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GLUCOSE METABOLIC RATE AND PROGRESSION OF ILLNESS IN ALZHEIMER'S DISEASE

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SUMMARY

Thirty-eight patients with mild to moderate Alzheimer's disease (AD) underwent a neuropsychological test battery and 18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) before beginning and at the end of a randomized double-blind study of an experimental treatment. Twelve of the patients took placebo. In the placebo patients, Mini-Mental State (MMS) score decreased and cortical metabolism increased significantly over the 6-month course of the study. Correlations of metabolism with neuropsychological performance were stable over time in the placebo group. Cortical metabolism correlated significantly with performance on the Blessed Information Subtest and the MMS and showed trend correlations with performance on the WAIS Digit Symbol and Word Fluency. Patients with high relative occipital metabolism tended to do poorly on word fluency. Low baseline relative metabolism in right frontal cortex and high baseline relative metabolism in left parietal and temporal cortices and in right occipital cortex predicted more 6-month deterioration on the World Fluency Test, suggesting that frontal metabolic deficits may precede neuropsychological deficits. Correlations of 6-month change in MMS, Blessed and Digit Symbol performance with initial glucose metabolism were not significant.

KEY WORDS—Alzheimer's disease; positron emission tomography; verbal memory

Alzheimer's disease (AD), the most common form of dementia, is characterized neuropathologically by cell loss, as well as senile plaques and neurofibrillary tangles, in association areas of the lateral cortex and in medial temporal structures (Brun and Englund, 1981). Imaging studies have demonstrated structural (Jobst *et al.*, 1992; Pearlson *et al.*, 1992), perfusion (Celsis *et al.*, 1987; Jagust *et al.*, 1987; Jobst *et al.*, 1992; Pearlson *et al.*, 1992) and glucose metabolic abnormalities (Benson *et al.*, 1983; Buchsbaum *et al.*, 1991; Cutler *et al.*, 1985; Duara *et al.*, 1986; Foster *et al.*, 1983; Friedland *et al.*, 1983; Kumar *et al.*, 1991) in these regions, particularly in parietal and temporal cortex. General neuropsychological performance correlates with whole brain metabolism (Johnson *et al.*, 1988) and with temporoparietal metabolism (Nyback *et al.*, 1991). Patients with lower left-sided metabolism have tended to have greater verbal intellectual impairment, while those with right hypometabolism showed visuospatial impairments (Foster *et al.*, 1983; Grady *et al.*, 1986; Haxby *et al.*, 1985, 1986).

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Longitudinal studies of brain glucose metabolism have demonstrated decreasing metabolism with time (McGeer *et al.*, 1990; Smith *et al.*, 1992), particularly in those brain areas most affected by the illness, specifically frontal, parietal and temporal association cortices. However, neuropsychological and metabolic asymmetries are stable over 1–2-year periods (Grady *et al.*, 1986).

Most studies of the course of AD have yielded no consistent predictors of the rate of cognitive deterioration (Stern *et al.*, 1992). Haxby *et al.* (1986) found that metabolic asymmetries occurred in the absence of non-memory neuropsychological changes in some patients with early Alzheimer's disease, suggesting that metabolic impairments may precede some cognitive changes in AD. However, we know of no functional brain imaging study that has sought metabolic predictors of illness course.

In the current study, we have analyzed data on 38 patients with early probable AD, 12 of whom took placebo during a 6-month medication study and all of whom were followed with neuropsychological testing and 18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET). Because the most prominent neuropathological findings in AD are in the cortex and medial temporal lobe, we excluded subcortical regions from our analysis *pre hoc*. We pursued the questions: (1) what neuropsychological and metabolic findings would change during the 6 months? (2) what initial metabolic findings might predict the course of the illness? and (3) what neuropsychological findings correlate with metabolism? The last question was studied in two groups of patients, those who took placebo and, in a replicatory analysis, those patients who were to take active drug, before they started taking it.

We predicted that, replicating other studies, over time there would be some deterioration in cognitive function and decreasing cortical and medial temporal metabolism with sparing of occipital and sensorimotor cortex. We also expected that low metabolic activity, particularly in parietotemporal cortex and medial temporal regions, would correlate with impaired cognitive function. Because of a lack of basis for a hypothesis, analyses predicting course of illness were exploratory.

