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Brain metabolism in Alzheimer's dementia: studies of ^{11}C-deoxyglucose accumulation, CSF monoamine metabolites and neuropsychological test performance in patients and healthy subjects

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Abstract

Thirteen patients with dementia of Alzheimer type and nine age-matched control subjects were examined by a battery of neuropsychological tests and by positron emission tomography (PET) with ^{11}C-deoxyglucose as a tracer for regional glucose metabolism in the brain. Concentrations of the monoamine metabolites HVA, MHPG and 5-HIAA were determined in the CSF from patients and controls. In the patients there was a diminished glucose metabolism in posterior parietal and superior temporal cortex areas to 60% of control levels. Other cortical areas showed similar changes, whereas the pre- and postcentral area, the cerebellum, the hippocampus and the basal ganglia showed less or no change. The decline in cortical metabolism in the patients was symmetrical but the variation in the left/right ratio was greater than in the controls. The CSF levels of monoamine metabolites did not differ between patients and controls. High levels of the metabolites were associated with low rates of glucose metabolism, possibly due to inhibitory influences of monoaminergic pathways upon cortical and subcortical neurons. The rate of glucose metabolism correlated positively with the neuropsychological test performance in both patients and controls. Verbal and memory performances were associated with greater left hemisphere metabolism in the patients, but not in the controls, whereas non-verbal abilities tended to be associated with right hemisphere metabolic dominance.

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Senile dementia of Alzheimer type has been associated with deficits in various monoaminergic neurotransmitter systems in the brain. The memory dysfunction and the intellectual decline have been shown to correlate with reduced levels of choline acetyltransferase in cortical brain biopsies and in postmortem brain material.[1–3] Also levels of noradrenaline, dopamine and serotonin and their metabolites are reduced in the brains of patients dying with dementia.[4 5] Studies of brain transmitter systems in living patients have to be performed with indirect methods. Measurements of levels of monoamine metabolites in the CSF have given controversial results with some authors reporting decreased levels in demented patients[6 7] and others reporting normal levels compared with control subjects.[8 9]

Using cerebral blood flow measurements, evidence of decreased metabolic activity in posterior parietal and temporal cortex areas of demented patients has been found.[10] A similar pattern of focal cortical changes has been described by positron emission tomography (PET) using ^{15}O for measurement of oxygen utilisation[11] or ^{18}F-deoxyglucose for measurement of regional glucose metabolism.[12–15] The results of these investigations are in good agreement with histopathological studies where the posterior parietal and temporal cortex areas have been reported to have the highest density of neuritic plaques.[16]

To further investigate the relationship between brain pathophysiology and cognitive defects in Alzheimer's disease we conducted a study using PET with ^{11}C-deoxyglucose as tracer. Patients with a clinical diagnosis of Alzheimer's disease and healthy volunteers were subjected to a thorough medical and psychological examination including an analysis of monoamine metabolites in the CSF. Correlations between regional glucose metabolism, neuropsychological test performance and CSF metabolites were calculated. A question particularly addressed was whether specific neuropsychological defects are related to the glucose metabolism of specific brain regions. The lateralisation of functions was also investigated by relating test results to the right/left ratios of hemispheric metabolism.

Subjects and methods

Thirteen patients, four men and nine women, with a mean age of 65 years (range 51–78) and a clinical diagnosis of senile or presenile dementia were recruited from nearby psychiatric and neurological outpatient units. The diagnosis of primary degenerative dementia, according to the DSM-III criteria, was attained through interviews with spouses and children, by physical examination, laboratory tests, EEG, brain CT scans, psychiatric ratings and psychological tests. Thus hypertensive, metabolic, cerebro-vascular and neurological disorders as well as psychiatric disturbances and drug abuse were excluded. The degree of the dementia was rated as mild (n = 2),

moderate (n = 4) or moderately severe (n = 7), that is, stages 3 to 5 according to the Global Deterioration Scale.[17] Other clinical rating scales were the NOSIE[18] and the geriatric rating scale of Adolfsson *et al.*[19] Nine of the patients were less than 65 years old and four were older.

All patients were free of neuroleptic and antidepressant drugs but a few of them occasionally received benzodiazepines for sedation or night-time sleep. Eleven of them were admitted to hospital only during the investigation whereas two had to be transferred afterwards for continued care at geriatric institutions.

The psychological tests used were a Swedish version (CVB) of the Wechsler-Bellevue Intelligence Scale (WBI), the Block Design, the Benton Visual Retention, the Trail Making and the Claesson-Dahl learning and memory tests. These tests were chosen because they cover different aspects of cognitive abilities and are known to be sensitive to various types of brain lesions.[20 21] A few of the most demented patients could not complete all subtests despite considerable efforts.

