Gray-Matter Degeneration in Presenile Alzheimer's Disease

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Previous comparisons between presenile Alzheimer's disease (AD) and senile dementia of the Alzheimer type (SDAT) did not control for disease severity and duration. In the current study, 18 patients with each diagnosis were matched for disease duration, cognitive dysfunction, and behavioral symptoms (using the modified Mini-Mental Status [mMMS] examination and the Blessed Dementia Rating Scale [BDRS]). Regional cerebral blood flow (rCBF) was quantified by the ^{133}xenon inhalation technique, and several indices of tissue perfusion were examined. The two variables of primary interest were relative gray-matter weight and a gray-matter perfusion index, the initial slope index. Presenile onset was associated with loss of gray-matter relative weight (35% in presenile patients versus 39% in senile patients and healthy control subjects, $p = 0.006$), with neither perfusion nor disease severity differences between the two dementia samples. This loss of gray matter was significantly related to both severity and duration of disease in the patients with presenile AD, but not in patients with SDAT. These findings lend support to previous suggestions of greater degenerative process in presenile AD and confirm the need to examine and control age of onset in future investigations of AD. Further, correlation analysis suggests greater proportion of common variance among clinical and physiological indices in presenile AD.

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Age at onset (AAO) of Alzheimer's disease (AD) may predict course and severity of the disease, but previous reports show little consensus on this point [1–4]. Most previous studies have suggested more severe disease manifestations associated with earlier onset. The Commission on Nosology, Epidemiology, Etiology and Pathophysiology [5], recognizing the similarity of clinical and pathological manifestations and the possibility of different causes, recommended the terms *Alzheimer's disease* for presenile onset and *senile dementia of the Alzheimer type (SDAT)* for senile onset.

Differences between the presenile and senile variants may reflect fundamental pathophysiological processes or may be a function of varying disease severity and rate of progression. For instance, if earlier onset is associated with more rapid progression, such patients may present with more severe degeneration and symptomatology at a given duration from diagnosis. This study is the first to compare presenile and senile onset patients matched for duration of disease as well as for symptomatic severity.

Measurements of regional cerebral blood flow (rCBF) appear to provide a sensitive, specific, and reliable marker of AD, even at early stages [6,7]. The largest study to date that examined rCBF in presenile and senile patients [6] reported subtle relative differences in regional cerebral perfusion but failed to control for severity. We here report the first investigation of AAO effects on CBF in early-stage AD, with strict control of severity of disease. Further, the study by Risberg and Gustafson [6] examined only one variable, the initial slope index (ISI), which is dominated by gray-matter perfusion. We report that the major AAO effect involves reduction of apparent gray-matter weight in presenile onset patients.

Methods

Subjects

Patients with clinically diagnosed AD in a community-based memory disorders clinic were eligible. We selected only patients who fulfilled NINCDS-ADRDA criteria [7]. We further selected patients with presenile and senile onset (less than 65 or 65 and greater) to yield sample means matched for severity. This was done because in our larger, unselected samples, presenile patients were more severely impaired. The analysis includes 36 patients with early AD, 18 of presenile onset, and 18 of senile onset. Table 1 provides a detailed list of their characteristics. Mean duration of disease in all AD patients was 3.25 ± 1.80 years, and there were no significant differences in disease severity between the two AAO subgroups. They differed significantly, as expected, in

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Table 1. Sample Characterization

Variable	Mean (SD) Presenile (n = 18)	Senile (n = 18)	p[a]
Age	60.22 (4.91)	76.00 (4.88)	0.001
AAO	56.67 (4.82)	72.61 (4.10)	0.001
Duration[b]	3.56 (1.67)	2.94 (1.87)	0.322
mMMS	27.89 (14.92)	32.11 (14.14)	0.403
BDRS	8.62 (3.50)	9.39 (4.04)	0.563
$PeCO_2$	38.91 (4.34)	38.61 (2.77)	0.806
Systolic BP	126.73 (20.84)	147.88 (19.78)	0.008
Diastolic BP	81.47 (12.50)	82.53 (12.24)	0.641
Hemoglobin	13.95 (1.26)	14.74 (1.10)	0.071

[a]Unpaired t tests, two-tailed.
[b]Clinically assessed, in years.