METHODS

Subjects

We recruited the patients, all of whom had a clinical diagnosis of probable AD, by referral and through advertisements. Diagnosis was confirmed by NINCDS–ADRDA criteria by a neurologist (AS). The patient group consisted of 38 elderly adults (19 men, 19 women, mean age ± SD = 73 ± 9, range 52–91). All patients were in good health based on medical history, physical examination and laboratory analyses. We excluded patients with any history of seizure disorder, requirement for neuroleptics, psychotic or major mood disorder, substance abuse or stroke. Patients selected for the study were early in the course of the illness, with a Mini-Mental State score of 12–26 (mean ± SD = 19 ± 5). MRI scans were negative except for atrophy in some patients, and the Hachinski score was less than 4 in all cases. Twelve patients who took placebo received PET scans and neuropsychological testing at the beginning of the study and at the end of the 6-month drug trial. No patient took psychotropic medications from at least 2 weeks prior to the beginning of the study until the end of the drug trial (with the exception of the study medication).

Neuropsychological testing

A research assistant, who had been trained by a neuropsychologist (DR), tested each patient at their initial screening and then approximately 6 months later. The test battery included the Wechsler Adult Intelligence Scale Digit Symbol Subtest (DS), the Mini-Mental State (MMS), the Blessed Dementia Information Subtest and Word Fluency (words beginning with the letters A and S). Initial and follow-up testing were both done within 2 weeks of their corresponding PET scans.

PET activation task

Words from a 150-item word list were presented on a monitor for 300 msec at 3-second intervals. Each word was presented a first time and subsequently repeated with a 6–18-second delay. All words were thus presented as novel (initial presentation) and familiar (second presentation) items. The subject's task was to press one key with the index finger when a novel stimulus was presented and another key with the ring finger for familiar stimuli. Response times of greater than 2 seconds were counted as errors.

Scan procedure

Patients, who had all fasted for at least 4 hours, performed a memory task in a darkened isolation room during uptake of the 18-F deoxyglucose

(FDG). The procedure of infusion and blood sampling for glucose quantification is described elsewhere (Buchsbaum *et al.*, 1987). All subjects received the verbal memory test during the 30 minutes following injection of 4–5.2 mCi of FDG. Research assistants continuously monitored task performance and observed patients to make sure that they were following instructions.

After 30–35 minutes of performing the task, patients moved to the scanner (CTI NeuroECAT IV). Patients' head positions were maintained using an individually prepared and molded thermoplastic mask. Repeat MRI scans with similar masks on occasions 2 weeks apart indicated repositioning errors of approximately 2 mm (Buchsbaum *et al.*, 1992). We obtained nine planes in 10 mm increments parallel to the canthomeatal line (CM) during the 45–100 minutes after FDG injection as described elsewhere (Buchsbaum *et al.*, 1987). We transformed scans to glucose metabolic rate (GMR) according to the model of Sokoloff *et al.* (1977), using an adaptation of Sokoloff's program. We used kinetic constants and the lumped constant as in Phelps *et al.* (1979).

Scan slice selection and cortical peel method

Because of differences in both head height and brain proportion, a rater chose slices for analysis based on resemblance to the Matsui and Hirano (1978) prototype atlas levels.

For each slice, the outer brain contour was outlined with a boundary-finding technique developed for skull on CT scans, as described elsewhere (Buchsbaum *et al.*, 1982, 1984). The region of interest methods were entirely automated using an edge-finding algorithm and automated region placement. As in our previous study (Buchsbaum *et al.*, 1989; see Fig. 1), 2 cm thick cortical regions were divided anatomically into frontal, parietal, temporal and occipital lobes based on the percentage of the brain perimeter accounted for by each lobe at each level in the Matsui and Hirano atlas. Each lobe was divided into four gyri using the same stereotactic method.

The validity and advantages of the cortical peel method were recently reviewed by Harris *et al.* (1991). The stereotactic region of interest method is similar to that employed by Reiman *et al.* (1989), with the modification that both the anteroposterior and lateral coordinates are expressed as proportional to brain dimensions, minimizing the methodological problems noted by Drevets *et al.* (1992).

