Human Brain Glucose Utilization and Cognitive Function in Relation to Age

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Brain oxidative metabolism was examined with positron emission tomography and [^{18}F]2-deoxy-D-glucose in 40 healthy men aged 21 to 83 years, under conditions of reduced visual and auditory stimulation. The mean cerebral metabolic rate for glucose (CMR_{glc}) equaled 4.6 to 4.7 mg · 100 gm^{-1} · min^{-1} and did not correlate significantly with age ($p > 0.05$). Regional cerebral metabolic rates for glucose ($rCMR_{glc}$) and Q ratios ($rCMR_{glc}/CMR_{glc}$), which had lower coefficients of variation than did $rCMR_{glc}$, also did not correlate with age. Hyperfrontality of cerebral metabolism was absent at all ages. Age decrements were demonstrated in the error score on the Benton Revised Visual Retention Test and in the Performance Subtest scaled score of the Wechsler Adult Intelligence Scale (WAIS) but not in the Verbal Subtest scaled score of the WAIS. The cognitive test scores did not correlate with brain metabolic rates. The results indicate that brain oxidative metabolism, when measured under resting conditions with reduced sensory input, is not reduced in relation to age in healthy men. Furthermore, no significant relations between intelligence and resting cerebral metabolism are evident.

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The relation between age and cerebral metabolism in humans has been examined repeatedly with the Kety-Schmidt technique [11, 12, 17, 22, 32, 55, 57], and more recently with positron emission tomography (PET) [13, 18, 20, 21, 33–35], but remains undetermined. Using PET, Frackowiak and colleagues [21] and Lammertsma and associates [34] reported that the cerebral metabolic rate for oxygen ($CMRO_2$) and cerebral blood flow (CBF) are reduced in elderly subjects, but these workers later concluded that CBF but not $CMRO_2$ is reduced [20]. In contrast, an extensive study by Kuhl and colleagues [33] of 40 subjects indicated that the cerebral metabolic rate for glucose (CMR_{glc}) and many regional cerebral metabolic rates for glucose ($rCMR_{glc}$) correlate negatively with age, and that the frontal lobes are hypermetabolic, compared with the remaining cortex, in young but not in old subjects.

We reported recently that $rCMR_{glc}$ and CMR_{glc} did not correlate significantly with age in 21 healthy men [18]. A large number of correlation coefficients verged on statistical significance, however, and the absence of significant correlations might have reflected the small number of subjects and the large coefficients of variation of the $rCMR_{glc}$ data, which were on the order of 20 to 25% [18, 27, 37, 48, 49]. In view of these considerations, and of the report by Kuhl and associates [33], we decided to extend our study to 40 subjects and to examine the reported age-related reduction in hyperfrontality of metabolism. Furthermore, we calculated $rCMR_{glc}/CMR_{glc}$ at each region, so as to reduce coefficients of variation of the metabolic data and to maximize the likelihood of demonstrating significant age correlations, if they existed. With 40 subjects we could divide data into four age groups and apply analyses of variance and tests of homogeneity of variance.

Many studies of brain metabolism and human aging have not characterized the subject population in terms of cognitive competence and have not employed rigid health screening to exclude subjects with diseases that could interfere with cerebral function [11, 12, 15, 17, 18, 22, 57]. Thus, it is likely that differences in health status account for some differences among reported results. We therefore applied rigid health screening to our subjects, characterized their cognitive abilities by means of several neuropsychological tests, and tried to relate the test results to cerebral metabolism. Although intelligence in healthy subjects has not been found to correlate with global cerebral metabolism [4], the relation between cognitive ability, and regional cerebral metabolism as determined with PET, has not been examined.

It has been suggested that elderly subjects fre-

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quently are ketotic [23, 57]. Because the ketone bodies 3-hydroxybutyrate (3-OHB) and acetoacetate (AcAc) can partially replace glucose as substrates for brain oxidative metabolism in the elderly [23, 57], we monitored blood concentrations of ketone bodies so as to evaluate their possible influence on $rCMR_{glc}$.

Abstracts of parts of this work have been published [16, 45, 46].

