loss of drive, withdrawal); and basic activities of daily living (ADL; eg, eating, dressing, toileting).[20]

Data analysis. Data were analyzed in two ways. First, repeated-measures analyses of variance (ANOVAs) were computed to compare the performance of early- and late-onset subjects at baseline and at 2-year follow-up. Separate ANOVAs were performed for mMMS total score, mMMS factor scores, BDRS total score, and BDRS factor scores. Second, multiple regression was used to assess age at onset as a predictor of rate of cognitive and functional decline. For each subject, the slope of change over time, expressed in terms of the 6-month follow-up intervals, was calculated. All available follow-up data were included in calculating slopes (ie, follow-up was not limited to 2 years). Between-group trends testing was performed to assess the presence of linear and nonlinear trends in rate of decline. Each slope estimate was weighted by the inverse of its standard error; therefore, data from subjects with more reliable slopes were more heavily weighted in the regression analyses.[21,22]

Results. The results described in this report were obtained from 127 subjects from the Predictors Study cohort who had completed 2 years of follow-up. Subjects not included in this report either died (12%) or were lost to follow-up (7%) prior to completing 2 years of study participation, did not receive an mMMS at their 2-year follow-up visit (3%), or had been enrolled in the study for less than 2 years (25%). The 127 subjects who were included did not differ from the remainder of the cohort in terms of age at intake ($t = 0.001$; $p = 0.97$), age at symptom onset ($t = 0.29$; $p = 0.59$), distribution of early versus late onset ($\chi^2 = 1.07$; $p = 0.30$), years of education ($t = 0.71$; $p = 0.40$), or gender distribution ($\chi^2 = 0.71$; $p = 0.40$). Included subjects did have a slightly but significantly longer estimated duration of illness at baseline than those subjects who were not included (mean duration = 4.3 versus 3.6 years; $t = 5.17$; $p < 0.03$).

Demographic characteristics of early- and late-onset subject groups are presented in table 1. The groups did not differ significantly from one another in gender distribution ($\chi^2 = 0.28$; $p = 0.60$) or symptom duration ($t = 1.86$; $p = 0.18$). There was a nonsignificant trend for subjects with an early age at onset to have completed more years of education than late-onset subjects ($t = 3.62$; $p < 0.06$). As anticipated, early-onset subjects were significantly younger than late-onset subjects at baseline ($t = 170.03$; $p < 0.0001$) as well as at symptom onset.

At baseline, early- and late-onset AD subject groups were comparable for overall dementia severity, as assessed by the mMMS and the BDRS (table 1). Both groups were mildly demented. Despite comparable overall baseline mMMS scores, there was a double dissociation between early- and late-onset subjects in terms of the pattern of im-

