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# Glucose metabolism in early onset versus late onset Alzheimer's disease: an SPM analysis of 120 patients

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**The aims of this cross-sectional study were (i) to compare the overall glucose metabolism between early onset and late onset Alzheimer's disease in a large sample of patients; and (ii) to investigate the pattern of glucose metabolism as a function of dementia severity in early onset versus late onset Alzheimer's disease, using a statistical parametric mapping (SPM) analysis. Subjects consisted of four groups: 74 patients with early onset Alzheimer's disease, 46 patients with late onset of the disease, and two control groups age matched to each patient group. All the subjects underwent 2-[$^{18}$F]fluoro-2-deoxy-D-glucose (FDG)-PET under the same scanning conditions. Severity of dementia was rated with the Clincial Dementia Rating (CDR). Voxel-based SPM99 was used for statistical analyses. Overall glucose hypometabolism of early onset Alzheimer's disease patients was much greater in magnitude and extent than that of late onset patients, though both groups were similar in dementia severity: the early onset group showed more severe hypometabolism in parietal, frontal and subcortical (basal ganglia and thalamus) areas. When the decline of glucose metabolism was compared as a function of CDR stage, the slope was steeper in early onset than in late onset Alzheimer's disease. The rapid decline occurred at CDR 0.5–1 in the early onset group, whereas similar changes occurred at CDR 2–3 in the late onset group. The greater hypometabolism in early onset than in late onset patients is required to reach the same severity of dementia, probably reflecting greater functional reserve in younger than in older subjects. Alternatively, the metabolic decline curve suggests that the early onset patients may take a more rapid course in the reduction of glucose metabolism than the late onset patients.**

**Keywords**: Alzheimer's disease; early onset; late onset; PET; statistical parametric mapping

**Abbreviations**: CDR = Clinical Dementia Rating; COWAT = Controlled Oral Word Association Test; FDG = 2-[$^{18}$F]fluoro-2-deoxy-D-glucose; MMSE = Mini-Mental State Examination; RCFT = Rey–Osterrieth Complex Figure test; ROI = region of interest; SNSB = Seoul Neuropsychological Screening Battery; SPM = statistical parametric mapping

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## Introduction

Alzheimer's disease is the most common cause of progressive degenerative dementia that results in global cognitive deterioration, behavioural disturbances and diffuse cortical atrophy associated with neuronal degeneration. Many heterogeneities exist in Alzheimer's disease with regard to genetic (Bird *et al.*, 1989; Levy-Lahad and Bird, 1996), neuropathological (Terry *et al.*, 1999) and neuropsychological aspects (McDonald, 1969; Martin *et al.*, 1986; Fisher *et al.*, 1997).

One of the factors related to the heterogeneities is the age of symptom onset. It has been reported that, with an arbitrary cut-off age of 65 years (Amaducci *et al.*, 1986), patients with Alzheimer's disease of early onset have more prominent focal

cortical symptoms such as aphasia, apraxia and agnosia than those with Alzheimer's disease of late onset (McDonald, 1969; Seltzer and Sherwin, 1983; Chui *et al.*, 1985), while those with late onset disease have more predominant impairment in memory function, especially verbal memory (Binetti *et al.*, 1993).

Recently, functional neuroimaging studies have investigated whether early onset Alzheimer's disease differs from late onset Alzheimer's disease in terms of topography and severity of cerebral perfusion or metabolic defects which may reflect the neuropsychological heterogeneity. However, the results are inconsistent. One study reported that the two groups did not differ in the topography of functional changes, i.e. the predominant temporoparietal hypometabolism (Grady *et al.*, 1987). In contrast, it has been reported that early onset Alzheimer's disease had a more focal reduction of glucose metabolism in the frontal and temporo-parietal cortex, whereas late onset Alzheimer's disease showed more diffuse hypometabolism (Mielke *et al.*, 1992). Other studies also found that early onset Alzheimer's disease, compared with late onset Alzheimer's disease, showed greater hypometabolism in the posterior cingulate region including the precuneus (Salmon *et al.*, 2000; Sakamoto *et al.*, 2002), or in the bilateral parietal area (Sakamoto *et al.*, 2002).

The pattern of involvement in brain regions over time is relatively uniform as the disease progresses. According to Braak and Braak's neuropathological staging of Alzheimer's disease (Braak and Braak, 1991), destructive processing progresses from mainly the transentorhinal region (stage I) and entorhinal region (stage II) in the early stage of the disease to the limbic area (stages III and IV), the neocortical high-order sensory association and the prefrontal area (stage V), and finally the primary sensory fields (stage VI). Recent advances in functional neuroimaging techniques allow observation of the functional change of Alzheimer's disease *in vivo* as the disease progresses. There have been longitudinal studies that showed that the decline in regional cerebral blood flow or glucose metabolism occurs initially in the posterior cingulate gyrus and precuneus and then extends to the hippocampus and parahippocampal gyrus (Kogure *et al.*, 2000), further spreading to the frontal areas in advanced Alzheimer's disease (Duara *et al.*, 1986; Brown *et al.*, 1996; Sachdev *et al.*, 1997; Matsuda *et al.*, 2002). However, these studies were usually focused on patients with mild cognitive impairments or the early stage of Alzheimer's disease and did not compare the metabolic difference between early onset disease and late onset disease. To the best of our knowledge, there have been no studies that compare the patterns of metabolic deterioration over time between early onset and late onset Alzheimer's disease.

Mean survival of this disease after symptom onset has been reported to be variable, ranging from 2 to >16 years (mean 9–10 years). Studies that investigated the rate of progression by measuring cognition and functional abilities over time demonstrated that the relationship between the rate of progression and onset of age is also variable. Some reports demonstrated that the early onset group shows a more rapid progression and shorter survival (Heston *et al.*, 1981; Seltzer and Sherwin, 1983; Heyman *et al.*, 1987; Jacobs *et al.*, 1994; Koss *et al.*, 1996), and others argued that the age of onset does not appear to be a major predictor of the rate of progression (Huff *et al.*, 1987; Berg *et al.*, 1988; Katzman *et al.*, 1988*a*; Ortof and Crystal *et al.*, 1989; Drachman *et al.*, 1990; Bracco *et al.*, 1994). However, there have been few reports that studied the rate of progression by measuring functional changes in neuroimaging longitudinally or cross-sectionally.

Most prior reports on functional neuroimaging in Alzheimer's disease have relied on visual inspection or a region of interest (ROI) method. Although the ROI technique is a useful method, it only analyses selected areas, thus many brain regions may be left unexplored. In contrast, recently developed voxel-based analysis using statistical parametric mapping (SPM) is expected to overcome this limitation and the relationship between the metabolic change and its anatomical basis can be investigated more accurately. To date, there have been a few studies that have used SPM analysis to compare the glucose metabolism or cerebral perfusion of early onset Alzheimer's disease with that of late onset Alzheimer's disease (Salmon *et al.*, 2000; Sakamoto *et al.*, 2002; Kemp *et al.*, 2003). These studies, however, recruited a relatively small number of patients and did not compare early onset and late onset Alzheimer's disease groups in terms of patterns of metabolic abnormalities according to the stage of disease severity.