AAO = age at onset; mMMS = modified Mini-Mental Status Examination; BDRS = Blessed Dementia Rating Scale; $PeCO_2$ = end-tidal determinations of CO_2 partial pressure; BP = blood pressure.

age and AAO. Thirty patients were drug free for at least 1 month; the other 6 were being treated with neuroleptic agents, coronary agents, methenamine mandelate, and chlorpropamide. There was no relation between AAO and medication status.

Twelve healthy elderly subjects were compared as control subjects. These subjects had no history of psychiatric or neurological disease and a mean age of 63.25 ± 8.11. They were recruited by advertising in community newspapers.

Diagnostic and Severity Measures

Patients were diagnosed by clinical criteria prior to other procedures. They underwent a physical and neurological examination, computed tomographic (CT) scan, blood workup (SMA 12), neuropsychological test battery, and electroencephalogram (EEG).

The two AD subsamples were matched on three dimensions: (1) estimated duration of the disease, (2) cognitive deficits, and (3) functional capacity. Duration was clinically assessed by interviewing patients and family members. Global cognitive deficit was quantified with the MMS (Mini-Mental Status examination [8]), as modified by Mayeux and colleagues [9] (here called mMMS). Functional capacity was assessed by the Blessed Dementia Rating Scale (BDRS) [10]. The majority of patients can be described as mildly demented (CDR 1 by the Berg and coworkers [11] criteria).

rCBF Procedures

rCBF was measured with a commercial system (Novo Cerebrograph 32c, Scan Detectronic A/S, Hadsund, Denmark), using 16 detectors covering each hemisphere. Detector placement reproducibility was achieved by means of light markers aligned with the auditory meatus and the orbitomeatal line. Extensive quality control measures were employed as detailed elsewhere [12]. These included careful documentation of xenon dosage and various computerized goodness-of-fit tests, as well as visual examination of clearance curves and their computed solutions. Two clearance curves (both in the anterior temporal pole) from 1 patient were excluded from analysis due to unsatisfactory quality. All procedures were performed with the patient's eyes closed and covered in a darkened and relatively silent room. Sedation was not employed: all patients could tolerate the procedure without medication.

Table 2. Mean Cerebral Perfusion Variables[a]

Variable	Mean ± SD Presenile		Senile		p[b]
M1					
ISI	44.43	7.13	46.85	6.10	0.28
w_g	0.356	0.054	0.394	0.031	0.02
M2					
ISI	39.99	6.33	41.88	5.75	0.35
CBF_{15}	31.51	4.32	34.19	4.43	0.07
f_g	54.25	8.27	53.96	8.14	0.92
k_2	0.093	0.013	0.102	0.016	0.07
w_g	0.352	0.050	0.395	0.025	0.002

[a]See Data Analysis section for definitions.
[b]Unpaired t tests, two-tailed.

Data Analysis

Clearance curves were analyzed by a six-unknown model (here termed M2), which yields more accurate results under low-flow conditions, as expected here [13–15], as well as the four-unknown model [16] (here called M1). Both models were used on 11 minutes of clearance monitoring. The M1 model was used only to confirm the findings: in all instances, results were qualitatively similar but quantitatively more significant with the M2 model. Most results below pertain to the more powerful M2 model; Table 2 also provides data from the standard M1 model for validation and comparison purposes.

The primary variables obtained from each model are p and k values for two parenchymal compartments, representing size and clearance rates; many secondary parameters can be derived from them. We routinely compute 17 primary and secondary variables from both models. The most sensitive and physiologically meaningful expression of cortical gray-matter perfusion is the flow gray (f_g) quantified in ml/100/gm/minute. However, it is known to suffer from lower reliability in low-flow conditions when compartmental distributions may be unstable, and therefore we use the initial slope index [15, 17] (ISI), which is more reliable and mostly influenced by gray-matter flow.