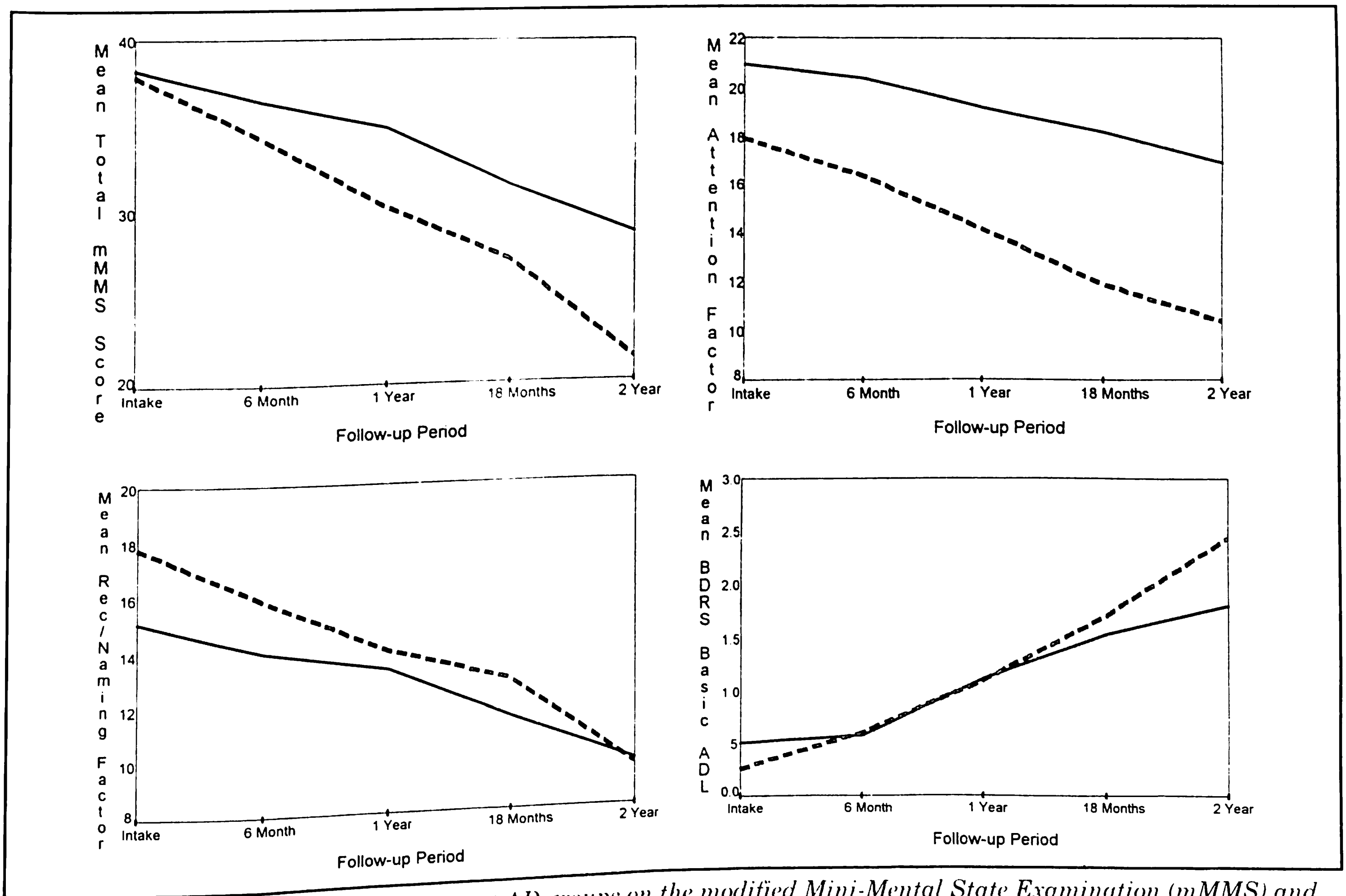

Figure. Performance of early- and late-onset AD groups on the modified Mini-Mental State Examination (mMMS) and the Blessed Dementia Rating Scale (BDRS) basic activities of daily living (ADL) factor (early-onset group denoted by dashed line, late-onset group by solid line). Note: higher scores on the BDRS represent greater functional impairment.

paired and preserved abilities on the mMMS factor scores. Early-onset subjects performed significantly worse than late-onset subjects on the attention factor of the mMMS ($t = 12.63$; $p < 0.001$), while late-onset subjects scored significantly lower on the recall/naming factor ($t = 12.15$; $p < 0.001$).

Informants' reports of disease onset and course also suggested differences between early- and late-onset subjects in terms of early/presenting symptoms. Seventy-five percent of late-onset subjects were reported to have memory decline as a primary symptom, while only 50% of early-onset subjects had changes in memory as a presenting symptom ($\chi^2 = 7.83$; $p < 0.01$). Conversely, language impairment was reported as a presenting symptom in 14% of early-onset subjects but only 4% of late-onset subjects ($\chi^2 = 4.39$; $p < 0.04$). Similarly, difficulty performing tasks was reported more frequently as a presenting symptom in early-onset (34%) than in late-onset (19%) subjects ($\chi^2 = 3.42$; $p < 0.07$). Early- and late-onset groups were comparable for frequency of behavior problems, depressed mood, disorientation, personality changes, and psychosis as reported initial symptoms.