The aims of this study thus were to examine, using an SPM analysis of 2-[$^{18}$F]fluoro-2-deoxy-D-glucose (FDG)-PET in a large sample of Alzheimer's disease patients: (i) which brain regions are differentially affected in early onset and late onset Alzheimer's disease; and (ii) how the pattern of metabolic impairment differs between the two groups according to the severity of dementia.

## Material and methods

### Subjects

#### *Patients*

The initial sample consisted of 737 patients who had been diagnosed as having Alzheimer's disease at the Memory Disorder Clinic at Samsung Medical Center, Seoul, Korea from April 1995 to October 2003. All the patients fulfilled the criteria for probable Alzheimer's disease proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann *et al.*, 1984). From this initial sample, 120 patients who had received FDG-PET scans were selected after excluding three patients with familial Alzheimer's disease with autosomal dominant inheritance, five with posterior cortical atrophy (Mendez *et al.*, 2002) and three with a frontal variant of Alzheimer's disease (Johnson *et al.*, 1999). At the initial visit, all the selected patients underwent clinical interview, neurological examination and a battery of neuropsychological tests called the Seoul Neuropsychological Screening Battery (SNSB) (Kang and Na, 2003), which is described later. Laboratory tests including CBC, chemistry, vitamin $B_{12}$/folate, syphilis serology and thyroid function tests did not show any cause to explain patients' dementia.

**Table 1** Demographics and MMSE scores of early onset and late onset of Alzheimer's disease patients and normal controls

| | Early onset group | | | Late onset group | | |
|---|---|---|---|---|---|---|
| | Alzheimer's disease ($n$ = 74) | Control ($n$ = 20) | $P$-value | Alzheimer's disease ($n$ = 46) | Control ($n$ = 13) | $P$-value |
| Age at onset | 55.7 ± 5.4 | – | – | 69.6 ± 3.1 | – | – |
| Age at examination | 59.1 ± 5.7 | 56.4 ± 4.9 | 0.053 | 72.8 ± 3.6 | 71.5 ± 2.0 | 0.084 |
| Sex (female %) | 66.2% | 55.0% | 0.354 | 71.7% | 30.8% | 0.01 |
| Duration of education (years) | 10.6 ± 4.9 | 11.6 ± 4.2 | 0.395 | 9.3 ± 5.3 | 11.1 ± 3.9 | 0.283 |
| CDR | 1.3 ± 0.9 | – | – | 1.3 ± 0.8 | – | – |
| MMSE scores | 17.4 ± 7.1 | 29.3 ± 0.7 | 0.000 | 18.5 ± 7.1 | 29.0 ± 0.9 | 0.000 |

MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating.

Brain MRI or CT scans were performed in all patients (MRI in 89 out of 120, CT in 31 out of 120) and confirmed that territorial cerebral infarction, brain tumour or other structural lesions were absent. One neuroradiologist blinded to the clinical information performed visual analysis of cerebral ischaemia in MRI or CT scans. Ischaemia in MRI was measured by the scale of Fazekas *et al.* (1987) which provides two different scores (periventricular and white matter score) each rated on a 4-point scale. Ischaemia in CT scan was rated by the scale of Blennow *et al.* (1991) which measures both extent and severity of white matter lesions each on a 4-point rating scale. The results showed that ischaemic scores in MRI for periventricular hyperintensity were rated as either 0 (absence, 52 out of 89 patients) or 1 (caps or pencil-thin lining, 37 out of 89), resulting in a mean ischaemic score of 0.4 ± 0.5, and those for white matter hyperintensity were rated as 0 (absence, 73 out of 89), 1 (punctate foci, 12 out of 89) or 2 (beginning confluence of foci, four out of 89), resulting in a score of 0.2 ± 0.5. Ischaemia on CT scan was also negligible, with the extent of white matter lesion rated as 0.2 ± 0.5 and the severity of white matter lesion rated as 0.2 ± 0.5. All the patients scored from 0 to 4 on the Hachinski's ischaemic scale (mean score, 0.25 ± 0.5) (Hachinski *et al.*, 1975).

The 120 patients consisted of 38 men and 82 women and their mean age was 64.4 ± 8.4 years (range: 41–82) and mean duration of education was 10.1 ± 5.1 years (range: 0–20). Severity of dementia was estimated at the initial visit by the Clinical Dementia Rating (CDR) (Hughes *et al.*, 1982; Morris, 1993) and Mini-Mental State Examination (MMSE). Mean CDR was 1.3 ± 0.8 (range: 0.5–3), and mean MMSE score was 17.8 ± 7.1 (range: 0–29). Mean disease duration was 3.3 ± 1.9 years (range: 1–10).

Onset age of dementia was determined on the basis of the information obtained from family members at the time of the patient's first visit to our memory disorder clinic. Then the patients were arbitrarily divided into two subgroups according to the age at onset: 74 patients belonged to the early onset group (age onset <65 years) with average onset age of 55.7 ± 5.4 years (range: 40–64) and the remaining 46 patients to the late onset group (onset age of ≥65 years) with average onset age of 69.6 ± 3.1 years (range: 65–76). This over-representation of early onset patients may have resulted from the fact that younger patients and patients with higher socio-economic status showed more active response to the physician's request to include FDG-PET as a diagnostic evaluation. The 74 patients with early onset Alzheimer's disease did not differ from those with early onset Alzheimer's disease from the initial sample (247 out of 737) in terms of sex ratio (percentage females of selected versus initial sample: 66.2 versus 67.2%, $P$ = 0.874), MMSE (17.4 ± 7.1 versus 16.3 ± 8.2, $P$ = 0.657) and CDR (1.3 ± 0.9 versus 1.3 ± 0.8, $P$ = 0.328), but age (59.1 ± 5.7 versus 61.3 ± 6.1 years, $P$ = 0.006) (onset age 55.7 ± 5.4 versus 57.4 ± 5.6 years, $P$ = 0.024) was younger and education (10.6 ± 4.9 versus 9.1 ± 5.5 years, $P$ = 0.025) was higher in the selected sample. Likewise, the 46 patients with late onset Alzheimer's disease did not differ from those with late onset Alzheimer's disease from the initial cohort (490 out of 737) in terms of sex ratio (percentage female 71.7 versus 69.2%, $P$ = 0.734), MMSE (18.5 ± 7.1 versus 16.2 ± 7.2, $P$ = 0.855) and CDR (1.3 ± 0.8 versus 1.4 ± 0.8, $P$ = 0.293), but that age (72.8 ± 3.6 versus 75.6 ± 5.1 years, $P$ = 0.000) (onset age 69.6 ± 3.1 versus 73.0 ± 5.3, $P$ = 0.000) was younger and education (9.3 ± 5.3 versus 7.4 ± 5.7 years, $P$ = 0.024) was higher in the selected group. Again, these age and education differences between the selected and initial samples in both early onset and late onset group may represent more active response to physicians' request to PET scanning in subjects of younger age and higher socio-economic status.