Region of interest analysis

Medial temporal structures were located in the Matsui and Hirano atlas, proportional locations

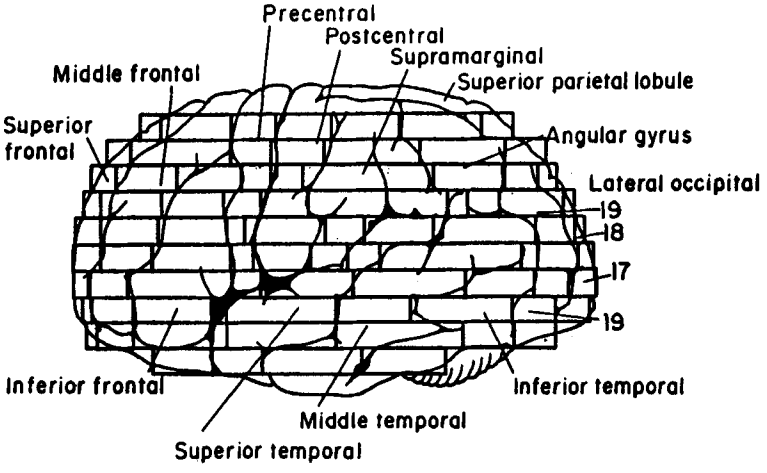

Fig. 1. Lateral view of the left cerebral cortex: technique for localization of cortical gyri on PET images. A digitized atlas was used to create a computer-generated outline based on the percentage of the cortical surface traversed by each gyrus at each slice level

defined on the anteroposterior and lateral directions were transferred automatically without operator intervention to the PET slices and mean glucose metabolic rates were calculated for the left- and right-sided boxes (right side as mirror image of left around vertical meridian) as described elsewhere (Buchsbaum *et al.*, 1987, 1989; Siegel *et al.*, 1992). The medial temporal areas examined in this study were the region of the hippocampus at atlas levels 9, 10 and 11 and the region of the uncus at the 11 level. Analysis was carried out on absolute GMR expressed in μmol/100g/min and as relative GMR. Cortical surface structures were calculated as weighted averages across slices and relative values expressed as ratio of regional GMR to whole brain GMR; medial temporal structures are calculated from single slices and thus expressed as ratio of regional GMR to whole slice GMR. In practice, whole brain and whole slice GMR are so highly correlated (0.90–0.98) that there is little difference introduced by denominator choice. Because of blood-sampling difficulties, glucose quantification could not be calculated for two of the placebo patients, so absolute metabolic rate data are available for 10 of the 12 patients.

Statistical analysis

To study time effects on brain metabolism, absolute and relative GMR data were analyzed using repeated measures analysis of variance (ANOVA) (BMDP 4V; Dixon, 1981) and *post hoc* *t*-tests (BMDP 3D) for the 10-patient placebo group only. This was a four-way ANOVA with time (baseline, 6 months) and repeated measures for hemisphere (right, left), region (lateral frontal, parietal temporal and occipital cortices and medial temporal lobe) and subregions (1–4; see Fig. 1 for subregion locations). We also evaluated by *t*-test, on an exploratory basis, data obtained on the 40 bilateral subregions.

To explore the relationship between metabolism and cognitive function, we calculated Pearson's product-moment correlations for regional absolute and relative metabolism in the five bilateral regions (10 total) with neuropsychological performance (MMS, Blessed, DS and Word Fluency scores). Correlations were calculated three times: for the placebo group, both at baseline and at the end of the 6-month study, and, as a replication, for the medication group at baseline only (unmedicated). Because correlations of metabolism with test scores in the baseline medication group served as a random replication of the baseline placebo correlations, correlations found to be significant in the placebo group were tested one-tailed in the baseline medication group as appropriate for a random split replication. To test the predictive value of baseline metabolism on course of illness, baseline metabolism in the five selected bilateral regions was correlated with change in neuropsychological test scores for the placebo group.

RESULTS

Longitudinal changes in cognitive function and metabolism

t-tests revealed a significant change in score on the MMS (initial score 19.7; final score 17.8; change −1.8, $t = -2.49$, $p = 0.03$, NS after Bonferroni correction), but on none of the other cognitive tests (Table 1).

Table 1. Neuropsychological test scores (mean ± SD) for the placebo group at baseline (B) and 6 months (6) and for the medication group at baseline

Patients	MMSE	Blessed	DS	Word Fluency
Placebo (B)	20 ± 4	8 ± 4	19 ± 13	14 ± 6
Placebo (6)	18 ± 5*	8 ± 4	20 ± 14	14 ± 9
Medication	19 ± 5	9 ± 4	15 ± 11	14 ± 9

*Differs from placebo baseline condition, 2-tailed *t*-test, $p < 0.05$.