Relative weight of gray matter (w_g) was also derived [18]. It must be emphasized that the rCBF technique used here provides no anatomical specificity, and the term *gray-matter relative weight* is inferential. Strictly speaking, this is the relative weight of the fast-clearing compartment. This does correspond to gray matter in the normal brain, and the perfusion differences between gray and white matter are so robust that this distinction is rarely lost. In a demented population, however, due to the low flows, a bicompartmental solution was not always obtained. Such monoexponential solutions yield a reliable ISI value, but no relative weight term and no white-matter clearance (k_2). These curves were considered missing data for the w_g and k_2 analyses. Of the total of 1,152

clearance curves obtained in the demented patients, 17 (1.5%) curves from 13 detector locations were monoexponential; no one detector showed a significant preponderance of monoexponential solutions, nor was there a difference between presenile and senile patients (10 and 7 monoexponential solutions, respectively). There were no missing data for whole-cortex means, and all cell sizes were complete.

Global and regional differences between AD patients and healthy control subjects were recently detailed elsewhere [7]; the present communication addresses AAO effects within the dementia sample. Therefore, major analyses were conducted between the presenile and senile onset groups.

Results

Whole-Brain Values

For both M1 and M2 models, whole-brain mean perfusion did not differ significantly between the two dementia samples. Both samples had significantly lower perfusion than the normal sample. The purest gray-matter perfusion variable, f_g, showed identical values for presenile and senile AD samples. ISI was slightly lower in the presenile sample, and k_2 and CBF_{15} were marginally significant ($p = 0.07$), lower in the presenile patients. However, w_g showed substantial and significant reductions in the presenile patients.

An analysis of variance, with w_g as the dependent variable and diagnosis (control subjects, presenile, and senile groups) as a grouping factor, demonstrated significant differences ($F_{2,45} = 5.83, p = 0.006$). Post-hoc t tests showed that the presenile sample was significantly lower than both the normal ($t_{28} = 2.37$, $p = 0.025$) and senile ($t_{34} = 3.14$, $p = 0.004$) groups. Data are provided in Table 2, and the bivariate discrimination of the three samples is depicted in Figure 1.

Regional Differences

The demented patients, as a whole, showed a strikingly different regional pattern of flow, compared to the control subjects. As expected [7], they demonstrated reductions in parietal and frontal association areas with relatively preserved occipital and perirolandic perfusion. However, no significant differences in regional flow distribution were found between the two dementia subsamples.

The differences in relative gray-matter weight between the presenile and senile patients appeared diffuse. When each regional value was expressed as % of mean, Bonferroni-corrected t values were not significant for any region.

Correlations of Global Values

Correlation matrices (Pearson product-moment coefficients) were computed among the following variables: age, age at onset, duration of disease, mMMS, BDRS, and global means of ISI and w_g; this was done within the total dementia sample and within each subsample.

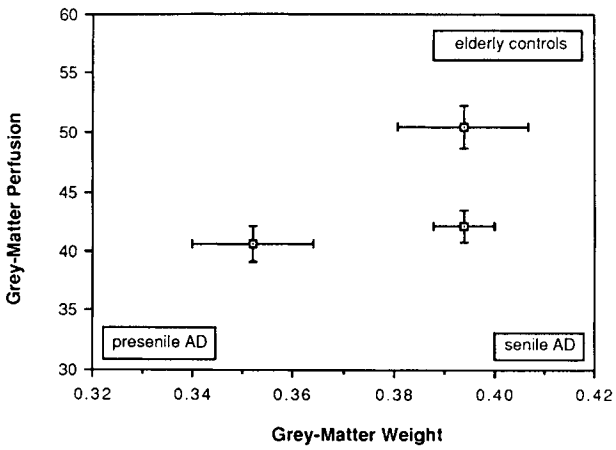

Fig 1. Mean gray-matter perfusion and relative weight (± SEM) in patients with presenile and senile onset Alzheimer's disease (AD) (n = 18 each) compared with that of healthy elderly control subjects (n = 12). Both AD samples show reduced perfusion, but only presenile onset is associated with loss of relative gray-matter weight.