Methods

Subjects

Forty healthy male volunteers between 21 and 83 years of age underwent rigorous medical, neurological, and laboratory screening [18]. Individuals were excluded from the study if they were at risk for cardiovascular, cerebrovascular, or neurosensory disorders, or had a history of drug or alcohol abuse or of a major psychiatric disorder. Such status was determined by the following procedures: a complete history and physical examination, chest roentgenogram, electrocardiogram, and laboratory evaluation of hematological, metabolic, and endocrine indices. Computed tomographic (CT) scans were taken parallel to and 5 to 100 mm above the externally defined inferior orbitomeatal (IOM) line.

All subjects had completed high school. They signed an informed consent that described the purpose and procedures of the study, and the risks involved (see Acknowledgments).

Positron Emission Tomography

After a subject had fasted for at least 4 hours, an indwelling catheter was placed in the dorsal vein of a heated hand and an arterial puncture was performed to obtain blood for determination of pH and arterial carbon dioxide and oxygen tensions. One hour later the subject was placed supine on a bed in a darkened room. His eyes were closed and covered with a mask, and his ears were plugged with cotton. Three to 5 mCi of [^{18}F]2-deoxy-D-glucose (^{18}FDG) was injected into an antecubital vein, and blood samples were removed at timed intervals thereafter, up to the end of scanning. The sample withdrawal schedule was as follows: every 15 seconds for the first 2 minutes; every minute until 6 minutes postinjection; every 2 minutes until 12 minutes postinjection; at 15 minutes postinjection; every 5 minutes until 45 minutes postinjection; and every 10 minutes until the end of the scan. The samples were centrifuged to provide plasma for measurements of radioactivity and glucose (Glucose Analyzer II, Beckman Instruments Co, Oxnard, CA).

Forty-five minutes after ^{18}FDG was injected, the blindfold and ear cotton were removed and the subject was asked to urinate to minimize radiation to the bladder. From 45 to 140 minutes after injection, up to seven serial PET slices were obtained parallel to and 5 to 100 mm above the external IOM line. PET scanning was performed with an ECAT II positron tomograph (ORTEC, Life Sciences, Oak Ridge, TN) in the medium-resolution mode (full width at half maximum, 1.7 cm in image and axial planes) [18, 27, 44]. PET slices had at least 750,000 coincidence counts and were 1.4 cm apart.

PET images were reconstructed and corrected for attenuation with the ORTEC-supplied attenuation correction program, using a uniform attenuation coefficient (μ = 0.088) and an operator-drawn ellipse to define the edge of the skull. PET slices, as well as CT images, were compared with anatomical sections from an atlas of a human brain [19]. Because of individual differences in head size and shape, the height above the IOM line of the slice in the atlas was assigned to the PET and CT scans. Comparison of PET and CT scans at identical heights above the IOM line, using the atlas, made it possible to identify anatomical regions of interest (ROIs) in the PET scans, as reported by Duara and colleagues [18]. Locations of different ROIs are illustrated in Figure 1 on lateral and medial projections and on a horizontal section of the cerebral hemispheres.

Mean ECAT numbers and mean areas of each ROI in a given slice were determined as described by Duara and colleagues [18]. ECAT numbers were converted to brain radioactivities (in microcuries per gram) with a calibration factor derived by prior scanning of a water-filled flask that contained a known uniform concentration of ^{18}FDG. Twenty-nine pairs of bilaterally symmetrical and three midline ROIs were identified and outlined, as were right and left hemispheric ROIs in each slice.

Data Analysis

$rCMR_{glc}$ was calculated in units of mg · 100 gm^{-1} · min^{-1} from brain radioactivity, time of scanning, plasma radioactivity, and plasma glucose level, by means of a four-transfer-constant operational equation [27]. The "lumped constant" in this equation was taken as 0.418. If a region appeared in one or more adjacent slices, a weighted mean $rCMR_{glc}$ was calculated by the following equation, where i = 1, 2 ... equals slice number, $rCMR_{glc}$ equals the cerebral metabolic rate for glucose in the region within slice i, and N_i is the area (in square centimeters) of the region within slice i,

$$rCMR_{glc} = \frac{\sum_i (rCMR_{glc})_i N_i}{\sum_i N_i} \quad (1)$$

When the ROI was an entire hemisphere, $rCMR_{glc}$ in equation 1 equaled the weighted mean hemispheric metabolic rate for glucose, CMR_{glc}, where i = 1, 2, ... 5 equal individual slices between 30 and 80 mm above the IOM line and N_i is the surface area of the hemisphere within slice i. CMR_{glc} was calculated with gray matter transfer constants [18]. The weighted mean metabolic rate for glucose in gray matter of a cerebral hemisphere, $(CMR_{glc})_{gray}$, also was calculated by equation 1, where N_i equals the area and $(rCMR_{glc})_{gray,\,i}$ the metabolic rate of each gray matter region that was examined in slices i between 30 and 80 mm above the IOM line, and $\Sigma_i N_i$ is their net area. $(rCMR_{glc})_{gray,\,i}$ is substituted for $(rCMR_{glc})_i$ in equation 1.