The test scores were standardised to z-scores and means for verbal, non-verbal and memory abilities were calculated. The verbal or left hemisphere function was made up of the results of Information, Comprehension, Similarities and Vocabulary. The non-verbal or right hemisphere function was made up of the results of Picture completion, Picture arrangement, Benton and Block design and the memory function was made up of the results of Digit span and Claesson-Dahl learning and retention test.

Following the clinical and psychological examinations a lumbar puncture was performed for the analysis of CSF concentrations of the monoamine metabolites homovanillic acid (HVA), 3-methoxy-4-hydroxyphenylglycol (MHPG) and 5-hydroxyindoleacetic acid (5-HIAA).[22] The subjects were fasting and confined to bed for at least nine hours before the spinal tap which was performed between 8.30 and 9.30 am. A sample of 12·5 ml of CSF was collected in ice-cooled centrifuge tubes with the subject in a sitting position.

Nine healthy volunteers, four men and five women with a mean age of 66 years (range 61–73) served as a control group. They were recruited through a questionnaire sent to a random sample of individuals aged between 60 and 80 years in the catchment area of the hospital. The volunteers were subjected to the same medical examination, laboratory tests, CT scan, psychiatric interview and psychological tests for the exclusion of diseases that could interfere with brain function. They spent the night before the spinal tap at the research ward to make the conditions for the CSF sampling identical between patients and controls.

^{11}C-2-Deoxyglucose was synthesised as described by Stone-Elander *et al.*[23] A bolus containing 100–300 MBq (2·7–8·1 mCi) of the tracer dissolved in 5–10 ml of sterile saline was injected iv with the subject in a sitting position, eyes open and ears plugged. The lights were dimmed and the ambient noise was limited as much as possible. Serial, arterial blood samples were taken from the contralateral arm for determination of radioactivity and glucose concentrations. After 26 minutes an individually fitted head fixation device[24] was put onto the subject who was laid down and fixed into the positron camera. The brain activity was collected during two consecutive scans of 10 minutes each. The head fixation technique allowed us to receive slices from the same planes as in the CT scanner. The positron camera (PC-384, Scanditronix AB) has four rings, each with 96 detectors that accept coincidences in both direct and oblique planes, thus producing seven simultaneous parallel images from the base of the skull to the vertex (10 cm).[25] The spatial resolution of the reconstructed images is 7·6 mm full width at half maximum (FWHM). Colour coded activity images were transformed to metabolic images by a computer program based on the mathematical formulas published by Sokoloff *et al.*[26] By use of a display cursor and guided by an adapted anatomical atlas,[27] about 70 regions of interest were delineated on the CT and PET images. These regions were then grouped into 13 larger cortical and subcortical areas (fig 3) where the glucose utilisation in μmol/100 g/min was determined.

Statistical differences between patients and controls were assessed by the two tailed Student's *t* tests. Relationships between psychological, biochemical and metabolic parameters were calculated using Pearson's product-moment correlations. Non-parametric rank correlations (Kendall) were also calculated but as the results were identical with the Pearson correlations only the latter are presented in this work.

The research protocol was approved by the Ethics Committee and the Isotope Committee of the Karolinska Hospital.

Table 1 Neuropsychological test results and CSF concentrations of monoamine metabolites (pmol/ml) in patients with Alzheimer's dementia (n = 13) and healthy control subjects (n = 9). Figures are means of raw scores (SD)

Tests	*Controls*	*Patients*	*p Value*
WBI-tests			
Information	35·3 (7·8)	15·8 (12·3)	< 0·001
Comprehension	18·9 (3·5)	7·9 (6·2)	< 0·001
Arithmetic	7·0 (1·9)	1·0 (1·0)	< 0·001
Digit span	11·0 (1·7)	7·0 (2·4)	< 0·001
Similarities	16·4 (2·5)	6·3 (6·4)	< 0·001
Vocabulary	37·0 (8·1)	19·2 (12·2)	< 0·001
Picture completion	11·3 (1·4)	7·0 (3·5)	< 0·003
Picture arrangement	13·9 (4·8)	2·4 (3·6)	< 0·001
Block design	22·1 (7·0)	7·6 (7·2)	< 0·001
Benton visual memory*	5·6 (4·6)	20·5 (5·9)	< 0·001
Claesson-Dahl learning*	101 (69)	381 (122)	< 0·001
Claesson-Dahl retention	74·7 (14·4)	10·7 (17·6)	< 0·001
Trail making A*	41·2 (16·7)	135 (80·1)	< 0·003
Trail making B*	89·8 (36·3)	341 (139)	< 0·001
IQ	105 (11·1)	74 (9·3)	< 0·001
Amine metabolites			
HVA	206 (100)	202 (87)	< 0·9
HMPG	40 (8·5)	40 (9·2)	< 1·0
5-HIAA	102 (34)	123 (38)	< 0·25

*Error scores or time used for correct solution.