As presented in Table 1, the early onset group did not differ from the late onset group in CDR (1.3 ± 0.9 versus 1.3 ± 0.8, $P$ = 0.920) and MMSE (17.4 ± 7.1 versus 18.5 ± 7.1, $P$ = 0.406).

Twenty-three of the 74 early onset patients belonged to CDR 0.5, 25 to CDR 1, 17 to CDR 2 and the remaining nine to CDR 3. Thirteen of the 46 late onset patients belonged to CDR 0.5, 16 to CDR 1, 13 to CDR 2, and the remaining four to CDR 3. Patients did not differ in age across the CDR stages in both early onset ($P$ = 0.294) and late onset ($P$ = 0.584) groups.

### *Controls*

Two control groups, one for early onset Alzheimer's disease and the other for late onset Alzheimer's disease, consisted of 33 healthy volunteers (20 young controls and 13 old controls) who were matched to the patients in age and education. Demographic features of control groups are also presented in Table 1. These controls were spouses of neurology out-patients at Samsung Medical Center and had neither a history of neurological and psychiatric illnesses nor abnormalities on neurological examinations. These subjects' cognition was confirmed to be within normal limits as assessed by MMSE (mean 29.2 ± 0.8) and SNSB. Informed consent for the neuropsychological tests and FDG-PET was obtained from all the controls.

## Neuropsychological tests

The SNSB, a standardized neuropsychological battery (Kang and Na, 2003), contains tests for attention, language, praxis, four elements of Gerstmann syndrome, visuoconstructive function, verbal and visual

memory, and frontal/executive function. Among these scorable tests were the digit span (forward and backward), the Korean version of the Boston Naming Test (Kim and Na, 1999), written calculations (three items each for addition, subtraction, multiplication and division; one point for each correct item), five items for ideomotor limb praxis (one point for each correct item), the Rey–Osterrieth Complex Figure test (RCFT: copying, immediate and 20 min delayed recall, and recognition), Seoul Verbal Learning Test (three learning-free recall trials of 12 words, 20 min delayed recall trial for these 12 items, and a recognition test), phonemic and semantic Controlled Oral Word Association Test (COWAT) and Stroop test (word and colour reading of 112 items in 2 min).

### PET imaging

The time interval from the initial clinical assessment to PET scan was on average 20.4 days. Participants fasted at least 6 h before the scan. PET scans of 30 min were acquired starting 40 min after intravenous injection of 4.8 MBq/kg FDG using a GE Advance PET scanner. To minimize the external stimuli during the FDG uptake period, participants stayed in a dimly lighted room with their eyes closed. In-plane and axial resolution of the scanner was 4.9 and 3.9 mm full-width at half maximum (FWHM), respectively. PET images were reconstructed using a Hanning filter (cut-off frequency = 4.5 mm) and displayed in $128 \times 128$ matrix (pixel size = $1.95 \times 1.95$ mm with a slice thickness of 4.25 mm). Attenuation correction was performed with a uniform attenuation coefficient (0.096/cm).

### SPM analysis of regional glucose metabolism

PET images were analysed using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) (Friston *et al.*, 1995), implemented using Matlab 5.3 (MathWorks Inc., Sherborn, MA). Prior to statistical analysis, all the images were spatially normalized into the MNI standard template (Montreal Neurological Institute, McGill University, Montreal, Canada) to remove inter-subject anatomical variability. Spatially normalized images were smoothed by convolution, using an isotropic Gaussian kernel with 16 mm FWHM. The aim of smoothing was to increase the signal-to-noise ratio and to account for the subtle variations in anatomical structures. The count of each voxel was normalized to the average count of the cerebellum with proportional scaling in SPM99. We applied cerebellar normalization instead of global normalization because cerebellum is known to be one of the least affected regions in Alzheimer's disease. After spatial and count normalization, statistical comparisons between groups were performed on a voxel-by-voxel basis using $t$ statistics, generating SPM ($t$) maps. We investigated hypometabolic brain areas at a height threshold of $P = 0.001$ (uncorrected) and an extent threshold of 100 voxels. For visualization of the $t$ score statistics (SPM{$t$} map), the significant voxels were projected onto the 3D rendered brain or a standard high-resolution MRI template provided by SPM99, thus allowing anatomical identification. The MNI coordinates of the local maximum of each cluster were converted into Talairach coordinates (Talairach and Tournoux, 1988).

## Results

### Results of neuropsychological tests

Although all 120 patients participated in the neuropsychological tests, six patients could not complete more than half the battery because their cognitive functions were so severely impaired (mean MMSE, 11.5 ± 8.4; mean CDR, 2.5 ± 0.5), and nine patients were excluded since their data were missing. Data of patients who refused parts of the battery or who were unable to perform parts of the test due to illiteracy (e.g. calculation and Stroop) were included. Thus, data of the remaining 105 patients (66 early onset Alzheimer's disease and 39 late onset Alzheimer's disease) were included in the analysis. Raw scores of the scorable tests were compared between early onset and late onset patients. As presented in Table 2, early onset more than late onset patients were significantly impaired at backward digit span, calculation, copy of RCFT, the supermarket item of COWAT and Stroop. A similar tendency was noted for forward digit span and limb praxis, although the difference did not reach significance. Conversely, early onset patients did not outperform late onset patients in any of the tests.

### Comparison of glucose hypometabolism between early onset and late onset Alzheimer's disease

When late onset Alzheimer's disease patients were compared with the old controls, hypometabolic brain regions in patients with late onset Alzheimer's disease were only in the right inferior temporal gyrus (Fig. 1B, Table 3). On the other hand, patients with early onset Alzheimer's disease compared with the young controls showed hypometabolism in the frontal lobe, basal ganglia and thalamus in addition to the temporoparietal areas (Fig. 1A, Table 3). Thus, the hypometabolism observed in the early onset group appeared much more extensive than in the late onset Alzheimer's disease group. To specify this difference further, both groups were directly compared. To minimize the possible confounding effect of dementia severity, individual MMSE score was taken as a covariate. The results showed that reduction of cerebral glucose metabolism was significantly greater in early onset Alzheimer's disease than in late onset Alzheimer's disease in the following regions (Fig. 1C upper row): right superior temporal gyrus, right inferior parietal lobule, right middle occipital gyrus and right precuneus. However, hypometabolic regions in late onset Alzheimer's disease compared with early onset Alzheimer's disease were only in the left superior temporal gyrus (Fig. 1C lower row).

The comparison of glucose metabolism between old versus young healthy subjects showed that the old control group had more severe hypometabolism in the frontal area than the young control group (Fig. 1D, Table 3).