Weighted regional cerebral metabolic rates for glucose, $rCMR_{glc}$, were divided by the mean cerebral metabolic rate for both hemispheres to provide normalized regional quotients, or Q values:

$$Q = \frac{rCMR_{glc}}{CMR_{glc}} \quad (2)$$

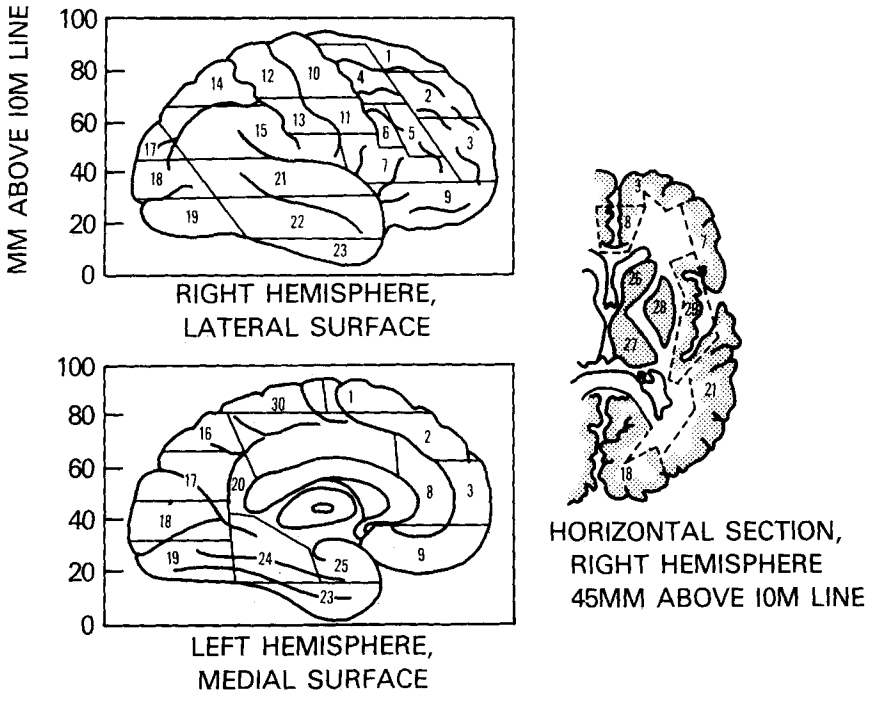

Fig 1. Lateral and medial projections and horizontal section of brain with regions of interest, as described by Duara and colleagues [18]. ROIs are identified as follows (millimeters above inferior orbitomeatal [IOM] *line are given in parentheses): 1: superior frontal gyrus (80 to 100 mm), 2: superior frontal gyrus (65 to 80), 3: superior frontal gyrus (35 to 60), 4: middle frontal gyrus (65 to 90), 5: middle frontal gyrus (45 to 65), 6: inferior frontal gyrus (50 to 70), 7: inferior frontal gyrus (35 to 50), 8: cingulate gyrus (35 to 70), 9: orbitofrontal gyrus (20 to 35), 10: precentral gyrus (70 to 100), 11: precentral gyrus (55 to 70), 12: postcentral gyrus (70 to 100), 13: postcentral gyrus (55 to 70), 14: superior parietal gyrus (70 to 100), 15: inferior parietal gyrus (45 to 70), 16: precuneus (65 to 80), 17: cuneus (45 to 65), 18: calcarine region (30 to 45), 19: lingual region (15 to 30), 20: retrosplenial gray (45 to 70), 21: superior temporal gyrus (30 to 45), 22: middle temporal gyrus (15 to 30), 23: inferior temporal gyrus (5 to 15), 24: hippocampal region (20 to 35), 25: anterior medial-temporal region (20 to 25), 26: caudate nucleus (35 to 55), 27: thalamus (40 to 50), 28: lenticular nucleus (35 to 45), 29: insula (40 to 60), 30: paracentral lobule (80 to 100).*

Other Measurements

Supine resting heart rate and systolic and diastolic blood pressures were measured prior to the injection of ^{18}FDG and were compared with respective values that had been determined after at least 5 minutes of rest in the supine position on a non-PET day. Venous blood was obtained on non-PET days, as well as on the PET day at least 60 minutes before the injection of ^{18}FDG, for the determination of 3-hydroxybutyrate (3-OHB) and acetoacetate (AcAc) [65].