Results

As expected, the cognitive performance was significantly impaired in the patients compared

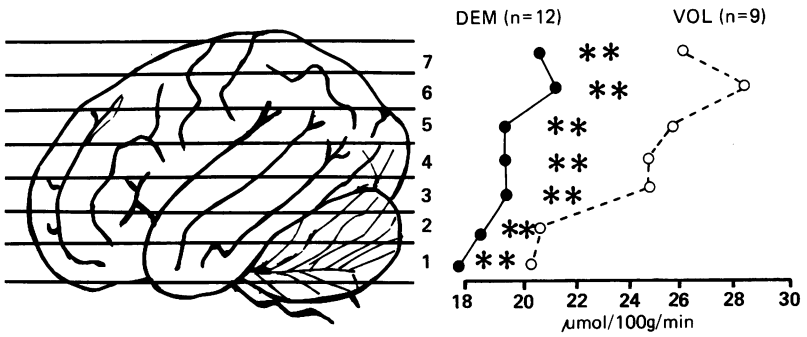

*Figure 1 Rates of glucose metabolism calculated from the ^{11}C-deoxyglucose accumulation in seven slices of the brains of demented patients (DEM) and healthy volunteers (VOL). **p < 0·01.*

with the control subjects (table 1). Despite their moderate degree of illness and their ability to live outside institutions the patients were seriously handicapped in verbal, non-verbal, spatial and memory tasks. The single tests that showed the highest correlation to the clinical grading of dementia were the Benton memory and the Picture arrangement. As previously reported for part of the present material[9] the levels of monoamine metabolites in the CSF did not differ between the two groups (table 1).

The accumulation of ^{11}C-deoxyglucose in the whole brain was lowered by 23% in the patients [18·7 (2·9) versus 23·8 (3·7) μmol/g/min in the controls]. The decrease at the seven slice levels is illustrated in fig 1. Although the decline was seen in all parts of the brain the change was most evident in the upper three slices where the superior temporal and the posterior parietal cortex seemed more affected than the occipital and the pre- and postcentral cortex (fig 2). The quantitative analysis was concordant with the appearance of the images

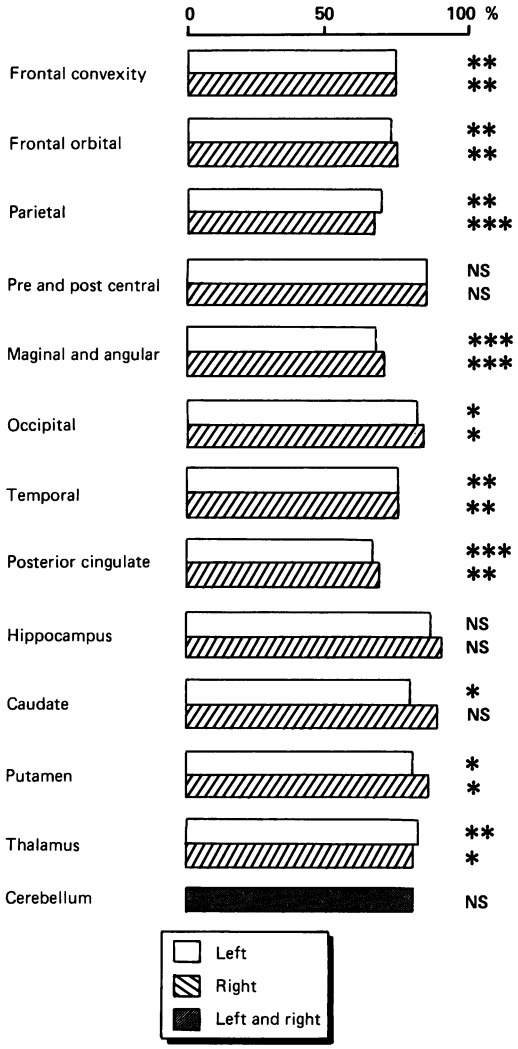

*Figure 3 Rates of regional glucose metabolism (micromol/100 g/min) in 12 patients with Alzheimer's dementia in per cent of rates obtained in nine healthy control subjects. *p < 0·05, **p < 0·01, ***p < 0·001.*