### Differences in glucose metabolism according to dementia severity

Hypometabolic areas in each Alzheimer's disease group compared with its control were analysed according to each CDR stage (CDR 0.5–3). As presented in Fig. 2 and Table 4, by the time patients with early onset Alzheimer's disease reached

**Table 2** The results of neuropsychological tests in early onset versus late onset Alzheimer's disease

| Neuropsychological tests (possible maximum score) | Early onset (*n*) | Late onset (*n*) | *P*-value |
|---|---|---|---|
| Attention | | | |
| Digit span: forward/backward | 4.6 ± 1.6 (66)/2.2 ± 1.4 (66) | 5.2 ± 1.5 (38)/2.9 ± 1.4 (38) | 0.062/0.013 |
| Language and related disorders | | | |
| K-BNT (60) | 30.5 ± 1.4 (63) | 26.6 ± 15.3 (39) | 0.179 |
| Calculation (12) | 7.0 ± 4.1 (41) | 9.7 ± 3.9 (24) | 0.011 |
| Ideomotor limb apraxia (5) | 3.0 ± 2.0 (52) | 3.7 ± 1.8 (34) | 0.096 |
| Visuospatial function | | | |
| RCFT (36) | 13.1 ± 12.9 (64) | 23.6 ± 10.9 (36) | 0.000 |
| Memory | | | |
| SVLT: sum of three free recall trials/delayed recall (12 + 12 + 12 = 36/12) | 9.3 ± 5.5 (65)/0.9 ± 1.7 (63) | 10.3 ± 5.1 (37)/0.9 ± 2.0 (37) | 0.385/0.937 |
| SVLT recognition: true positive-false positive | 3.2 ± 3.4 (56) | 4.3 ± 2.5 (31) | 0.107 |
| RCFT immediate/delayed recall (36/36) | 2.1 ± 3.9 (63)/1.7 ± 4.1 (62) | 3.3 ± 3.8 (34)/2.6 ± 3.4 (35) | 0.131/0.283 |
| RCFT recognition: true positive-false positive | 2.5 ± 3.6 (49) | 3.6 ± 2.9 (20) | 0.261 |
| Frontal/executive function | | | |
| COWAT, semantic: animal/supermarket items | 7.3 ± 4.5 (65)/6.8 ± 5.0 (64) | 8.3 ± 4.3 (38)/9.7 ± 5.8 (38) | 0.274/0.009 |
| COWAT, phonemic: sum of three letters | 8.2 ± 9.1 (61) | 10.8 ± 10.2 (37) | 0.196 |
| Stroop test: letter reading/colour reading in 2 min each (112/112) | 78.3 ± 37.9 (47)/29.6 ± 28.4 (43) | 99.0 ± 22.7 (21)/47.5 ± 31.6 (21) | 0.007/0.033 |

*n* = number of patients whose data were available for analysis; K-BNT = Korean version of the Boston Naming Test; RCFT = Rey–Osterrieth Complex Figure Test; SVLT = Seoul Verbal Learning Test; COWAT = Controlled Oral Word Association Test.

CDR 1, the hypometabolism had involved temporal and parietal association cortices extending even to the frontal lobe. This hypometabolism appears increased as the CDR stage increases further, but was a small amount. Late onset Alzheimer's disease differed from early onset Alzheimer's disease in glucose metabolism according to the CDR stage, i.e. the glucose hypometabolism in the late onset patients with CDR 0.5 was negligible and, as the CDR stage advances further, the hypometabolism increased gradually, maintaining primarily a temporoparietal pattern without frontal involvement even in CDR 3.

To quantify the differences in glucose metabolism as the severity of dementia increases, the number of hypometabolic voxels in maps after SPM analysis (Fig. 3) was counted and plotted against the CDR stage. As presented in Fig. 3, in the early onset Alzheimer's disease patients, the number of hypometabolic voxels abruptly increased as CDR transited from 0.5 to 1, but slightly increased as the dementia progressed further to CDR 2 and CDR 3. However, in late onset Alzheimer's disease, the change in the number of hypometabolic voxels was small between CDR 0.5 and CDR1 which then slowly increased as the dementia progressed to CDR 2 and 3.

## Discussion

Regarding the topography of functional changes in early onset versus late onset Alzheimer's disease, our study involving a large sample of patients replicates and extends the results of previous studies. Previous SPM studies (Salmon *et al.*, 2000; Sakamoto *et al.*, 2002; Kemp *et al.*, 2003) matched the severity of dementia between early onset and late onset groups with MMSE or ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale) scores that reflect only the cognitive aspects of dementia. Unlike these studies, in matching the two groups, we also used the scale which reflects functional aspects of dementia (CDR). Nevertheless, the glucose hypometabolism of early onset Alzheimer's disease patients was much more severe in magnitude and extent than that of late onset patients, replicating the results of the study of Sakamoto *et al.* (2002).

Previous SPM studies reported that early onset Alzheimer's disease led to more severe functional changes than late onset Alzheimer's disease in posterior cingulate (Salmon *et al.*, 2000) or bilateral parietal lobes including precuneus (Sakamoto *et al.*, 2002; Kemp *et al.*, 2003). In our study, the hypometabolic pattern, which was more severe in the early onset than in the late onset group, included all the regions reported in the previous studies (parietal and posterior cinguluum), a result also compatible with pathological reports that early onset Alzheimer's disease patients show more severe parietal lobe involvement than do those with late onset Alzheimer's disease (Bigio *et al.*, 2002). Additionally, our study showed that the frontal lobe and the subcortical structures such as basal ganglia and thalamus were more hypometabolic in early onset than in late onset patients. These results may be consistent with those of previous reports that histopathological changes and neurochemical abnormality are most severe in the youngest patients and the frontal cortex is usually spared in the older patients (Rossor *et al.*, 1984; Bigio *et al.*, 2002). Regarding the involvement of thalamus and basal ganglia in Alzheimer's disease, no pathological reports supporting our results are available, but the clinical findings of the prior study that extrapyramidal symptoms are

