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Positron Emission Tomographic Studies of Aging and Alzheimer Disease

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In this study the positron emission tomographic (PET)-^{18}F-2-deoxy-2-fluoro-D-glucose (FDG) technique was used to study both normal aging and senile dementia. The results derived from 15 young normal subjects (mean age, 26 ± 5 years) and 22 elderly normal subjects (mean age, 66 ± 7 years) failed to indicate significant metabolic changes associated with age. A group of 24 patients with senile dementia (mean age, 73 ± 7 years) showed consistent diminutions in regional glucose use relative to the elderly normals. Across all brain regions the diminutions were 17%–24%. There were also significant correlations between the measures of glucose use and the measures of cognitive functioning. Discriminant function classification analysis results indicate that better than 80% classification accuracy can be achieved for individual PET measures. These data suggest a possible future diagnostic use of PET in senile dementia.

The study of human cerebral blood flow (CBF) and metabolism began with the Kety-Schmidt technique [1]. With the development of diffusible isotopes and extracerebral scintillation detectors, local CBF measures have been possible. With these techniques the study of CBF and cerebral metabolism in normal aging and in senile dementia has produced contradictory results. Several investigations indicated that CBF and cerebral metabolism decrease with age [2–4]. However, others have found that when subjects are carefully screened there are no changes with advancing age [5, 6]. With respect to the study of the degenerative dementias, nearly all investigations have reported decreases in CBF and/or cerebral metabolism relative to age-matched control subjects [3, 7–12].

The development of positron emission tomography (PET) and the tracer ^{18}F-2-deoxy-2-fluoro-D-glucose (FDG) permits for the first time the tomographic and regional study of cerebral metabolism. A recent PET–FDG study identified consistent metabolic diminutions associated with normal aging, but these changes were not statistically significant [13]. Our early PET–FDG studies of senile dementia of the Alzheimer type (SDAT) revealed highly significant diminutions in metabolism relative to elderly controls [14]. We also found that these metabolic diminutions were associated with deficits in measures of intellectual functioning. More recently a study using PET and the $^{15}O_2$ technique demonstrated diminished oxygen utilization and CBF in SDAT relative to controls and a correlation between this diminution and intellectual deficit [15]. We now report the findings of our PET–FDG study of normal aging and our study of a larger sample of SDAT patients.

Subjects and Methods

All subjects received an extensive medical, neurologic, psychiatric, neuropsychologic, neuroradiologic, and clinical laboratory evaluation. These evaluations led to the identification of 15 young normal subjects (average age, 26.1 ± 5.1 years); 22 elderly normal subjects (average age, 66.6 ± 7.6 years, of whom 11 had an average age of 60.3 ± 4.2 years and 11 had an average age of 72.9 ± 3.1 years); and 24 SDAT patients (average age, 73.4 ± 6.9 years). For the comparison between SDAT and elderly normals, one 50-year-old normal was excluded to improve the overall age match between the two groups (21 elderly controls, average age 67.4 ± 6.7 years.) The severity range of the SDAT patients was mild to very severe [16].

The PET technique used FDG as a physiologic tracer for glucose metabolism. The details of this procedure are presented elsewhere [17]. The PET studies were conducted at the Brookhaven National Laboratory using the PET III scanner. The intrinsic spatial resolution of the PET III is 1.7 × 1.7 × 1.7 cm, full-width–half-maximum. Blood samples were taken during the study using either a short intraarterial cannula into the radial or ulnar artery at the patient's wrist or an intravenous line inserted in the back of the hand and drawing arterialized venous blood (42°C). Each patient received an intravenous bolus of 5–10 mCi (185–370 MBq) of FDG into a vein in the arm contralateral to the one being blood-sampled. Scanning began after a 30 min tracer uptake period, during which the subjects rested in the dimly lit quiet scanning room. With PET III, each scan takes 9–12 min. At least five scans were obtained for each patient.

CT scans were available for all patients. The CT studies were obtained in the same planes as the PET studies, using the same head-holder. Matched pairs of PET and CT scans were determined based on information from the recorded table positions and on the subjective alignment of slice features. In computing rates of regional glucose use, anatomic regions of interest were identified by measurement of their location relative to the center of the image on the matched CT scan. These locations were then translated to the corresponding spatial location on the PET scan.

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TABLE 1: **Rates of Regional Glucose Utilization in Young and Elderly Normal Subjects**