Prior to and during PET scanning, an investigator maintained a record of the subject's verbal comments of distress, facial expression, motor activity (fidgeting), and evidence of excessive sweating or hyperventilation. These observations were ranked on an anxiety scale of 0 (minimal anxiety) to 3 (intense anxiety).

Cognitive function was evaluated with the Wechsler Adult Intelligence Scale (WAIS) [62, 63] and the Benton Revised Visual Retention Test, Form C, Administration A [1, 3], a test of visual performance and memory.

Statistical Analysis

Correlation coefficients and partial correlation coefficients were used to examine relations among different variables. Individual means were compared by paired t tests. In addition, the 40 subjects were divided into four groups as follows: age 21 to 35 years (10 subjects), 36 to 50 years (10), 51 to 65 years (12), and 66 years and older (8). Data for these groups were subjected to analysis of variance and Bonferroni t statistics for multiple comparisons [39]. Homogeneity of variance was examined with Bartlett's test [39]. The criterion of significance was $p \leq 0.05$.

Results

Table 1 summarizes demographic and physiological data on the 40 subjects and includes measures from non-PET days as well as from the day of PET scanning. The mean age of the group was 50 years (range, 21 to 83 years). Thirty-seven men were white and 3 were black (aged 30, 46, and 57 years), and 36 had at least 4 years of college. Heart rate, systolic and diastolic blood pressures, and blood concentrations of AcAc and 3-OHB did not correlate significantly with age. Significant differences in heart rate and systolic and diastolic blood pressures were not found between non-PET and PET days, although the concentrations of 3-OHB and AcAc on PET days were higher than on non-PET days. Arterial pH was correlated positively and arterial

Table 1. Characteristics of Subjects

Variable	Mean ± SD
No. of subjects	40
Age (yr)	50 ± 17
Weight (kg)	78 ± 8
Post–high school education (yr)	5.8 ± 6.4
MEASUREMENTS ON NON-PET DAY	
Heart rate (beats/min)	72 ± 11
Systolic blood pressure (mm Hg)	131 ± 16
Diastolic blood pressure (mm Hg)	79 ± 17
Blood acetoacetate (μM)	14.1 ± 11.7
Blood 3-hydroxybutyrate (μM)	41.5 ± 64.1
MEASUREMENTS ON PET DAY	
Heart rate (beats/min)	66 ± 11
Systolic blood pressure (mm Hg)	127 ± 16
Diastolic blood pressure (mm Hg)	78 ± 10
Blood acetoacetate (μM)	24.4 ± 17.6[a]
Blood 3-hydroxybutyrate (μM)	98.4 ± 100.5[a]
Anxiety rating (0–3)	1.4 ± 0.5[b]
Arterial oxygen tension (mm Hg)	85 ± 13
Arterial carbon dioxide tension (mm Hg)	38 ± 4[c]
Arterial pH	7.40 ± 0.02[d]

[a]Statistically significant difference from mean on non-PET day by paired t test ($p < 0.05$).
Significantly correlated with age ($p < 0.05$): [b]$r = -0.54$; [c]$r = -0.40$; [d]$r = 0.42$.

PET = positron emission tomography.

carbon dioxide tension negatively with age; the anxiety rating during PET was correlated negatively with age.

Table 2 presents mean test values for the 40 subjects on the WAIS and the Benton Revised Visual Retention Test, as well as anxiety scores, and their correlations with age. Scores in individual age groups as a whole are provided, as well as results of analyses of variance, of Bonferroni t statistics, and of Bartlett's test for homogeneity of variance for scores that were correlated significantly with age.