Correlations for the total dementia sample were previously discussed [7]. ISI was significantly correlated with w_g ($r = 0.51$, $p < 0.01$); w_g showed significant correlations with age ($r = 0.49$, $p < 0.01$), age at onset ($r = 0.53$, $p < 0.001$), and mMMS ($r = 0.386$, $p < 0.05$). In all three, age and age at onset were almost perfectly correlated (0.92 to 0.98). Also in all three groups, there were significant correlations between the mMMS and BDRS (−0.57 to −0.81), reflecting the common variance between cognitive deficits and functional incapacitation.

Of note, the correlations appeared to be different between the two AAO subsamples. As Table 3 shows, all variables showed more powerful relationships within the presenile sample than within the senile sample. Not only was w_g better correlated to clinical variables in the presenile sample, but also the correlations among AAO, illness duration, BDRS, and mMMS were all significant for the presenile patients, whereas only the relationship between mMMS and BDRS was significant for the senile patients. Gray-matter weight was related to flow within the senile sample ($r = 0.47$, $p < 0.05$), but not to any other variable. In contrast, within the presenile sample, w_g was powerfully related to flow ($r = 0.55$, $p < 0.05$), as well as to all three severity measures: duration ($r = -0.53$, $p < 0.05$), mMMS ($r = 0.48$, $p < 0.05$), and BDRS ($r = -0.50$, $p < 0.05$), indicating loss of gray matter with greater disease severity.

Interactions with Duration

To assess possible interactions of AAO with estimated disease duration, all patients were divided into short

Table 3. Correlations Among Clinical Indices and rCBF Parameters[a]

	Age	AAO	Duration	mMMS	BDRS	M2 ISI	M2 w_g
Age		0.95***	0.04	0.35	−0.57*	0.36	0.20
AAO	0.92***		−0.28	0.54*	−0.74***	0.39	0.36
Duration	0.37	−0.01		−0.67**	0.64*	−0.12	−0.53*
mMMS	−0.38	−0.36	−0.14		−0.81***	0.30	0.48*
BDRS	0.42	0.43	0.08	−0.57*		−0.35	−0.50*
M2 ISI	0.30	0.35	−0.08	0.17	−0.19		0.55*
M2 w_g	0.21	0.12	0.26	0.18	0.09	0.47*	

[a]All values represent the Pearson product-moment correlation coefficient.

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

rCBF = regional cerebral blood flow; AAO = age at onset; mMMS = modified Mini-Mental Status Examination; BDRS = Blessed Dementia Rating Scale; M2 = six-unknown model; ISI = initial slope index; w_g = relative gray-matter weight.

Table 4. Short- and Long-Duration Samples

	Mean ± SD					
Variable	Short-Duration		Long-Duration		Difference[a]	Interaction[b]
AAO	66.68	8.76	62.82	10.45	ns	ns
Duration	1.74	0.73	4.94	0.97	< 0.001	ns
mMMS	36.11	10.26	23.18	16.53	0.007	ns
BDRS	7.90	4.07	10.34	3.22	ns	ns
M2 ISI	41.49	5.77	41.16	6.37	ns	ns
M2 w_g	0.386	0.035	0.358	0.050	ns	0.031

[a]Independent *t* test between the short and long duration samples, *p* value.
[b]Interaction between duration and AAO, two-way ANOVA, *p* value.

ns = not significant; other abbreviations are the same as in Table 3.

duration (n = 19, 11 senile and 8 presenile onset) and relatively long duration (n = 17, 7 senile and 10 presenile onset); short duration was defined as 3 years or less. Two-way ANOVAs were then conducted to assess the effects of AAO, duration, and their interaction. These samples are characterized in Table 4.

Mean duration of illness in the two samples was about 2 versus 5 years. As expected, the short-duration sample was less cognitively impaired ($p = 0.007$) and rated less severely on the BDRS ($p = 0.06$). Cerebral perfusion was identical in the two samples, and w_g was not significantly lower in the long-duration sample. Gray-matter weight was significantly associated with AAO ($F_{1,32} = 11.67$, $p = 0.002$), as expected, but there was also a significant interaction with duration ($F_{1,32} = 5.17$, $p = 0.03$). This interaction is illustrated in Figure 2, showing that at short durations the two dementia samples were similar, whereas at longer durations w_g was reduced in the presenile sample only.