Region	Mean Rates in Normal Subjects (SEM)		*t* test*	% Change
	Young	Elderly		
Level of basal ganglia (CM + 40 mm):				
No. of subjects	14	22		
Frontal white:				
Right	3.63 (0.21)	3.51 (0.13)	−0.52	−3
Left	3.57 (0.20)	3.38 (0.12)	−0.90	−6
Caudate:				
Right	4.15 (0.23)	4.42 (0.15)	1.03	+6
Left	4.08 (0.22)	4.35 (0.16)	1.03	+7
Thalamus:				
Right	3.89 (0.14)	4.33 (0.16)	1.93	+11
Left	3.87 (0.15)	4.24 (0.16)	1.60	+10
Temporal:				
Right	3.67 (0.15)	3.78 (0.17)	0.44	+3
Left	3.35 (0.16)	3.36 (0.14)	0.03	0
Level of centrum semiovale (CM + 70 mm):				
No. of subjects	12	16		
Frontal:				
Right	3.57 (0.19)	3.75 (0.12)	0.82	+5
Left	3.48 (0.21)	3.60 (0.12)	0.55	+3
Parietal:				
Right	3.31 (0.12)	3.53 (0.12)	1.23	+6
Left	2.92 (0.09)	3.18 (0.14)	1.42	+9
White matter:				
Right	2.75 (0.14)	3.11 (0.14)	1.80	+13
Left	2.68 (0.11)	3.00 (0.16)	1.56	+12

* No significant differences were found.

TABLE 2: **Rates of Regional Glucose Utilization in Middle-Aged and Old Normal Subjects**

Region	Mean Rates in Normal Subjects (SEM)		*t* test	% Change
	Middle-Aged	Old		
Level of basal ganglia (CM + 40 mm):				
No. of subjects	11	11		
Frontal white:				
Right	3.58 (0.14)	3.44 (0.21)	−0.55	−4
Left	3.52 (0.11)	3.24 (0.20)	−1.24	−9
Caudate:				
Right	4.69 (0.20)	4.13 (0.19)	−2.07*	−14
Left	4.59 (0.15)	4.11 (0.27)	−1.58	−12
Thalamus:				
Right	4.58 (0.17)	4.09 (0.26)	−1.60	−12
Left	4.53 (0.17)	3.95 (0.25)	−1.91	−15
Temporal:				
Right	3.94 (0.20)	3.61 (0.26)	−0.99	−9
Left	3.50 (0.17)	3.21 (0.21)	−1.08	−8
Level of centrum semiovale (CM + 70 mm):				
No. of subjects	8	8		
Frontal:				
Right	3.97 (0.14)	3.52 (0.16)	−2.11	−13
Left	3.80 (0.13)	3.41 (0.19)	−1.73	−11
Parietal:				
Right	3.68 (0.16)	3.39 (0.17)	−1.18	−8
Left	3.24 (0.17)	3.11 (0.24)	−0.45	−4
White matter:				
Right	3.33 (0.18)	2.89 (0.19)	−1.68	−15
Left	3.17 (0.22)	2.83 (0.23)	−1.10	−12

* $p \leq 0.05$

In the present study images taken through the basal ganglia level of the brain, about canthomeatal (CM) + 40 mm and through the centrum semiovale level about CM + 70 mm, were used. The sampled regions at CM + 40 mm included frontal white matter, head of the caudate nucleus (probably including some anterior limb of the internal capsule), thalamus (possibly including some posterior limb of the internal capsule), and temporal lobe (posterior to the sylvian fissure and lateral to the atrium of the lateral ventricles). At CM + 70 mm the regions of interest included the frontal cortex, the white matter, and the temporoparietal cortex.

Results

Comparisons between the young normal and the combined group of elderly normal subjects are shown in table 1, between the middle-aged and the old normal subjects in table 2, and between the SDAT patients and the elderly group in table 3. These tables list the mean rates of glucose use (± SEM) for all regions of interest studied at the basal ganglia (CM + 40 mm) and centrum semiovale levels (CM + 70 mm).

The results failed to show any statistically significant differences in glucose use due to normal aging. That is, when young normal subjects are compared with elderly normal subjects there are no significant between-group differences. In fact, for some of the brain regions studied there was a trend toward elevated metabolic rates in the older group. However, regional comparisons made within the older group indicate a trend toward reduced metabolism with increasing age. This trend did not reach statistical significance. Pearson product correlations between metabolic rate and age for the studied brain regions failed to show any significant relationships.

The results for dementia study (table 3) indicated a consistent

TABLE 3: **Rates of Regional Glucose Utilization in Aging and Dementia Subjects**

Region	Mean Rates (SEM)		*t* test	% change
	Elderly Controls	Dementia		
Level of basal ganglia (CM + 40 mm):				
No. of subjects	21	23		
Frontal white:				
Right	3.50 (0.13)	2.75 (0.14)	3.91†	−21
Left	3.38 (0.12)	2.60 (0.15)	3.91†	−23
Caudate:				
Right	4.37 (0.15)	3.62 (0.15)	3.57†	−17
Left	4.33 (0.17)	3.46 (0.17)	3.63†	−20
Thalamus:				
Right	4.31 (0.16)	3.51 (0.14)	3.72†	−19
Left	4.22 (0.17)	3.33 (0.15)	4.01†	−21
Temporal:				
Right	3.77 (0.17)	3.03 (0.16)	3.12*	−20
Left	3.38 (0.14)	2.68 (0.16)	3.28*	−21
Level of centrum semiovale (CM + 70 mm):				
No. of subjects	15	13		
Frontal:				
Right	3.72 (0.12)	2.91 (0.18)	3.78†	−22
Left	3.60 (0.13)	2.87 (0.18)	3.35†	−20
Parietal:				
Right	3.49 (0.12)	2.65 (0.17)	4.12†	−24
Left	3.19 (0.15)	2.43 (0.17)	3.36†	−24
White matter:				
Right	3.09 (0.15)	2.54 (0.18)	2.35*	−18
Left	3.00 (0.17)	2.41 (0.17)	2.43*	−20