To assess longitudinal change, repeated-measures ANOVAs were computed for the mMMS and the BDRS total scores and factor scores. Significant group-by-time interactions were obtained for all mMMS comparisons. Early-onset subjects progressed significantly more rapidly than late-onset subjects on the mMMS total score ($F = 12.50$; $p < 0.001$), the mMMS attention factor ($F = 9.67$; $p < 0.01$), and the mMMS recall/naming factor ($F = 8.34$; $p < 0.01$) (figure). Significant main effects for group and time were obtained for the mMMS total score and attention factor. A significant main effect of time but not group was obtained for the recall/naming factor. At follow-up, early-onset subjects performed significantly more poorly than late-onset subjects on mMMS total score and attentional tasks, while the two groups performed comparably on recall/naming tasks at follow-up. Repeated-measures ANOVAs of the BDRS revealed a significant group-by-time interaction for the basic ADL factor ($F = 4.75$; $p < 0.05$). Early-onset subjects progressed significantly more rapidly than late-onset subjects in terms of assistance required for basic self-care (figure). Analyses of the BDRS total score and IADL, personality change, and apathy factors revealed significant main effects of time (all p's < 0.001) but not group, or group-by-time interactions.

Between-group trends testing (two groups by five time points), performed on 102 subjects with complete data for all five visits, confirmed the presence of a significant linear trend for each group in

Table 2. Mean (SD) change per 6-month interval for early- and late-onset AD patients on the mMMS and the BDRS

	Early-onset	Late-onset
mMMS total score*	−4.02 (2.35)	−2.65 (2.41)
mMMS attention factor*	−1.84 (1.06)	−1.21 (1.42)
mMMS recall/naming factor*	−2.00 (1.32)	−1.35 (1.03)
BDRS total score*†	+1.31 (0.91)	+0.95 (1.04)
BDRS cognitive factor	+0.42 (0.29)	+0.35 (0.30)
BDRS personality change factor	+0.19 (0.33)	+0.12 (0.40)
BDRS apathy/withdrawal factor	+0.15 (0.18)	+0.09 (0.23)
BDRS basic self-care factor*	+0.55 (0.58)	+0.37 (0.51)

* Age at onset was a significant predictor of rate of change.
† Higher BDRS scores represent greater functional impairment.

mMMS Modified Mini-Mental State Examination.
BDRS Blessed Dementia Rating Scale–Part 1.

rate of decline on the mMMS total score ($F = 7.27$; $p < 0.01$), attention factor score ($F = 9.07$; $p < 0.01$), and recall/naming factor score ($F = 4.24$; $p < 0.05$). Tests of nonlinear, higher-order trends were not significant. Thus, we concluded that linear regression best fit the longitudinal data.

Multivariate linear regression analyses indicated that age at symptom onset was a strong predictor of slope of cognitive change ($\beta = 1.4$; $p < 0.001$), even after controlling for symptom duration, gender, family history of dementia, and baseline mMMS score (table 2). On average, subjects with age at onset of symptoms prior to age 65 declined 1.4 points faster on the mMMS than did late-onset subjects per 6-month period. Results also were significant when age at symptom onset was treated as a continuous variable ($\beta = 0.05$, $p < 0.01$). Of the variables entered as covariates, only baseline mMMS score provided an additional significant independent contribution to the regression equation ($\beta = 0.11$; $p < 0.001$). Age at symptom onset also significantly predicted rate of decline on the attention factor ($\beta = 0.68$; $p < 0.01$) and the recall/naming factor ($\beta = 0.71$; $p < 0.001$) of the mMMS, again after controlling for symptom duration, gender, family history of dementia, and baseline factor score. Early-onset subjects declined more rapidly than late-onset subjects on both factors of the mMMS. None of the covariates significantly contributed to the prediction of the rate of decline on the attention factor; symptom duration ($\beta = 0.09$; $p < 0.01$) and family history of AD ($\beta = -0.40$; $p < 0.05$) independently contributed to the recall/naming factor regression equation.