Discussion

Previous work suggested that a more virulent disease process is associated with an earlier onset of AD. On neuropathological examination, presenile onset patients manifest greater densities of senile plaques, neurofibrillary tangles, cell loss, and choline acetyltransferase (ChAT) depletion [19–22]. Greater cognitive and behavioral deficits [19, 23], biochemical abnormalities [24, 25], and shorter life expectancy [4] have also been reported in the younger presenile patients.

It is unclear whether AAO predicts the course of Alzheimer's disease or its pathophysiology, independently of severity. If, as suggested, presenile onset is associated with greater behavioral severity or a more rapid progression, then a comparison of senile and presenile patients may yield differences attributable simply to the greater severity of the presenile variant. To determine whether presenile onset is associated with a fundamentally different process, severity of disease must be controlled, and duration of disease may not suffice if rates of progression confound the severity findings. This distinction has not, to our knowledge, been made in previous studies.

Our samples were selected so as to minimize this bias: senile and presenile patients had the same duration of disease, cognitive impairments, and functional

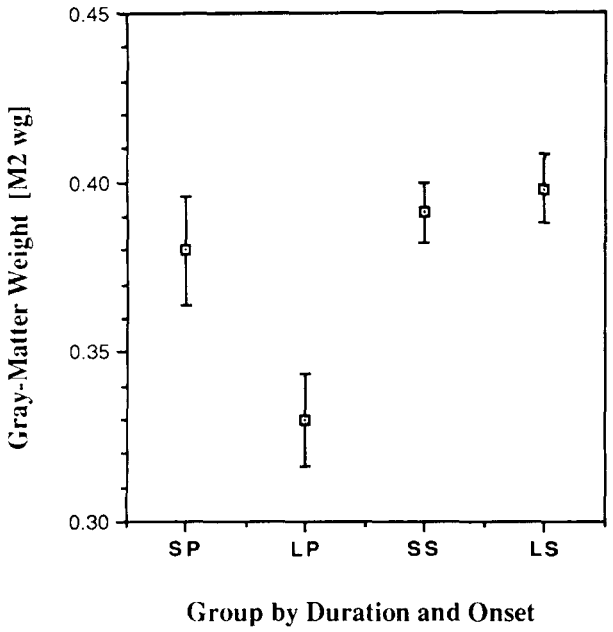

Fig 2. Relative gray-matter weight (± SEM) by age of onset as well as duration of Alzheimer's disease (AD). SP = short-duration, presenile; LP = long-duration, presenile; SS = short-duration, senile; LS = long-duration senile. A significant reduction of gray-matter weight was found only for patients with presenile onset and relatively long duration of disease.

capacity. Our results suggest, therefore, that even when duration and severity are equal, there is greater loss of gray matter with presenile onset. One could argue, if the hypothesis of greater severity in presenile onset is accepted, that our matched samples represent atypical patients. Even in that case, however, the current results demonstrate that presenile onset, per se, is associated with greater atrophy without the necessary concomitant of symptomatic severity.

Some corroboration for greater cerebral atrophy in presenile onset can be found in the literature. Kohlmeyer and Shamena [26] reported greater cortical atrophy in computed tomographic (CT) scans of presenile AD patients than in those with SDAT, and Albert and colleagues [27] found similar differences in CT density measurements. This loss of tissue raises questions regarding the validity of flow and metabolism determinations. Findings by positron emission tomography (PET) and single-photon emission computed tomography methods, using tracer trapping and distribution models rather than clearance, have been questioned with regard to the effect of atrophy: the reduction of flow or metabolism may be an artifactual consequence of loss of nerve tissue, despite normal function of the remaining viable tissue [28]. Moroi and coworkers [29] reported that metabolic PET images are distorted by atrophy, but the distortion does not substantially alter the typical findings of temporoparietal deficits. Xenon, however, providing dynamic clearance data, yields flow results in ml/100 gm/minute which are independent of tissue volume. The loss of gray matter we found suggests that PET studies not corrected for atrophy may indeed find artifactually low flow and metabolism in presenile AD.