* $p \leq 0.01$
† $p \leq 0.001$

TABLE 4: **Significant Pearson Product Correlations ($p \leq 0.05$) between Rate of Glucose Utilization and Cognitive Impairment in Aging and Dementia Subjects**

Measure	CM + 40 mm (n = 44)								CM + 70 mm (n = 28)					
	Frontal White		Caudate		Thalamus		Temporal		Frontal		Parietal		White matter	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L
Guild memory test:														
Paragraph recall:														
Immediate	0.61	0.64	0.60	0.57	0.58	0.62	0.60	0.58	0.67	0.62	0.73	0.67	0.54	0.52
Delayed	0.60	0.62	0.56	0.52	0.58	0.60	0.55	0.53	0.65	0.59	0.69	0.64	0.49	0.48
Paired associates:														
Immediate	0.61	0.61	0.54	0.57	0.55	0.60	0.57	0.57	0.63	0.54	0.66	0.53	0.55	0.46
Delayed	0.57	0.57	0.52	0.50	0.49	0.54	0.49	0.56	0.50	0.48	0.56	0.52	0.45	0.43
Memory for designs	0.58	0.55	0.56	0.57	0.49	0.50	0.41	0.42	0.39	0.33	0.41	0.25*	0.17*	0.17*
WAIS:														
Vocabulary	0.58	0.62	0.50	0.47	0.51	0.53	0.55	0.54	0.66	0.62	0.63	0.57	0.39	0.43
DSST	0.61	0.61	0.56	0.51	0.52	0.55	0.55	0.54	0.59	0.52	0.64	0.52	0.40	0.41
Digits forward	0.48	0.52	0.47	0.39	0.45	0.45	0.61	0.49	0.60	0.57	0.66	0.59	0.42	0.49
Digits backward	0.43	0.44	0.42	0.37	0.45	0.44	0.56	0.47	0.52	0.48	0.61	0.47	0.38	0.41
Global impairment:														
MSQ	−0.61	−0.61	−0.56	−0.55	−0.53	−0.57	−0.52	−0.55	−0.60	−0.61	−0.66	−0.57	−0.50	−0.52
GDS	−0.65	−0.67	−0.60	−0.61	−0.59	−0.64	−0.60	−0.61	−0.63	−0.60	−0.73	−0.62	−0.49	−0.47

Note.—R = right; L = left.
* Not significant.

pattern of significant diminution in SDAT relative to elderly controls. These diminutions were 17%–23% at the basal ganglia level and 18%–24% at the centrum semiovale level.

In the elderly patients and controls, we also examined the extent to which changes in the rate of glucose utilization are related to clinical and cognitive changes. Table 4 lists the statistically significant ($p \leq 0.05$) correlations for these measures. The cognitive and clinical measures included the subtests of the Guild Memory Test, some subtests of the WAIS, and two measures of global functioning, the Mental Status Questionnaire MSQ [18] and the Global Deterioration Scale GDS [16]. The results of this analysis indicated consistent correlation across all brain regions between the metabolic rate and the patient's cognitive performance.

We also examined the extent to which the metabolic rate can be used statistically to classify patients as belonging to either the young or elderly group, or to the dementia or control group. A series of discriminant classification analyses were carried out using as predictors individual metabolic rates for specific PET regions of interest. The results indicated that the overall classification accuracy of the normals as either young or elderly was about 50%. This level of accuracy could have been achieved by chance alone. However, the SDAT patients and the elderly controls were correctly classified with an accuracy greater than 80%.

Discussion

The results of the present study indicate that there are no regional metabolic changes that are associated with age. These results are consistent with the results of some of the CBF and metabolism studies using other techniques [5, 6]. Primarily these negative studies and our own share the careful selection of study subjects. The results of Kuhl et al. [13] using PET and FDG are also similar to our own. These authors also did not find significant diminutions with age in regional glucose metabolism. However, Kuhl et al. did report a consistent trend of decreasing rates with age. It is possible that after our extensive and careful screening, only the elite elderly survivors remain. It is possible that this select group will continue to show no changes until they are either considerably older or develop certain disease conditions.

The results for SDAT have extended our earlier findings [14] and further strengthen the conclusion of significant metabolic diminutions in this disorder. These data also confirm highly consistent correlations between measures of glucose utilization and cognitive impairment. The results of this regional study are consistent with the earlier reports of diminished CBF and whole-brain metabolism, and with the more recently reported PET study by Frakowiak et al. [15]. Frakowiak et al. reported regional diminutions in SDAT of 19%–29%. These diminutions are very similar to those we have found. With respect to our discriminant classification analyses, our results suggest a future diagnostic importance of PET for SDAT.

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