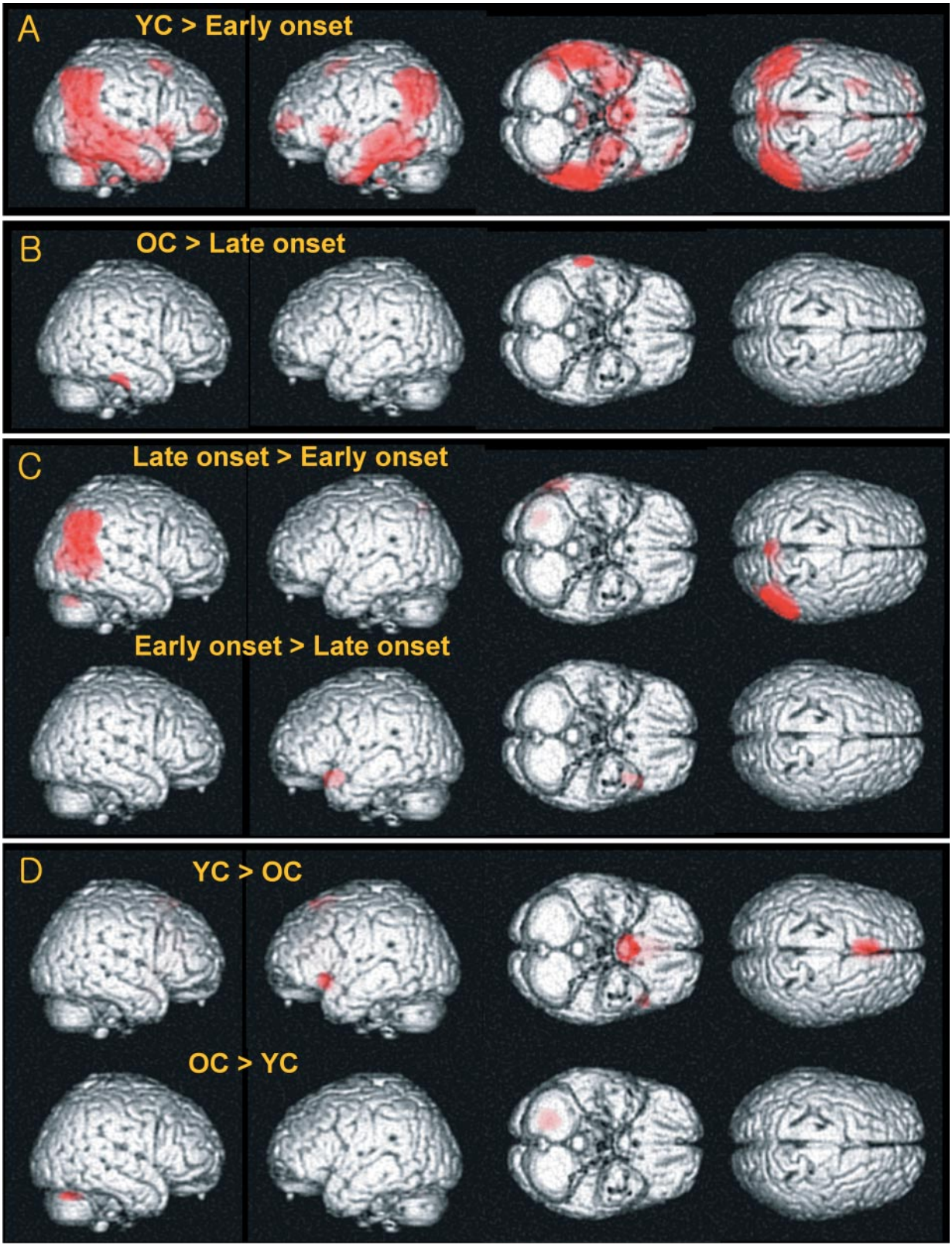


**Fig. 1** Hypometabolic regions in early onset Alzheimer's disease patients compared with young controls (**A**) and in late onset Alzheimer's disease patients compared with old controls (**B**). (**C**) Direct comparison of patients with early onset and late onset disease. Hypometabolic regions in early onset Alzheimer's disease patients compared with late onset patients (upper row) and in late onset Alzheimer's disease patients compared with early onset patients (lower row). (**D**) Comparison of young controls with old controls. Hypometabolic regions in young controls compared with old controls (upper row) and in old controls compared with young controls (lower row). The hypometabolic regions (red colour) are displayed on rendering images at the threshold of $P < 0.001$ uncorrected, $k = 100$.

**Table 3** Regions of decreased metabolism in early onset and late onset groups of Alzheimer's disease patients compared with age-matched normal controls ($P < 0.001$ uncorrected, $k = 100$)

| Variables | Regions | BA | Stereotaxic coordinates | | | *T* value | Cluster size |
|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | |
| Young age controls > early onset AD | Rt.posterior cingulate gyrus | BA23 | 2 | −32 | 27 | 6.14* | 37203 |
| | Lt.caudate head/body | | −4 | 6 | 2 | 5.87* | |
| | Rt.caudate head | | 4 | 6 | 0 | 5.82* | |
| | Lt.middle temporal gyrus | BA21 | −59 | −41 | −8 | 5.79* | |
| | Rt.inferior temporal gyrus | BA20 | 59 | −30 | −22 | 5.73* | |
| | Lt.inferior parietal lobule | BA40 | −44 | −56 | 43 | 5.66* | |
| | Lt.inferior temporal gyrus | BA20 | −53 | −26 | −24 | 5.56* | |
| | Rt.middle temporal gyrus | BA21 | 65 | −33 | −8 | 5.53* | |
| | Rt.inferior parietal lobule | BA40 | 50 | −54 | 43 | 5.44* | |
| | Rt.superior temporal gyrus | BA39/BA38 | 53 | −57 | 25 | 5.20* | |
| | Lt.superior temporal gyrus | BA39 | −50 | −61 | 21 | 5.16* | |
| | Lt.thalamus/MD, AN | | −4 | −19 | 12 | 5.04* | |
| | Rt.thalamus/pulvinar | | 2 | −9 | 8 | 4.84* | |
| | Rt.uncus | BA28/BA34 | 22 | −9 | −30 | 4.75* | |
| | Lt.uncus | BA36 | −20 | −6 | −33 | 4.73* | |
| | Rt.middle frontal gyrus | BA10/BA6 | 38 | 56 | 3 | 3.97 | |
| | Lt.inferior frontal gyrus | BA47 | −46 | 13 | −4 | 3.73 | |
| | Lt.superior frontal gyrus | BA8/BA10 | −24 | 16 | 51 | 3.71 | 445 |
| | Rt.medial frontal gyrus | BA10 | 2 | 57 | 6 | 3.51 | |
| | Rt.superior frontal gyrus | BA8 | 2 | 18 | 56 | 3.46 | 203 |
| | Rt.inferior frontal gyrus | BA47 | 55 | 31 | −2 | 3.28 | |
| Old age controls > late onset AD | Rt.inferior temporal gyrus | BA20 | 65 | −28 | −22 | 3.82 | 170 |
| Late onset AD > early onset AD | Rt.superior temporal gyrus | BA39 | 51 | −57 | 18 | 3.80 | 3407 |
| | Rt.inferior parietal lobule | BA40 | 51 | −52 | 43 | 3.67 | |
| | Rt.middle occipital gyrus | BA19 | 40 | −73 | 9 | 3.51 | |
| | Rt.precuneus | BA7 | 4 | −64 | 49 | 3.32 | 279 |
| Early onset AD > late onset AD | Lt.superior temporal gyrus | BA38 | −42 | 15 | −10 | 4.38 | 926 |
| Young controls > old controls | Rt.anterior cingulate | BA24 | 2 | 24 | 19 | 5.42* | 4842 |
| | Lt.caudate head | | −6 | 10 | 5 | 4.96 | |
| | Rt.caudate head | | 8 | 12 | 3 | 4.42 | |
| | Lt.superior frontal gyrus | BA6 | −4 | 24 | 56 | 4.30 | |
| | Lt.inferior frontal gyrus | BA47 | −42 | 17 | −11 | 3.84 | 265 |
| Old controls > young controls | Rt.cerebellar declive | | 22 | −63 | −20 | 5.12 | 377 |

AD = Alzheimer's disease; BA = Brodmann area; Lt. = left; Rt. = right; MD = medial dorsal nucleus; AN = anterior nucleus. *Areas highlighted in an SPM analysis with the threshold of $P < 0.05$ corrected, $k = 100$.

more common in early onset than in late onset may be consistent with our results (Chui *et al.*, 1985).