The ANOVA (time × region × subregion × hemisphere) for absolute glucose showed a trend time effect ($F = 4.14$, $df = 1,18$, $p < 0.06$) with patients displaying higher metabolism during the second scan (27.9 μmol/100g/min) than during the first (19.3; Table 2). There were no significant effects for relative metabolism. Exploratory *t*-test analyses of subregions revealed a decrease in the region of the lower half of the left Brodmann's area 17 of the occipital cortex (change = −0.097, $p = 0.003$; after Bonferroni correction, $p = 0.12$). The cortical asymmetry and its variance did not change over time.

Correlations of metabolism with neuropsychological performance

Correlations of baseline and 6-month metabolism in the placebo group were quite similar

Table 2. Regional cortical glucose metabolic rates (μmol/100g/min; mean (SD)) at baseline and after 6 months in AD patients taking placebo ($N = 10$)

Region	Baseline	6 months
Prefrontal	20.3 (8.4)	29.8 (13.4)
Parietal	20.6 (7.7)	30.7 (13.6)
Lateral temporal	17.3 (5.3)	24.6 (9.8)
Occipital	22.7 (7.5)	32.1 (12.5)
Medial temporal	15.7 (7.2)	22.2 (11.9)
Total cortex	19.3 (7.7)	27.9 (12.9)

*Differs from baseline at a trend level, time × region × subregion × hemisphere ANOVA, time effect, $F = 4.14$, $df = 1,18$, $p < 0.06$.

(Table 3). MMS and Blessed performance correlated positively with absolute GMR in most regions, suggesting a correlation with metabolism in the cortex as a whole. Similarly, Digit Symbol and Word Fluency showed trend correlations with absolute metabolism in many regions (Tables 3 and 4). Predicted significant correlations of cognitive dysfunction and medial temporal cortical relative metabolism were not present. The only positive correlation of relative metabolism with neuropsychological score was the left frontal cortex with MMS in the placebo group at baseline. There were several negative correlations of posterior cortical regions with test scores. The right occipital cortex relative GMR showed negative correlations with Blessed score in the medication group at baseline and with Word Fluency in the placebo group for both scans. Right lateral temporal relative GMR correlated negatively with Word Fluency in the medication group at baseline and with MMS in the placebo group at 6 months. Left temporal relative GMR correlated negatively with MMS and Blessed scores in the placebo group at 6 months.

Table 3. Correlations of baseline (B) and 6-month (6) neuropsychological test scores with initial absolute (AD patients on placebo, $N = 10$, $df = 8$) and relative regional GMR ($N = 12$, $df = 10$)

Region		MMSE		Blessed		DS		Word Fluency	
		B	6	B	6	B	6	B	6
Prefrontal cortex									
Absolute	Left	0.80†	0.83*	0.79†	0.81*	0.66§	0.53	0.64§	0.55
	Right	0.73	0.76‡	0.79†	0.82*	0.59	0.48	0.57	0.55
Relative	Left	0.67‡	0.37	0.52	0.45	0.47	0.35	0.22	0.38
	Right	0.54	0.25	0.56	0.47	0.41	0.28	0.16	0.39
Parietal cortex									
Absolute	Left	0.76‡	0.92**	0.66§	0.73‡	0.61	0.69§	0.63§	0.46
	Right	0.76‡	0.88**	0.74‡	0.82*	0.62	0.61	0.58	0.51
Relative	Left	−0.32	0.32	−0.36	0.06	−0.35	0.34	−0.42	−0.30
	Right	0.19	0.40	0.13	0.32	0.12	0.36	−0.19	−0.10
Temporal cortex									
Absolute	Left	0.80†	0.83*	0.80†	0.76‡	0.86*	0.62	0.59	0.48
	Right	0.78†	0.78†	0.80†	0.79†	0.81*	0.58	0.69	0.52
Relative	Left	−0.53	−0.58§	−0.45	−0.61§	−0.26	−0.37	−0.14	−0.37
	Right	−0.43	−0.63§	−0.35	−0.51	−0.09	−0.40	−0.01	−0.30
Occipital Cortex									
Absolute	Left	0.86*	0.92**	0.80†	0.79†	0.76‡	0.67§	0.64§	0.47
	Right	0.80†	0.85*	0.85*	0.83*	0.66§	0.55	0.54	0.44
Relative	Left	−0.05	−0.06	−0.12	−0.29	0.13	0.14	−0.24	−0.42
	Right	−0.45	−0.28	−0.16	−0.19	−0.39	−0.30	−0.71†	−0.71†
Medial temporal lobe									
Absolute	Left	0.78†	0.80†	0.85*	0.72‡	0.65§	0.50	0.47	0.49
	Right	0.58	0.69§	0.73‡	0.77†	0.44	0.42	0.38	0.51
Relative	Left	0.20	0.40	0.24	−0.05	0.12	0.16	0.03	0.08
	Right	−0.21	−0.01	−0.06	0.06	−0.30	−0.17	−0.08	0.04