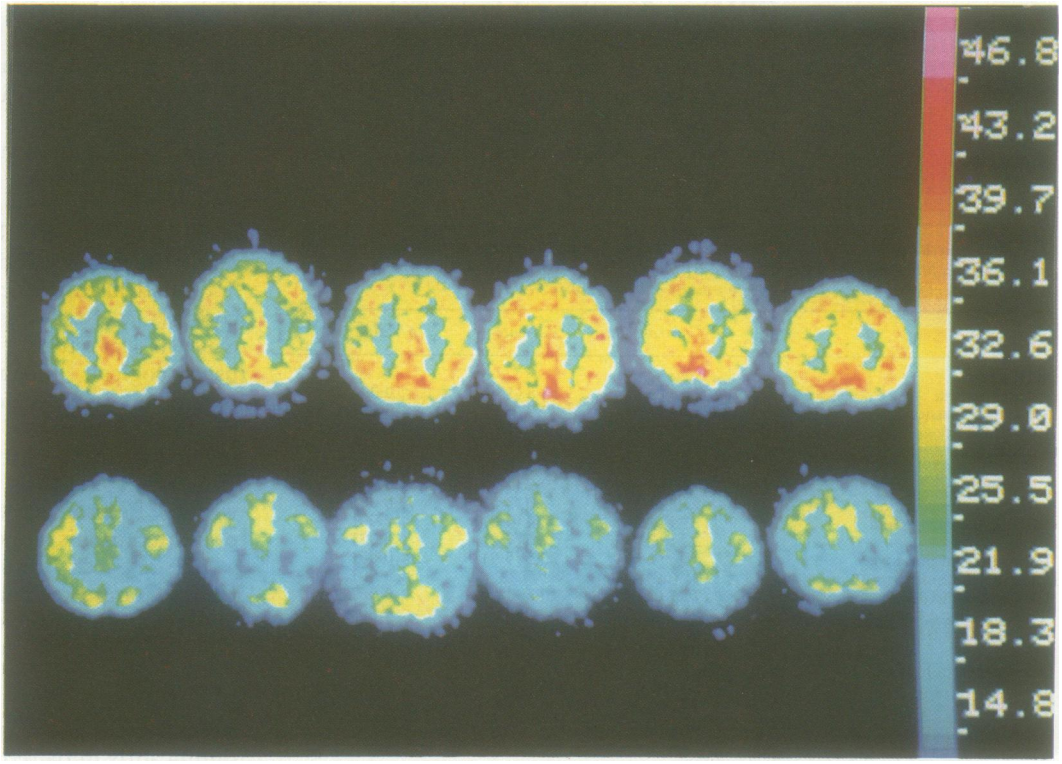

Figure 2 ^{11}C-deoxyglucose accumulation in the sixth brain slice of six control subjects (upper row) and six Alzheimer patients (lower row). Figures and colour scale indicate the calculated glucose utilisation in micromol/100 g/min.

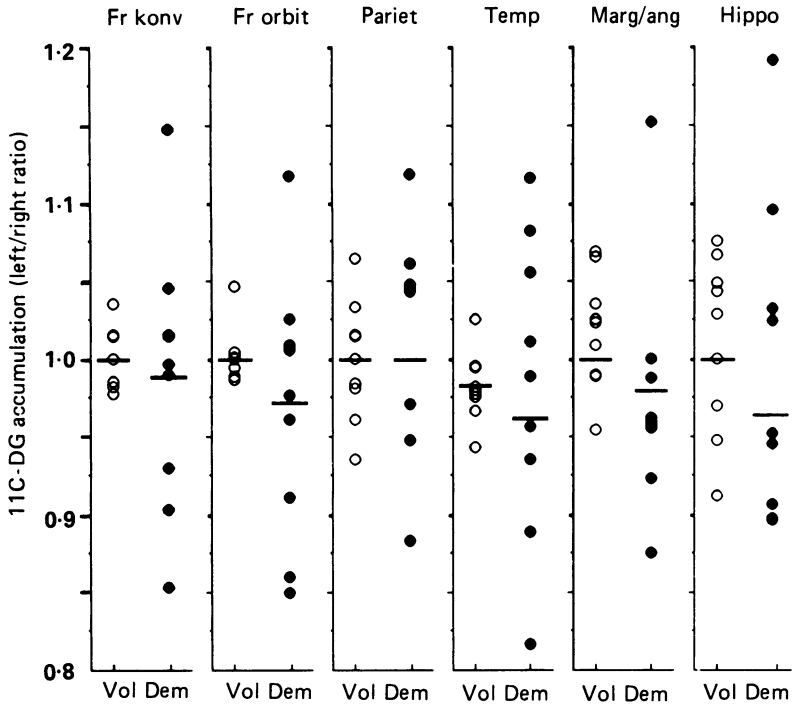

Figure 4 Cortical asymmetries of ^{11}C-deoxyglucose utilisation in healthy controls (open circles) and demented patients (filled circles). The variance is significantly greater ($p < 0·01$) in the patients in all areas except the hippocampus.