Our SPM analysis of FDG-PET may be consistent with neuropsychological findings. In the normal population, when a general cognitive index such as the MMSE was matched, young subjects usually perform better than old subjects in neuropsychological testing (Davis and Klebe, 2001; Tsang and Lee, 2003). Likewise, with comparable brain injury, younger patients' performances in neuropychological tests would be better than those of older subjects. Contrary to this expectation, test scores of early onset patients were comparable with those of late onset patients in most tests, and in some tests late onset patients even outperformed early onset patients. Thus, this difference in neuropsychological performance may be consistent with the greater hypometabolism in early onset than late onset patients. Furthermore, the neuropsychological profile may also be compatible with imaging findings. Neuropsychological domains tending to be more affected in the early onset than the late onset group were visuoconstructive ability, calculation, praxis, attention/working memory (digit span and the word reading part of the Stroop test) and inhibitory control (the colour reading part of the Stroop test). Although these cognitive functions are mediated by a wide area of neural networks, visuoconstructive ability, calculation and praxis primarily represent parietal function, while working memory and inhibitory control are associated with frontal association cortices. It remains unknown, however, why early onset patients with greater neuropsychological deficits and greater hypometabolism in PET scanning have scores in CDR and MMSE comparable with those of late onset patients. This could be attributed to the fact that younger subjects tend to use residual cognitive functions more efficiently than older subjects, which would allow younger subjects to compensate for their cognitive deficits in daily activities.

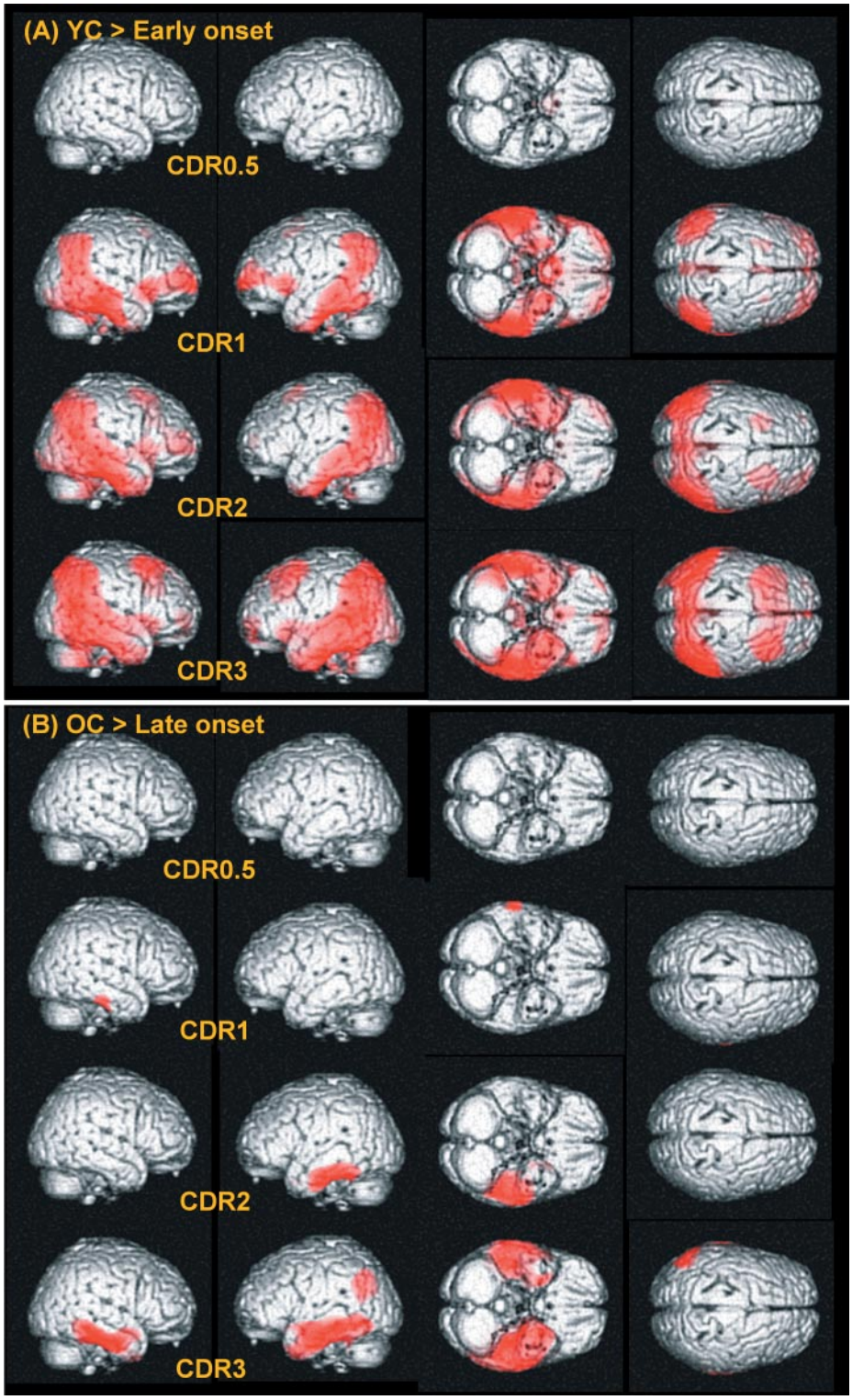


**Fig. 2** Comparison of glucose metabolism in early onset patients versus young controls in each CDR stage (**A**) and in late onset patients versus old controls (**B**). The hypometabolic regions (red colour) are displayed on rendering images at the threshold of $P < 0.001$ uncorrected, $k = 100$.