Although repeated-measures ANOVA on the BDRS total score did not yield a significant onset-age by follow-up interaction term, regression analyses indicated that age at symptom onset was a significant predictor of decreasing overall functional capacity as assessed by the BDRS ($\beta = -0.34$; $p < 0.05$) (table 2). In addition, age at onset was a significant predictor of increasing need for assistance with basic ADLs, such as eating, dressing, and toileting ($\beta = -0.16$; $p < 0.05$). Early-onset subjects progressed more rapidly than late-onset subjects in terms of functional impairment. Symptom duration, gender, family history of dementia, and baseline BDRS score were treated as covariates in the regression analyses. None of the covariates significantly contributed to the prediction of the rate of functional decline. Thus, the more rapid cognitive decline evidenced by early-onset patients on the mMMS was also associated with more rapid decline in function.

Co-morbid medical or psychological diseases did not appear to account for the obtained results. Early- and late-onset subject groups did not differ significantly in terms of history of diabetes, myocardial infarction, congestive heart failure, hypercholesterolemia, epilepsy, thyroid disease, depression, or other psychiatric disorders. History of hypertension was more prevalent in the late-onset group ($p < 0.04$). When included in the regression analysis, history of hypertension did not contribute to the prediction of rate of decline.

Discussion. This prospective longitudinal study provides evidence of more rapid cognitive and functional decline in patients with onset of AD symptomatology prior to age sixty-five. Although several previous cross-sectional studies have suggested more rapid clinical progression associated with early-onset AD, longitudinal confirmation of this result has been lacking.

Previous cross-sectional studies have compared the performance of early- and late-onset AD patients on a comprehensive neuropsychological test battery.[2,10,23] These investigations found more severe impairment in early-onset AD subjects than in late-onset subjects, even after controlling for symptom duration. Teng et al[24] reported that early-onset subjects performed more poorly than late-onset subjects on the majority of test items on the standard MMSE but that the two groups showed comparable rates of decline with duration of illness. A limitation of these cross-sectional studies, however, is that rate of decline was inferred from estimated duration of symptoms and current test performance.

Huff et al[4] and Katzman et al[5] examined progression of AD symptomatology longitudinally. In these studies, however, the duration of follow-up varied from patient to patient. Huff et al[4] followed subjects for a minimum of 3 months (maximum duration of follow-up was not reported) and found more rapid decline in late-onset than in early-onset subjects on a summary measure of the Blessed Information-Memory-Concentration test (IMC) and the BDRS. Katzman et al followed subjects for a minimum of 1 year and a maximum of 6 years and found no significant difference in annual rate of change on the Blessed IMC between early- and late-onset subjects. A limitation of both of these studies is the variability of follow-up interval. Differences between subjects in length of follow-up may have contributed to the results. Evidence for this is provided by a recent study that reassessed AD subjects on the BDRS and IMC after 1 year of follow-up and found significantly *faster* decline in early-onset AD patients.[25]

Boller et al[6] and Ortof and Crystal[26] also examined longitudinal rate of decline in early- and late-onset AD patients. These investigators reported no significant influence of age at symptom onset on rate of longitudinal decline; however, these negative results may be attributable to limited statistical power. In both studies, there was a strong trend for early-onset subjects to decline more rapidly. Boller et al[6] defined subjects as fast decliners (N = 18) and slow decliners (N = 15) based on their performance on the standard MMSE over a 2-year period. The "fast decliners" were an average of 3.65 years younger than the "slow decliners." Although Ortof and Crystal[26] concluded that age at onset exerted no significant influence on rate of progression, they reported a significant correlation between age at onset and rate of decline on the Blessed IMC ($r = -0.38$; $p < 0.05$). Their subjects who were less than 65 years of age declined an average of 1.9 points faster per year than subjects over age sixty-five. Finally, Rasmusson et al[27] described predictors of disease course in a series of autopsy-confirmed AD patients. As in our study, these authors found a significant association between early age at symptom onset and rapidity of cognitive and functional decline.