In this article, we describe a functional loss of gray matter: the amount of tissue perfused at typical gray matter levels is reduced in presenile patients whose disease is of relatively long duration. This observation was not made in the three previous studies of w_g in AD. A reduction of w_g in SDAT patients (presenile patients were not examined) was recently reported by Deutch and Tweedy [30], but these authors did not exclude monoexponential solutions that yielded $w_g = 0$, resulting in low means and high variance. Their patients were not characterized by a standard clinical scale, but the very low perfusion values would suggest severe impairment. In fact, the authors used M1 ISI $\leq$ 30 to differentiate SDAT patients; this perfusion level was completely absent in our sample of 36 mild AD patients, and only 1 patient had M1 ISI between 30 and 35. Obrist and associates [31] examined 10 patients with "senile dementia" and 8 with "presenile dementia." Both dementia samples demonstrated significantly lower values of mean tissue perfusion, gray-matter perfusion, and w_g; the presenile, but not senile, patients also showed reductions of white-matter perfusion similar to our findings. These authors also reported correlations of rCBF results with severity rankings. The reasons for the lack of w_g differences due to AAO in this study are unclear, but both clinical methodology and rCBF technology were not comparable to ours. Other findings are also inconsistent: Obrist and associates [31] found focal deficits in frontotemporal regions, whereas current consensus implicates parietotemporal regions [7].

Whether the w_g reduction reflects actual loss of neurons, known to occur in AD [32], or only a reduced function to white-matter levels remains to be rigorously established. Gray-matter tissue may be perfused at white-matter levels without permanently losing viability [33], and the findings reported here do not necessarily imply irreversible tissue damage. Although the w_g term represents gray-matter weight only inferentially (strictly speaking, we have found loss of "fast-clearing compartment" in the presenile AD cases), this compartment does represent gray matter in the normal brain, and it is established that no white matter achieves clearance rates comparable to gray matter [34]. Second, because the term represents relative weight only, in relation to total tissue observed, the results could be interpreted as "gain" of white matter or glial cells. This is highly improbable: although Brun and Englund [35] reported a mild reactive astrocytic gliosis in AD, their major finding was a loss of

white matter consistent with chronic hypoperfusion in about two-thirds of their patients. Finally, dissociations between flow and w_g confirm our quality control measures in suggesting the absence of "slippage" [12] as a determinant of the observed w_g differences. Slippage refers to a mathematical artifact caused by inadequate match between observed data and the physiological model; the most common variant yields overestimated flow and underestimated weight. If this occurred in the current material, w_g reductions in the presenile sample should have been associated with higher flow values. In fact, the f_g data demonstrate no differences between the samples.

Of note, common slippage raises k_2, in addition to f_g. Our data show lower k_2 values in the presenile sample, as well as reduced w_g. If presenile onset is associated with some portion of gray matter being perfused at very low levels approaching white-matter flow, but no absolute loss of perfused tissue, k_2 should be elevated as well as p_2. In fact, k_2 was lower in presenile patients and p_2 showed no difference. Considering the distributions proposed by Reivich and colleagues [34], the combined observations of unchanged f_g, lower k_2, and lower w_g may indicate a loss, rather than a shift, of gray matter. Older literature appears to be consistent with this interpretation. Høedt-Rasmussen and Skinhøj [36], using intracarotid administration of ^{133}xenon, reported a mean w_g of 48.8 ± 4.5% in uncharacterized normal subjects. The value dropped to 38.9 ± 8.0% in 8 patients with "degenerative brain disease." In addition, the authors suggested that there was a further decline of w_g in the presence of severe dementia or severe cerebral atrophy (as visualized by pneumoencephalography). Unfortunately, neither the patients nor the control subjects were characterized. Of major relevance, however, are the reported validity tests. Høedt-Rasmussen and Skinhoj reported an excellent correlation between xenon uptake and known distributions of gray and white matter in vitro, and no correlation between perfusion rate and w_g estimates in vivo. The relationship observed with atrophy also suggested that the w_g index was a valid measure of tissue loss. We therefore propose that there is actual tissue destruction in presenile AD, although the evidence at present is inconclusive.