The sum of WAIS Performance Subtest scaled scores correlated negatively with age for the 40 subjects. The mean sum of Performance Subtest scaled scores for the oldest group was 1.4 SD below that of the youngest group ($p < 0.05$), compared with a difference of 1.9 SD reported in normative studies [62, 63]. The mean Full Scale IQ of the 40 subjects equaled 124 and was more than 1 SD above the norm (100 ± 15) [63]. The Verbal IQ and Full Scale IQ, both of which are age corrected, correlated positively and significantly with age. These IQs were higher in the oldest than in the youngest group. The error score on the Benton Revised Visual Retention Test correlated significantly with age. The magnitude of the difference in the mean error scores between the oldest and youngest group, 1.2 SD, corresponds to reported differences in normative studies [1, 3]. Bartlett's test indicated no significant difference in the coefficient of variation between young and old groups for the WAIS scaled scores and IQs but a significantly higher coefficient of variation in the Benton error score of the oldest compared to the younger groups.

As described in Table 3, the weighted hemispheric cerebral metabolic rate for glucose, CMR_{glc}, equaled 4.60 mg · 100 gm^{-1} · min^{-1} on the right side and 4.67 mg · 100 gm^{-1} · min^{-1} on the left side in the 40 subjects. Neither value correlated significantly with age. The right/left ratio for $rCMR_{glc}$ did not differ significantly from 1 and did not correlate with age. Figure 2 illustrates individual values for hemispheric CMR_{glc} and their relation to age for the 40 subjects. The weighted CMR_{glc} in gray matter, $(CMR_{glc})_{gray}$, equaled 5.28 mg · 100 gm^{-1} · min^{-1} on the right side and 5.33 mg · 100 gm^{-1} · min^{-1} on the left. This value did not differ significantly on the right and left sides, and did not correlate significantly with age.

Table 3 also presents weighted mean values for $rCMR_{glc}$ in gray matter of the individual lobes of the cerebral hemispheres, and ratios of frontal $rCMR_{glc}$ to

Table 2. Mean Scores on the Wechsler Adult Intelligence Scale, Benton Revised Visual Retention Test (Form C, Administration A), and Anxiety Scale for 40 Healthy Subjects[a]

Age Range (yr)	Mean Age (yr)	No. of Subjects	Wechsler Adult Intelligence Scale Score: Subtest Scaled Scores: Verbal	Per-formance	Full Scale	Intelligence Quotient: Verbal	Per-formance	Full Scale	Benton Revised Visual Retention Test Error Score	Anxiety Scale Score
21–83	50 ± 17	40	82 ± 12	55 ± 10[b]	137 ± 12	126 ± 14[c]	119 ± 11	124 ± 12[c]	3.6 ± 2.3[c]	1.4 ± 0.5[b]
21–35	28 ± 5	10	...	60 ± 10	...	119 ± 12	...	118 ± 11	3.2 ± 2.1	1.9 ± 0.6
36–50	44 ± 5	10	...	56 ± 8	...	123 ± 12	...	123 ± 10	2.6 ± 1.5	1.1 ± 0.6[d]
51–65	58 ± 4	12	...	55 ± 9	...	127 ± 14	...	126 ± 13[d]	3.2 ± 1.5	1.2 ± 0.8
66–83	73 ± 5	8	...	46 ± 10[d]	...	138 ± 11[d]	...	133 ± 10[d]	5.8 ± 2.8[d]	0.5 ± 0.5[d]

[a]All values are expressed as means ± SDs. Analysis of variance and Bonferroni t statistics were used when scores for the subjects were correlated significantly with age.
[b]Correlated significantly and negatively with age ($p < 0.05$).
[c]Correlated significantly and positively with age ($p < 0.05$).
[d]Significantly different from mean in 21- to 35-year-old group, by Bonferroni t statistics ($p < 0.05$).

Table 3. Hemispheric and Lobar Cerebral Metabolic Rates and Lobar Ratios[a]

Metabolic Rate	Right Side	r[b]	Left Side	r[b]	Right/Left Ratio	r[b]
Hemispheric CMR_{glc}	4.60 ± 1.08	0.01	4.67 ± 1.09	−0.09	0.99 ± 0.04	0.14
Hemispheric $(CMR_{glc})_{gray}$	5.28 ± 1.20	−0.01	5.33 ± 1.21	−0.03	0.99 ± 0.04	0.15
Frontal lobe $rCMR_{glc}$	5.41 ± 1.35	−0.05	5.45 ± 1.35	−0.07	1.00 ± 0.05	0.02
Parietal lobe $rCMR_{glc}$	5.45 ± 1.32	0.01	5.50 ± 1.36	0.12	0.99 ± 0.04	−0.03
Temporal lobe $rCMR_{glc}$	4.48 ± 1.25	0.03	4.58 ± 1.16	−0.05	0.97 ± 0.06	0.27
Occipital lobe $rCMR_{glc}$	5.39 ± 1.23	0.02	5.44 ± 1.25	0.03	0.98 ± 0.05	−0.01
Frontal/parietal ratio	1.00 ± 0.08	−0.17	1.00 ± 0.11	−0.15	...	...
Frontal/temporal ratio	1.24 ± 0.23[c]	−0.12	1.22 ± 0.22[c]	−0.02	...	...
Frontal/occipital ratio	1.01 ± 0.17	−0.09	1.01 ± 0.16	−0.15	...	...