— the decline in glucose utilisation in the patients reaching down to 60% in the parietal and temporal cortex and the region in between, the angular and the marginal gyri (fig 3). The decline in the pre- and postcentral cortex as well as that in the hippocampus, the caudate and the cerebellum did not reach statistical significance ($p > 0·05$), nor did the differences between the right and the left side, although in several patients the left hemisphere seemed to be more affected than the right.

The left/right quotients were close to one in the control subjects but slightly below one, indicating a relative left-sided hypometabolism, in the patients (fig 4). The variance in the left/right ratio was significantly greater in the demented patients indicating a greater asymmetry of brain activity than in the healthy controls.

Rates of ^{11}C-deoxyglucose accumulation were highly correlated between the different cortical regions in both patients and healthy subjects. Also between the basal ganglia and cortical areas were significant correlations obtained in the controls, but not so in the demented subjects (table 2). Especially between the left caudate and cortical areas were low correlation coefficients obtained in the patients.

^{11}C-Deoxyglucose accumulation and CSF levels of monoamine metabolites correlated negatively in many areas, particularly in the controls (table 3). Thus high levels of MHPG correlated significantly with low rates of glucose metabolism in several hemispheric cortical areas and in the cerebellum of the healthy controls.

The relationships between regional glucose metabolism and test performance were mostly positive (table 4). In the healthy subjects a high metabolic rate in the marginal and angular and other cortical areas correlated significantly with a good performance in the WBI-tests and in the Trail making test. In the demented patients the WBI-tests and memory tests correlated significantly with activities of several cortical and subcortical regions. In fig 5 some of these relationships are illustrated graphically, showing tests and brain regions which were significantly correlated in controls and/or patients.

As some of the tests used are claimed to reflect activity of the left or the right hemisphere specifically left/right ratios were correlated to verbal, non-verbal and memory abilities. We found, in the patients but not in the controls, that verbal and memory performances were associated with relative left hemisphere hypermetabolism (fig 6) whereas non-verbal abilities were more associated with a relative right hemisphere hypermetabolism.

Table 2 Correlations between rates of glucose metabolism in basal ganglia and cortical areas in healthy controls ($n = 9$) and patients with Alzheimer's dementia ($n = 13$).

		Controls				*Patients*			
		Caudate		*Putamen*		*Caudate*		*Putamen*	
		Left	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
Frontal, convexity	left	0·72*	0·85**	0·69*	0·83**	0·44	0·67*	0·68*	0·62*
	right	0·69*	0·84**	0·69*	0·81**	0·40	0·79**	0·62*	0·46
Frontal, orbital	left	0·89**	0·93**	0·76*	0·85*	0·46	0·55	0·71**	0·57*
	right	0·86**	0·94**	0·76*	0·83**	0·42	0·67*	0·64*	0·44
Parietal	left	0·56	0·71*	0·60	0·70*	0·15	0·77**	0·29	0·35
	right	0·49	0·67*	0·51	0·64	0·10	0·76**	0·28	0·25
Temporal	left	0·89**	0·91**	0·77*	0·91**	0·63*	0·81**	0·64*	0·57*
	right	0·93**	0·90**	0·82**	0·92**	0·57*	0·84**	0·52	0·41
Occipital	left	0·82**	0·81**	0·81**	0·88**	0·43	0·79**	0·50	0·52
	right	0·77*	0·73*	0·68*	0·85*	0·51	0·79**	0·51	0·60*
Cingulate	left	0·50	0·76*	0·53	0·65	0·39	0·72**	0·49	0·52
	right	0·61	0·81**	0·51	0·73*	0·40	0·70**	0·59*	0·56*
Pre- and post-cental	left	0·67*	0·77*	0·72*	0·73*	0·21	0·69**	0·55	0·54
	right	0·63	0·71*	0·74*	0·72*	0·17	0·66*	0·56*	0·44
Marginal and angular	left	0·63	0·77*	0·66*	0·80*	0·35	0·74**	0·51	0·46
	right	0·54	0·75*	0·58	0·72*	0·38	0·75**	0·48	0·29
Hippocampus	left	0·89**	0·81**	0·80**	0·81*	0·48	0·45	0·49	0·64*
	right	0·78*	0·83**	0·78*	0·73*	0·59*	0·45	0·55	0·50
Thalamus	left	0·84**	0·94**	0·73*	0·89*	0·23	0·71**	0·45	0·23
	right	0·84**	0·78*	0·71*	0·88*	0·21	0·73**	0·38	0·19
Cerebellum	l + r	0·74*	0·76*	0·68*	0·74*	0·24	0·36	0·32	0·45
Mean		0·73*	0·81**	0·69*	0·79**	0·37	0·69**	0·51	0·46

*$p < 0·05$, **$p < 0·01$.