In addition to differences in mean values, the pattern of w_g correlations showed dissimilarities between the presenile and senile subsamples. In the presenile patients, w_g was significantly predicted by all three severity dimensions, with a total multiple regression of 0.57: 32% of w_g variance is thus predicted by severity. In contrast, no significant correlations were observed in the senile sample. It appears, thus, that in presenile AD this loss is related to the duration and severity of the disease, possibly with causal significance.

Within both samples there was a significant positive correlation between perfusion and w_g. This positive relationship was expected: the ISI represents perfusion in both gray and white matter, and a decline in the relative amount of fast-clearing tissue must reduce the ISI value. In several other respects, the w_g findings are dissociated from perfusion abnormalities. As Figure 1 depicts, there were no differences in gray-matter blood flow between the two dementia subsamples (globally or regionally), and both were significantly reduced in this respect from normal values. Gray-matter weight was reduced only in the presenile sample, and it differed significantly from both control and senile values. Such dissociation between w_g and perfusion was also evident when duration effects were examined (see Table 4). Further, the correlations between w_g and duration and severity within the presenile sample were all significant, whereas none of these correlations was significant with flow. Finally, whereas the perfusion differences between demented patients and control subjects show a sharp regional pattern [7], the w_g reduction in presenile onset was diffuse.

It appears, therefore, that the process associated with loss of gray matter in presenile AD leads to qualitatively dissimilar phenomena from the process which causes a global and focal reduction of cerebral perfusion and metabolism in AD. This dissociation is reminiscent of the sequelae of lesions in the nucleus basalis of Meynert (NbM) in animal models: recovery of memory functions and cerebral glucose utilization occur despite persistent ChAT deficits and cell loss [37, 38]. Similarly, Neary and colleagues [39] have shown in 17 presenile AD patients that severity of dementia was correlated with loss of large cortical neurons but not with reduction in ChAT activity.

It is reasonable, therefore, to hypothesize that there are two processes in AD. Cerebral perfusion is associated with the disease, possibly through cholinergic mechanisms, and perfusion abnormalities are not a function of age at onset, similarly to the recently reported elevation of membrane fluidity [40]. Structural damage to cortical tissue is dissociated from perfusion deficit both in the NbM model and in our findings, where it is associated with earlier onset and greater symptomatic severity. Presenile onset of AD entails relative loss of cerebral gray matter, proportional to symptomatic severity and duration, but such loss is not seen following senile onset, with similar duration, severity, and perfusion deficits. Perfusion abnormalities are independent of age at onset and may represent more a threshold phenomenon than a gradual worsening, because they appear with full magnitude even in very mildly impaired patients [7].

The differences between the current two AAO samples extended also to the clinical indices. Although they were matched on illness duration and two severity scales, the relationships among those indices were dif-

ferent: mMMS and BDRS were related to AAO and illness duration in the presenile patients, but not within the senile-onset patients. The same was true for the loss of gray matter: whereas at short durations the samples are similar in w_g, longer durations are associated with lower w_g in the presenile, but not senile, patients. Although interpretation of these observations must await replication, they indicate further fundamental differences between the two disease variants. With presenile onset, there is a greater proportion of common variance among the clinical indices as well as related loss of gray matter.

We conclude that in the early stages of presenile AD, but not in AD of senile onset, there is a loss of cortical gray matter, even when the two samples are carefully matched for duration and severity of disease. This loss of gray matter is diffuse, and unaccompanied by perfusion differences, suggesting that the remaining viable tissue functions at similar metabolic levels. This loss of gray matter is related to duration and symptomatic severity in presenile AD, indicating a fundamental relationship to the disease process that is not apparent in senile-onset patients. Further, the correlational structure of severity and duration variables appears to indicate a substantial common variance in presenile, but not senile, patients. Gray-matter perfusion abnormalities are also evident in the early stages of the disease, but they are identical in presenile and senile onset patients.

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