* $p < 0.005$, 2-tailed, † $p < 0.01$, 2-tailed; ‡ $p < 0.02$, 2-tailed; § $p < 0.05$, 2-tailed; ** $p < 0.001$, 2-tailed.

Table 4. Correlations of baseline neuropsychological test scores with baseline whole brain absolute GMR (AD patients assigned to medication group, $N = 24$, $df = 23$) and relative regional GMR ($N = 26$, $df = 24$)

Region	Hemi	MMSE	Blessed	DS	Word Fluency
Prefrontal cortex					
Absolute	Left	0.34‡	0.30	0.39‡	0.22
	Right	0.40	0.34‡	0.39	0.18
Relative	Left	0.14	0.02	0.42*	0.51†
	Right	0.36	0.17	0.40*	0.41*
Parietal cortex					
Absolute	Left	0.31	0.27	0.35	0.18
	Right	0.36‡	0.37‡	0.31	0.08
Relative	Left	0.00	−0.09	0.16	0.23
	Right	0.06	0.13	−0.03	−0.13
Temporal cortex					
Absolute	Left	0.35‡	0.31	0.29	0.13
	Right	0.40‡	0.36‡	0.33	0.01
Relative	Left	−0.19	−0.22	−0.20	0.00
	Right	−0.05	−0.07	−0.19	−0.42*
Occipital cortex					
Absolute	Left	0.31	0.28	0.37‡	0.19
	Right	0.33	0.27	0.32	0.14
Relative	Left	−0.18	−0.27	0.21	0.33
	Right	−0.26	−0.43*	−0.13	0.01
Medial temporal lobe					
Absolute	Left	0.33	0.39‡	0.26	0.01
	Right	0.33	0.41‡	0.17	−0.06
Relative	Left	0.04	0.25	−0.11	−0.08
	Right	−0.08	0.17	−0.38	−0.38

*$p < 0.05$, 2-tailed; †$p < 0.01$, 2-tailed; ‡$p < 0.05$, 1-tailed replication.

Correlations of initial metabolism with changes in neuropsychological performance

Changes in MMS, DS and Blessed performance were not predicted by absolute or relative metabolism in any cortical or medial temporal region. There were, however, significant correlations of final minus baseline word fluency score with right frontal ($r = 0.68$, $df = 8$, $p < 0.02$) and left parietal ($r = -0.59$, $df = 8$, $p < 0.05$) and temporal ($r = -0.58$, $df = 8$, $p < 0.05$) and right occipital ($r = -0.62$, $df = 8$, $p < 0.05$) relative GMR. The only significant correlations of absolute GMR with final minus baseline word fluency were in left ($r = 0.67$, $df = 10$, $p < 0.01$) and right ($r = 0.71$, $df = 10$, $p < 0.01$) prefrontal cortex.

DISCUSSION

Numerous correlations of GMR with neuropsychological test scores were calculated in this study, so findings should be interpreted with caution. However, the 12 Alzheimer's patients scanned twice with a 6-month interval and 26 patients with a baseline medication-free PET scan showed some consistent trends in their correlations of brain metabolism with neuropsychological performance. Two of four test scores showed significant positive correlations with cortical absolute metabolism and the other two showed a similar trend. The significant correlations of neuropsychological performance with cortical metabolism are consistent with SPECT cerebral blood flow (CBF) studies and with PET FDG studies (Cutler *et al.*, 1985; Duara *et al.*, 1986). This effect suggests that those patients with greater general cortical hypofunction have greater cognitive impairment. It is not clear whether the lower metabolic rates in the more impaired patients are due to partial voluming with CSF and white matter due to more cortical atrophy and/or to hypoactivity in remaining functional neurons.