The current results suggest that early-onset AD is characterized not only by more rapid clinical decline, but also by a differential pattern of impaired and preserved cognitive abilities. Subjects with onset of symptoms prior to age 65 were more impaired than late-onset subjects on the attentional items of the mMMS, while late-onset subjects were more impaired on the recall and naming items. In addition, early-onset subjects had a steeper rate of decline on the attention factor of the mMMS than did late-onset subjects. Although neuropsychological studies have shown a decline on measures of memory and naming in healthy older adults, studies of AD patients have been inconsistent regarding the relationship between age and language function. While several previous investigations have reported predominant language dysfunction associated with early-onset AD,[1,7,28] others have found greater impairment with late-onset AD.[8,9] Selnes et al[29] found no significant differences in the severity of language dysfunction between early- and late-onset AD subject groups. Consistent with the current results, however, Selnes et al did find that early-onset AD patients were significantly more impaired on tasks requiring sustained attention and concentration. Loring and Largen[23] also reported greater attention/concentration impairment in subjects with early onset of symptoms.

In general, informants' reports of symptom onset and course were consistent with the baseline differences in pattern of performance between early- and late-onset subjects on the mMMS. Late-onset subjects were significantly more likely to have memory as a presenting symptom, while early-onset subjects were more likely to have language or other performance difficulties. Although informants reported language impairment as a presenting symptom more frequently in early-onset than in late-onset subjects, this difference was not reflected in the mMMS performance of early-onset subjects. The brief screening of language provided by the mMMS may not be sensitive to the language difficulties perceived by family members of the early-onset subjects.

Several investigators have reported differences in cerebral metabolism and pathology between early- and late-onset AD patients. Koss et al[30] reported greater right than left hemisphere impairment of cortical glucose metabolism on PET in subjects with onset of symptoms prior to age sixty-five. This impairment of right hemisphere glucose metabolism was associated with greater impairment on visuospatial tasks in early-onset subjects. Prohovnik et al[31] matched senile- and presenile-onset subjects for duration of symptoms and disease severity and compared the groups using regional cerebral blood flow. They found a significantly greater loss of gray matter relative weight in early-onset patients. Further, loss of gray matter was related to disease severity and duration only in the early-onset patients, suggesting a greater degenerative process in presenile AD. Rossor et al[32] examined neurochemical characteristics of early- and late-onset AD in a postmortem series. They reported that neurochemical changes in older subjects with AD were confined to the temporal lobe and consisted of reduced choline acetyltransferase and somatostatin. Younger patients, however, had diffuse and severe neurochemical changes, with losses of choline acetyltransferase and somatostatin in all cortical areas examined; decreased GABA in amygdala, hippocampus, temporal cortex, and frontal cortex; and decreased noradrenaline in the hippocampus, temporal cortex, and cingulate cortex. The cholinergic deficit in frontal cortex was age-dependent and more profound in younger subjects.

Only nine of the 127 subjects included in the current study have died, two of whom had early onset of symptoms. Four of the nine subjects consented to autopsy, and all four had pathologically confirmed AD. All autopsied cases were from the late-onset group. Thus, at this time we are unable to assess whether pathological as well as behavioral differences exist between these two subject groups. The findings of Rossor et al[32] of greater frontal pathology in younger patients is relevant in light of our current finding that early-onset patients are particularly impaired on attentional tasks, which are known to be sensitive to frontal system dysfunction. We are continuing to follow this cohort longitudinally and may be able to assess and compare clinical-anatomic associations in these subject