As has been described already, our results showed that early onset Alzheimer's disease differed from late onset Alzheimer's disease in magnitude and extent of hypometabolism. In order to learn at which stage this difference occurs, we further investigated glucose metabolism as a function of dementia severity. The results showed that the hypometabolism of early onset Alzheimer's disease was mild at CDR 0.5 but became widespread, even extending to the frontal area at

**Table 4A** Regions of decreased metabolism as dementia severity increased ($P < 0.001$ uncorrected, $k = 100$)

| Variables | Region | BA | Stereotaxic coordinates | | | *T* value | Cluster size |
|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | |
| Young age controls > CDR 0.5 of EAD | Fornix/anterior cingulate gyrus | | 0 | 8 | 0 | 4.13 | 554 |
| | Lt.caudate head/body | | −4 | 6 | 2 | 4.05 | |
| | Rt.caudate head/body | | 6 | 6 | 2 | 4.03 | |
| | Lt.posterior cingulate gyrus | BA23 | 0 | −28 | 27 | 3.79 | 296 |
| Young age controls > CDR 1 of EAD | Rt.middle temporal gyrus | BA21 | 63 | −41 | −13 | 7.20* | 45544 |
| | Lt.inferior temporal gyrus | BA20 | −55 | −32 | −24 | 6.62* | |
| | Lt.caudate head | | −8 | 14 | 3 | 6.61* | |
| | Lt.middle temporal gyrus | BA21/BA39 | −59 | −45 | −13 | 6.60* | |
| | Lt.uncus | BA36 | −22 | −9 | −33 | 6.17* | |
| | Rt.caudate head | | 6 | 10 | 0 | 6.10* | |
| | Lt.parahippocampal gyrus | BA35/BA19 | −20 | −13 | −30 | 5.97* | |
| | Lt.posterior cingulate gyrus | BA23/BA30 | 0 | −32 | 27 | 5.64* | |
| | Lt.inferior parietal lobule | BA40 | −46 | −52 | 45 | 5.56* | |
| | Rt.superior temporal gyrus | BA39 | 53 | −59 | 29 | 5.42* | |
| | Rt.uncus | BA28 | 26 | −13 | −31 | 5.22* | |
| | Rt.inferior parietal lobule | BA40 | 50 | −54 | 41 | 5.16* | |
| | Lt.superior frontal gyrus | BA10/BA8 | −22 | 66 | 0 | 4.89* | |
| | Rt.superior temporal gyrus | BA38 | 48 | 15 | −7 | 4.68* | |
| | Rt.superior frontal gyrus | BA10/BA8 | 34 | 62 | −1 | 4.63* | |
| | Rt.middle frontal gyrus | BA10 | 36 | 58 | 1 | 4.62* | |
| | Lt.thalamus/MD/AN | | −4 | −13 | 12 | 4.49* | |
| | Rt.parahippocampal gyrus | BA19 | 20 | −39 | −3 | 4.37 | |
| | Lt.inferior frontal gyrus | BA47 | −42 | 17 | −1 | 4.14 | |
| | Rt.thalamus/pulvinar | | 6 | −23 | 10 | 4.09 | |
| | Rt.anterior cingulate | BA33/24 | 2 | 20 | 21 | 3.67 | |
| Young age controls > CDR 2 of EAD | Rt.middle temporal gyrus | BA21 | 67 | −41 | −8 | 10.47* | 54747 |
| | Rt.superior temporal gyrus | BA39/BA22 | 57 | −59 | 21 | 8.52* | |
| | Lt.middle temporal gyrus | BA39/BA37 | −51 | −67 | 25 | 8.51* | |
| | Lt.inferior parietal lobule | BA40 | −50 | −58 | 42 | 8.37* | |
| | Rt.inferior parietal lobule | BA40 | 50 | −56 | 45 | 8.19* | |
| | Posterior cingulate gyrus | BA30 | 0 | −48 | 19 | 8.08* | |
| | Lt.inferior temporal gyrus | BA20/BA28 | −53 | −27 | −26 | 7.50* | |
| | Rt.uncus | BA28 | 26 | −15 | −28 | 5.87* | |
| | Lt.uncus | BA28 | −20 | −11 | −31 | 5.44* | |
| | Lt.caudate head | | −8 | 18 | 3 | 5.07* | |
| | Rt.caudate head | | 12 | 18 | 3 | 4.94* | |
| | Rt.middle frontal gyrus | BA6/BA10/BA9 | 32 | 16 | 53 | 4.74 | |
| | Rt.thalamus/pulvinar | | 8 | −27 | 12 | 4.48 | |
| | Lt.middle frontal gyrus | BA6/BA10 | −24 | 16 | 56 | 4.48 | 741 |
| | Rt.lingual gyrus | BA18 | 12 | −94 | −5 | 3.83 | |
| | Rt.cuneus | BA17 | 20 | −97 | 0 | 3.80 | |

CDR 1. In late onset Alzheimer's disease, however, the metabolic reduction was mild until CDR 2, and hypometabolism comparable with, albeit less severe than, CDR 1 of early onset Alzheimer's disease occurred at CDR 3.

How can we explain that the hypometabolic pattern of early onset Alzheimer's disease is more severe in extent and magnitude and occurs at earlier stages than that of late onset Alzheimer's disease? First, our findings may be consistent with the cognitive reserve theory. Katzman *et al.* (1988*b*) introduced the cognitive reserve theory to explain that the severity of neuropathological manifestations of Alzheimer's disease did not always correlate with the severity of the disease. Several investigators noted that patients with higher premorbid educational levels had more severe neuropathological changes than those with lower pre-morbid educational levels, even though the two groups were able to maintain the same clinical status (Katzman, 1993). These findings were explained by the postulate that patients with higher educational level, IQ (intelligence quotient), occupational status, extracurricular activities and lifestyle may have a higher threshold for brain insult before the clinical deficit appears, since they might have a greater number of neurons and synaptic density (Albert, 1995; Scarmeas and Stern, 2003).

A few studies have investigated the changes of cerebral blood flow, glucose metabolism or neuropathological findings in healthy subjects as a function of age. Some studies demonstrated the selective reduction of blood flow in the frontal cortex in older age groups (Shaw *et al.*, 1984;