We unexpectedly found an increase in glucose metabolism over the course of the study to a level (27 μmol/100 g/min) approximately equal to that in age-matched controls (26 μmol/100 g/min). We found no evidence of change in metabolism in a group of controls scanned during the same period of time. While the increase in glucose metabolic rate after 6 months seems counterintuitive, increased glucose metabolic rates have also been observed to be associated with relatively poorer performance on abstract reasoning tasks in normal subjects (Haier *et al.*, 1988; Parks *et al.*, 1988). In these studies, high global metabolic rate correlated with poor performance. The lower metabolic rate in the most skilled subjects was interpreted as indicating greater neural efficiency. Similarly, patients with Down's syndrome and other forms of mental retardation also show increased global metabolic activity (Cutler, 1986; Haier *et al.*, in press; Schwartz *et al.*, 1983). In the current study, well-educated and highly motivated subjects may have made more effort in executing the task during the second scan when the dementing process had progressed further.

The negative correlations of relative lateral temporal and occipital metabolism with cognitive function suggest a relative sparing of those areas by the illness. That is, in those patients in whom cognitive function and anterior cortical regions are most im-

paired, the lateral temporal and occipital cortices show higher relative metabolism. This finding is not unlike that of Cutler *et al.* (1985), who found high relative occipital FDG metabolism in the most severe AD cases, and is consistent with neuropathological sparing of the occipital cortex (Brun and Englund, 1981). Our findings suggests that there may also be relative sparing of lateral temporal cortex in early AD. This is inconsistent with the neuropathological findings in a woman with possible early AD (Hof *et al.*, 1992) which suggest that lateral temporal cortical pathology begins before frontal cortical changes in AD.

The absence of correlations of GMR with change in Digit Symbol, MMS and Blessed scores is consistent with previous studies finding no predictors of the course of illness (Stern *et al.*, 1992). However, it is possible that we found no such predictors because of type II error related to our small number of patients and to the relatively brief period of time over which the patients were studied. We are addressing this issue currently by examining neuropsychological function in these patients, retested 1–2 years after the completion of this study.

Because the medial temporal cortex is less than 6 mm wide in a substantial proportion of AD patients (Jobst *et al.*, 1992), in those patients it is not possible to exactly localize and measure metabolism of specific medial temporal structures, such as hippocampus and amygdala, with a camera whose resolution is 7.6 mm. Thus, relationships of metabolism in those small structures to cognitive function might not be found (type II error) due to effects of surrounding tissue and CSF on GMR measurement (partial voluming).

It is also possible that our attempt to predict the course of neuropsychological changes with initial GMR data was generally unsuccessful because the MMS and Blessed include several heterogeneous tests of cognitive function. This may also account for our finding of more significant correlations of cognitive function with absolute metabolism, whose variance is greatly accounted for by variance in global metabolism, than with regional relative metabolism. However, we did find that change in performance on the Word Fluency Test correlated positively with baseline frontal absolute and relative activity, while showing negative correlations in other cortical regions. In contrast to the MMS and Blessed, Word Fluency is a more homogeneous test, whose performance requires only a few kinds of cognitive function, including some that are thought to be subsumed by the frontal cortex. Correlations were absent for the other frontal lobe-related task, the Digit Symbol, however. This finding for the Word Fluency Test indicates that AD patients with relative frontal lobe hypoactivity will deteriorate more on this frontal lobe test, suggesting that the metabolic dysfunction may precede the cognitive dysfunction. This is consistent with Haxby *et al.*'s (1986) finding of metabolic asymmetries in early AD patients without non-memory impairments. This finding also suggests, as does the variable course of the illness and increase in the variance of metabolic asymmetry in AD (Grady *et al.*, 1986), that different patients show different patterns of neuropathological deterioration. Whether these different patterns of deterioration suggest one neuropathological process with a large variance of brain changes in different patients or if they suggest discrete subgroups of prognostic and/or therapeutic significance is as yet unclear. It is possible that cluster analyses of metabolic data, as calculated by Grady *et al.* (1990), may be informative if subgroups with similar metabolic patterns, cognitive impairments and/or progression of illness can be widely replicated. Studies measuring regional atrophy with MRI or receptor density with PET or SPECT (Weinberger *et al.*, 1992) may also prove useful.

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