[a]All rates expressed as means ± SDs in mg · 100 gm^{-1} · min^{-1} for 40 subjects. $rCMR_{glc}$ at a lobe represents the weighted mean for lobar gray matter.
[b]Correlation with age (none was statistically significant at $p < 0.05$).
[c]Ratio differs significantly from 1 ($p < 0.05$).

CMR_{glc} = cerebral metabolic rate for glucose; $rCMR_{glc}$ = regional cerebral metabolic rate for glucose.

$rCMR_{glc}$ in the other lobes. No lobar $rCMR_{glc}$ correlated significantly with age, nor was any right/left lobar ratio related to age. The frontal/parietal and frontal/occipital ratios for $rCMR_{glc}$ did not differ significantly from 1 and were not correlated significantly with age. The frontal/temporal ratio equaled 1.24 on the right and 1.22 on the left side but was not age related.

Table 4 presents values for $rCMR_{glc}$ in twenty-nine pairs of bilaterally symmetrical and in three midline brain regions, as well as their correlations with age and information about their right/left ratios. The coefficients of variation of the means of $rCMR_{glc}$ (SD/mean) were on the order of 20 to 25%. Three of the right/left ratios correlated positively and significantly with age: at the inferior frontal gyrus (35 to 50 mm above the IOM line), orbitofrontal gyrus (20 to 35 mm), and thalamus.

Figure 3A relates $rCMR_{glc}$ to age in a typical brain region, the right superior temporal gyrus, and demonstrates a nonsignificant correlation ($p > 0.05$). As shown in Table 4, with exceptions not more frequent than chance, $rCMR_{glc}$ was not related significantly to age. Factoring out IQ from the analyses did not alter the results. $rCMR_{glc}$ was highest in parietal and frontal lobe gray matter (as high as 6.52 mg · 100 gm^{-1} · min^{-1} at the precuneus and 6.02 mg · 100 gm^{-1} · min^{-1} at the paracentral lobule), and lowest at temporal lobe regions (3.53 mg · 100 gm^{-1} · min^{-1} at the inferior temporal region [5 to 15 mm above the IOM line] and 3.96 mg · 100 gm^{-1} · min^{-1} at the anterior-medial temporal region [20–35 mm]). The gray/white ratio, taken as $rCMR_{glc}$ at the left precuneus divided by $rCMR_{glc}$ at the left centrum semiovale, equaled 2.47 ± 0.56 (SD) (n = 37).

Table 5 presents quotients (Q values), $rCMR_{glc}$/CMR_{glc}, at the different brain regions, where the denominator is the mean metabolic rate for both cerebral hemispheres. These Q values generally exceeded 1 except at regions of the temporal lobes. Their coefficients of variation ranged from 8 to 21%, with a mean of 13%, approximately half that for the $rCMR_{glc}$ values. No Q value correlated significantly with age, with or without IQ factored out from the correlation analysis. Q values in the right superior temporal gyrus are illustrated in Figure 3B.