**Table 4B** Regions of decreased metabolism as dementia severity increased ($P < 0.001$ uncorrected, $k = 100$)

| Variables | Region | BA | Stereotaxic coordinates | | | *T* value | Cluster size |
|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | |
| Young age controls > CDR 3 of EAD | Rt.middle temporal gyrus | BA21 | 65 | −49 | −1 | 8.85* | 57709 |
| | Lt.inferior temporal gyrus | BA20 | −50 | −49 | −13 | 8.73* | |
| | Rt.superior temporal gyrus | BA22 | 48 | −57 | 16 | 8.41* | |
| | Rt.inferior temporal gyrus | BA37/20 | 55 | −43 | −15 | 8.04* | |
| | Lt.middle temporal gyrus | BA39/BA21 | −44 | −58 | 14 | 7.98* | |
| | Rt.fusiform gyrus | BA20 | 55 | −23 | −24 | 7.66* | |
| | Lt.inferior parietal lobule | BA40 | −40 | −64 | 46 | 7.65* | |
| | Rt.inferior parietal lobule | BA40 | 48 | −50 | 47 | 7.48* | |
| | Lt.posterior cingulate gyrus | BA31 | 0 | −37 | 28 | 6.53* | |
| | Rt.superior frontal gyrus | BA8/BA10 | 30 | 16 | 51 | 6.32* | 11247 |
| | Lt.uncus | BA36 | −20 | 0 | −30 | 6.11* | |
| | Lt.caudate head/body | | −8 | 8 | 5 | 5.94* | |
| | Lt.superior frontal gyrus | BA8/BA10 | −28 | 16 | 51 | 5.81* | |
| | Lt.precuneus | BA7 | −4 | −69 | 51 | 5.73* | |
| | Rt.uncus | BA28 | 22 | −9 | −28 | 5.55* | |
| | Rt.caudate head | | 12 | 10 | 3 | 5.09* | |
| | Lt.thalamus/anterior nucleus | | −10 | −11 | 17 | 4.63 | |
| | Rt.thalamus/LD | | 6 | −2 | 7 | 4.54 | |
| | Lt.superior temporal gyrus | BA22 | −53 | −6 | −5 | 4.53 | |
| | Lt.inferior frontal gyrus | BA47 | −46 | 23 | −10 | 4.24 | |
| | Rt.middle frontal gyrus | BA9 | 44 | 23 | 28 | 4.18 | |
| Old age controls > CDR 0.5 of LAD | – | – | – | – | – | – | |
| Old age controls > CDR 1 of LAD | Rt.inferior temporal gyrus | BA21 | 67 | −28 | −25 | 4.84 | 258 |
| Old age controls > CDR 2 of LAD | Lt.fusiform gyrus | BA20 | −40 | −38 | −15 | 6.16* | 3474 |
| | Lt.uncus | BA28/BA36 | −20 | 1 | −27 | 4.00 | 196 |
| Old age controls > CDR 3 of LAD | Lt.parahippocampal gyrus | BA36/BA35 | −34 | −28 | −15 | 9.04* | 10152 |
| | Lt.middle temporal gyrus | BA21 | −51 | −45 | −10 | 7.52* | |
| | Rt.fusiform gyrus | BA20/BA36 | 46 | −34 | −17 | 6.77* | 5887 |
| | Rt.inferior temporal gyrus | BA37 | 51 | −38 | −15 | 6.70* | |
| | Lt.inferior temporal gyrus | BA21 | −59 | −9 | −15 | 5.42 | |
| | Lt.fusiform gyrus | BA20 | −59 | −17 | −23 | 5.35 | |
| | Rt.middle temporal gyrus | BA21 | 53 | 5 | −15 | 4.52 | |
| | Lt.superior temporal gyrus | BA39/BA38 | −59 | −59 | 23 | 4.47 | 1084 |
| | Lt.inferior parietal lobule | BA40 | −48 | −60 | 40 | 4.42 | |

EAD = early onset group of Alzheimer's disease; LAD = late onset group of Alzheimer's disease; CDR = Clinical Dementia Rating; BA = Brodmann area; Lt. = left; Rt. = right; MD = medial dorsal nucleus; AN = anterior nucleus; LD = lateral dorsal nucleus.
*Areas highlighted in an SPM analysis with the threshold of $P < 0.05$ corrected.

Gur *et al.*, 1987). Another study reported a similar finding in a cross-sectional study that cerebral glucose metabolism of the middle frontal cortex was significantly correlated with age (Mielke *et al.*, 1998). Our SPM analysis of old versus young controls also demonstrated that older healthy subjects are more hypometabolic in anterior cingulate, and superior and inferior frontal areas compared with young subjects. On the basis of these findings, it is likely that patients with early onset age may have more synapses in the brain than those with late onset age. Thus, more synaptic loss in the brain should have occurred for the early onset Alzheimer's disease patients to reach the same stage of cognitive impairment as in late onset Alzheimer's disease. This account is supported further by the neuropathological findings of a study which found significantly greater burden of neuritic plaques and neurofibrillary tangles in early onset than in late onset Alzheimer's disease in frontal and parietal lobes (Bigio *et al.*, 2002).

Alternatively, the greater hypometabolic pattern in early onset Alzheimer's disease can be explained, at least in part, by the results of previous studies that early onset Alzheimer's disease progresses more rapidly than late onset disease. As has been illustrated in Fig. 3, our results also support this account. Although metabolic changes in stages before CDR 0.5 were not measured, our early onset patients' curve may be reminiscent of the trilinear model proposed by Brooks'Alzheimer's disease group, i.e. the pattern of initial stability–rapid decline–late stability (Fig. 3) (Brooks *et al.*, 1993). Likewise, our metabolic decline curve of late onset patients may also be consistent with the trilinear model, although the late stability could not be demonstrated because the patients with CDR $\geq$4 were not included in this study. If the more extensive and

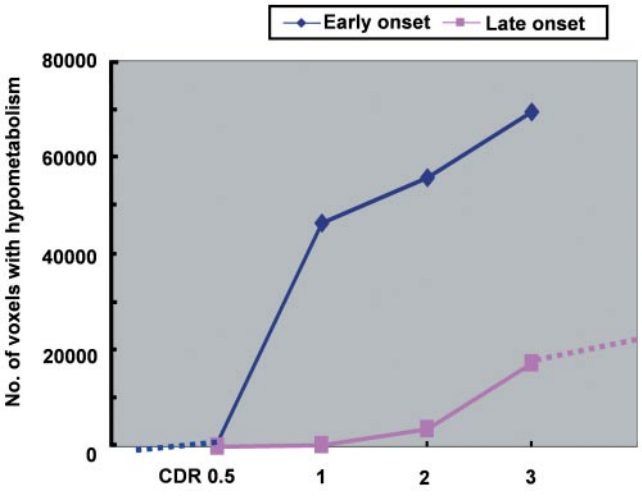


**Fig. 3** The number of hypometabolic voxels in maps after SPM analysis (Fig. 2) was counted and plotted against the CDR (Clinical Dementia Rating) stage (blue line, early onset Alzheimer's disease; pink line, late onset Alzheimer's disease). Dotted lines in each curve are drawn to illustrate the trilinear model of cognitive decline in Alzheimer's disease (see text for details).

earlier involvement of glucose metabolism in early onset Alzheimer's disease relies solely on the cognitive reserve theory described above, the metabolic decline curves of early onset and late onset groups (Fig. 3) should run parallel, the early onset curve being shifted to the left from the late onset curve. However, the early onset curve was generally steeper than the late onset curve, suggesting that metabolic decline as measured by the amount of hypometabolism may be more rapid in early onset Alzheimer's disease. Our analysis of hypometabolism in terms of topography further supports this conclusion. For instance, when comparing the hypometabolic map (Fig. 2) of early onset CDR 1 with that of late onset CDR 2 or 3, if the early onset curve were to 'shift to the left', then the two images should show comparable topography of hypometabolism. However, frontal and subcortical (basal ganglia and thalamus) involvement was seen only in early onset Alzheimer's disease, even though the hypometabolism in the temporoparietal area was similar; this suggests that early onset Alzheimer's disease may take the more rapid course in reduction of glucose metabolism at earlier stages of the disease than late onset Alzheimer's disease.

In conclusion, our study demonstrates that early onset Alzheimer's disease differs from late onset Alzheimer's disease in terms of overall metabolic patterns along with metabolic reduction as the severity of dementia increases. This difference may result not only from age-related cognitive reserve but also from the different progression rate of the two groups. One of the limitations of this study, however, is that our analysis of glucose metabolism was not based on a longitudinal study but a cross-sectional study, thus it does not allow the absolute quantitation but rather the relative spatial distribution of glucose metabolism between the two groups.

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