Table 3 Correlations between regional glucose metabolism and CSF monoamine metabolites in healthy controls (n = 9) and patients with Alzheimer's dementia (n = 13).

		Controls			Patients		
		HVA	*MHPG*	*5-HIAA*	*HVA*	*MHPG*	*5-HIAA*
Frontal, convexity	left	−0·39	−0·68*	−0·55	−0·18	−0·15	0·12
	right	−0·39	−0·71*	−0·55	−0·19	−0·18	−0·09
Frontal, orbital	left	−0·27	−0·39	−0·45	−0·25	−0·16	−0·06
	right	−0·29	−0·41	−0·47	−0·27	−0·22	−0·20
Parietal	left	−0·30	−0·73*	−0·40	−0·13	0·06	0·18
	right	−0·38	−0·78*	−0·45	−0·14	0·11	0·04
Temporal	left	−0·21	−0·44	−0·38	−0·03	−0·18	0·16
	right	−0·26	−0·49	−0·43	−0·08	−0·07	0·03
Occipital	left	−0·37	−0·73*	−0·55	−0·13	−0·10	0·18
	right	−0·56	−0·82**	−0·69*	−0·13	0·04	0·21
Cingulate	left	−0·29	−0·65	−0·44	−0·24	0·10	0·04
	right	−0·44	−0·63	−0·57	−0·36	−0·04	−0·15
Pre and post-central	left	−0·26	−0·73*	−0·37	−0·39	−0·23	−0·06
	right	−0·23	−0·77*	−0·37	−0·36	−0·19	−0·13
Marginal and angular	left	−0·36	−0·74*	−0·54	−0·17	0·01	0·09
	right	−0·42	−0·77*	−0·57	−0·13	0·06	−0·07
Hippocampus	left	0·02	−0·29	−0·13	−0·15	0·07	0·32
	right	0·13	−0·31	0·00	−0·21	−0·02	0·03
Caudate nucl	left	−0·25	−0·44	−0·41	0·20	−0·23	0·06
	right	−0·14	−0·27	−0·35	0·00	−0·20	−0·06
Putamen	left	0·07	−0·39	−0·20	−0·34	−0·52	−0·38
	right	−0·28	−0·54	−0·51	−0·51	−0·14	−0·18
Thalamus	left	−0·32	−0·35	−0·55	−0·32	−0·50	−0·32
	right	−0·18	−0·20	−0·42	−0·25	−0·44	−0·30
Cerebellum	l + r	−0·24	−0·66*	−0·33	−0·57*	−0·09	−0·10

*p < 0·05, **p < 0·01.

Discussion

Using PET with ^{18}F-2-deoxyglucose as tracer, decreased rates of glucose metabolism have been found in the posterior parietal and temporal areas in demented patients.[12–14] This pattern of change agrees with the distribution of neuropathological changes[16] and was also found in this investigation. Part of the hypometabolism may of course be due to a loss of neurons and an increased CSF space. However, as the CT images of the patients showed only minor morphological changes we interpret the decline in glucose utilisation as evidence for inactive or malfunctioning neurons.

Almost all brain regions displayed a significant decline in glucose utilisation which is in line with the global decrease in mental performance during the progress of the disease. With a relative sparing of the occipital and the pre- and postcentral cortex it can be imagined that the patients have their primary visual and sensory-motor ability preserved while they lack the associated cortex areas to put the visual information and the sensory-motor ability into a meaningful context.

The lack of decrease of glucose metabolism in the hippocampus was not expected as this region, according to postmortem analyses, is profoundly involved in the pathological process. The reason for this discrepancy may lie in the fact that our patients were still in the beginning of their disease, whereas the neuropathological studies were carried out following the final stage and death of the patients. Moreover, anatomical identification of the hippocampus is difficult in the horizontal sections received with our PET system. Despite the lack of decline in hippocampal metabolism we found a positive correlation between glucose utilisation in this region and the memory ability of the patients (fig 5).

The closer correlation between glucose utilisation in various brain regions in the controls than in the patients (table 2), indicates that the appearance of plaques and deficits in cholinergic and other pathways leads to a desynchronisation of brain activity at rest in the Alzheimer patients. Other research groups have also found greater disturbances of the metabolism in the left,[28] or the right,[29] hemisphere than in the contralateral side.

The greater variance in the left/right asymmetry of brain activity in the patients (fig 4) agrees with the findings of Haxby *et al*[30] and indicates that homologous areas of either the right or the left hemisphere may be specifically more affected in patients with Alzheimer's dementia.

By measuring CSF levels of monoamine metabolites in the same patients and controls that were examined by PET we obtained two different measures of brain metabolism. This allows us to speculate on the interaction between monoaminergic transmission and neuronal activity, as reflected in the glucose utilisation, of cells receiving monoaminergic input. The overall negative relationships be-

Table 4 Relationships between neuropsychological test results and rates of regional glucose utilisation in control subjects and patients with Alzheimer's dementia. Listed are tests and brain regions with a correlation coefficient above 0·66 (p < 0·05) in the control and 0·55 (p < 0·05) in the patient group

Test	*Brain region*
Controls (n = 9)	
WBI—Information	Marginal and Angular cortex, Occipital cortex
WBI—Similarities	Frontal, Temporal, Occipital, Cingulate, Marginal and Angular cortex, Caudate nucleus, Putamen, Thalamus
WBI—Picture arr	Marginal and Angular cortex, Putamen
Benton memory	Putamen
Trail making A	Parietal and Occiptal cortex, Putamen
IQ	Marginal and Angular cortex
Patients (n = 13)	
WBI—Similarities	Caudate nucleus, right
WBI—Vocabulary	" " "
WBI—Picture arr	Marginal and Angular cortex
Benton memory	" " " "
CD—learning	Orbitofrontal cortex
CD—retention	" " "
	Pre- and postcentral, Cingulate, and Temporal cortex, Hippocampus
Trail making B	Marginal and Angular cortex, right, Parietal cortex, right
Dementia rating[19]	Temporal and Occipital cortex
" "	Marginal and Angular cortex

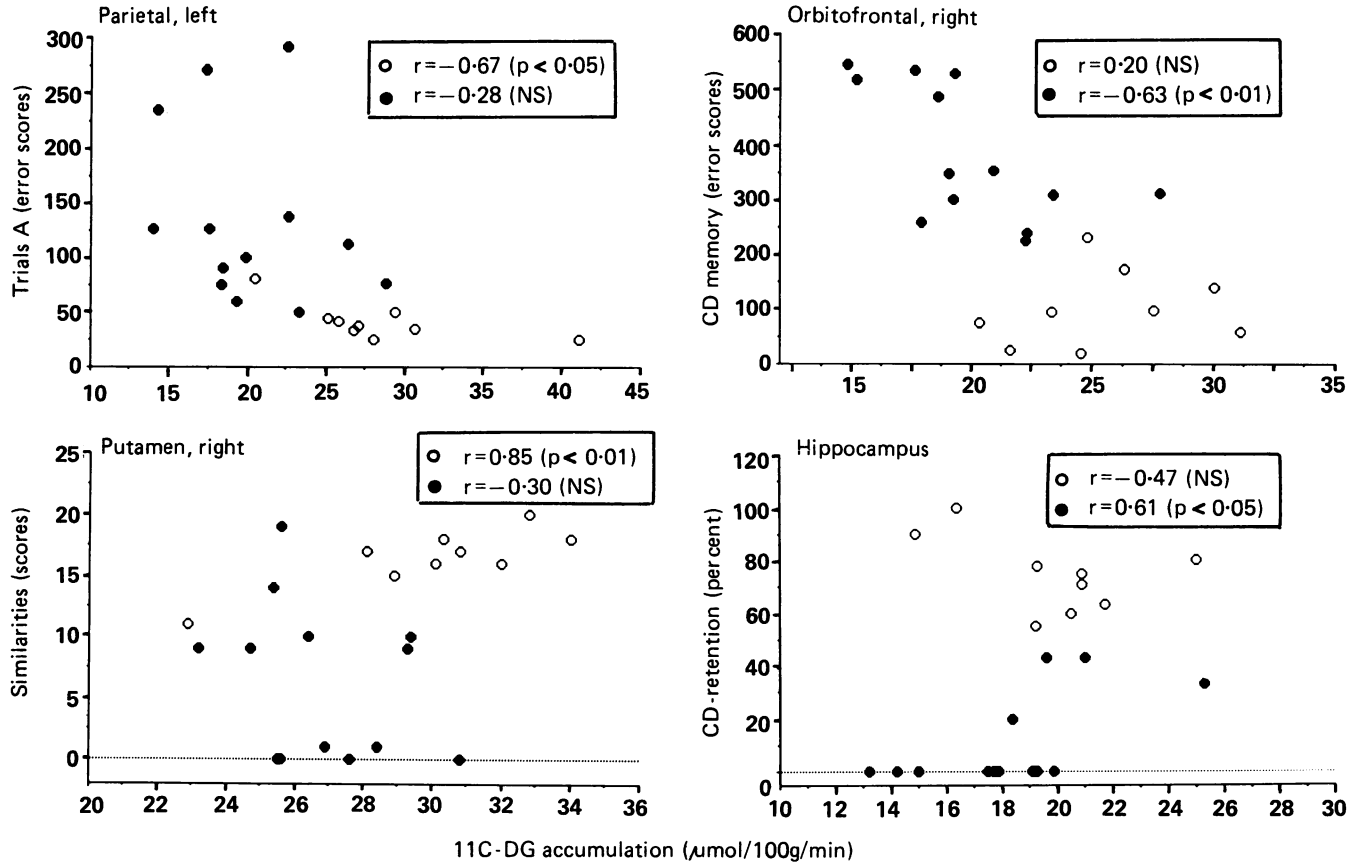

Figure 5 Correlations between psychological test results and ^{11}C-deoxyglucose utilisation in brain regions of healthy controls (open circles) and Alzheimer's disease patients (filled circles).

tween metabolite levels and glucose utilisation (table 3) may indicate an inhibitory influence of dopaminergic, noradrenergic and serotoninergic pathways upon neurons in cortical and subcortical terminal areas. This agrees with neurophysiological and pharmacological studies which have classified these monoamines as inhibitory transmitters in most, although not all, synapses.[31 32]

Thus the significant negative correlation between MHPG levels and glucose utilisation in cortical areas and the cerebellum may reflect an inhibition of cortical and cerebellar (Purkinje) neurons by noradrenergic input of locus coeruleus neurons.[33] Since the locus coeruleus neurons are reduced in number in Alzheimer's disease,[34] it is not surprising that no negative correlation was found between MHPG and glucose utilisation in the patients.

In accordance with previous investigations[11 12] we found, both in patients and controls, positive and significant correlations between cognitive abilities and utilisation of ^{11}C-deoxyglucose in several cortical and subcortical regions (table 4). This was also true for the visual memory which in a ^{18}F-deoxyglucose study on healthy men[35] was unrelated to regional brain metabolism. The reason for this discrepancy may lie in differences in test procedures or in PET-methodologies. Although significant correlations may appear by chance among the great number of tests and

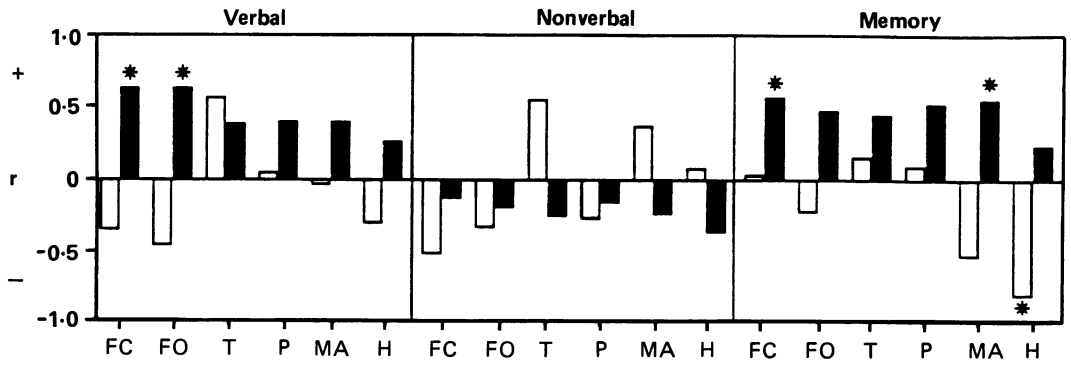

*Figure 6 Relationship between laterality of cortical glucose metabolism (left/right ratio) and neuropsychological abilities in control subjects (open columns) and demented patients (filled columns). Positive correlation coefficients (r) associate a better performance with a relatively higher left hemisphere metabolism whereas negative coefficients associate a better performance with a relatively higher right hemisphere metabolism. *p < 0·05.*
FC = Frontal convexity; FO = Frontal orbital; T = Temporal; P = Parietal; MA = Marginal and angular; H = Hippocampus.

brain regions involved the coefficients were with few exceptions positive, some of them reaching significant levels.

The association of results from tests claimed to be sensitive to left hemisphere function with glucose utilisation in regions of the same hemisphere (fig 6) constitutes a corroboration of current theories about lateralisation of verbal and non-verbal abilities.

Despite the significant correlations between regional glucose utilisation and neuropsychological test results (table 4, figs 5 and 6) our findings do not indicate a simple relationship between local brain activity and specific cognitive abilities. The results rather support the view that verbal, non-verbal and memory functions involve a cooperation between various neuronal systems with different cerebral extensions.

An alternative conclusion could of course be that the PET technique with ^{11}C-deoxyglucose is still a crude instrument for describing brain work in relation to mental capacities. The evolution of new PET instruments with higher resolution and studies of brain activity during the performance of cognitive tasks may in the future provide us with further knowledge of the relation between regional brain activity and neuropsychological functions.

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