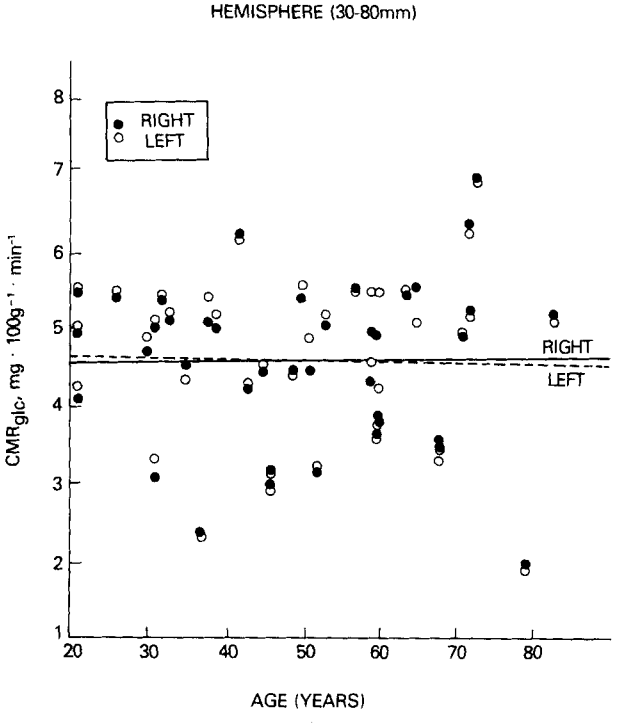

Fig 2. Relation of cerebral metabolic rate for glucose (CMR_{glc}) to age in 40 subjects. The regression coefficients are statistically nonsignificant.

Application of Bartlett's test for homogeneity of variance indicated that coefficients of variation increased significantly with age in only two of sixty-one regions for Q values and in only five of sixty-one re-

Table 4. Weighted Mean Regional Cerebral Metabolic Rates, Their Right/Left Ratios, and Correlations with Age[a]

Brain Region	Distance Above Inferior Orbitomeatal Line (mm)	No. of Subjects	Right Side		Left Side		Right/Left Ratio	
			$rCMR_{glc}$	r[b]	$rCMR_{glc}$	r[b]	Value	r[b]
Frontal lobe								
Superior frontal gyrus	80–100	37	5.72 ± 1.49	−0.04	5.62 ± 1.46	−0.06	1.02 ± 0.06	0.11
	60–80	38	5.69 ± 1.48	0.04	5.61 ± 1.42	−0.04	1.01 ± 0.05	0.31
	35–60	39	5.36 ± 1.44	0.06	5.37 ± 1.41	0.04	0.99 ± 0.05	0.07
Midfrontal gyrus	65–90	37	5.96 ± 1.63	0.04	6.02 ± 1.51	−0.02	0.99 ± 0.07	0.20
	45–65	38	5.56 ± 1.47	0.01	5.63 ± 1.54	0.03	0.99 ± 0.06	−0.05
Inferior frontal gyrus	50–70	33	5.84 ± 1.49	0.20	5.88 ± 1.51	0.17	0.99 ± 0.07	0.07
	35–50	37	5.54 ± 1.37	0.08	5.62 ± 1.42	0.01	0.99 ± 0.06	0.32[c]
Orbitofrontal gyrus	20–35	34	4.85 ± 1.15	0.07	5.00 ± 1.21	0.07	0.97 ± 0.06	0.45[c]
Cingulate gyrus	35–70	40	5.69 ± 1.38	−0.06	(Midline)	...	...	...
Precentral gyrus	70–100	37	6.04 ± 1.53	−0.05	6.08 ± 1.46	0.01	0.99 ± 0.07	−0.20
	55–70	33	5.76 ± 1.56	−0.07	5.92 ± 1.51	0.00	0.97 ± 0.10	0.18
Paracentral lobule	80–100	36	6.02 ± 1.39	−0.09	(Midline)	...	...	...
Parietal lobe								
Postcentral gyrus	70–100	37	5.63 ± 1.35	0.06	5.67 ± 1.37	0.09	1.00 ± 0.09	−0.09
	55–70	33	5.38 ± 1.45	0.04	5.50 ± 1.46	0.11	0.98 ± 0.09	−0.25
Superior parietal gyrus	70–100	37	5.48 ± 1.37	0.04	5.55 ± 1.42	0.05	0.99 ± 0.07	0.07
Inferior parietal gyrus	45–70	40	5.21 ± 1.33	−0.02	5.32 ± 1.38	0.02	0.99 ± 0.10	−0.03
Precuneus	65–80	34	6.52 ± 1.43	0.04	6.48 ± 1.37	−0.03	1.00 ± 0.06	0.32
Temporal lobe								
Superior temporal gyrus	30–45	40	4.97 ± 1.10	0.03	5.07 ± 1.24	0.01	0.99 ± 0.08	0.07
Inferior and middle temporal gyri	15–30	26	4.39 ± 0.94	0.02	4.59 ± 1.07	−0.11	0.97 ± 0.10	0.31
Inferior temporal gyrus	5–15	24	3.56 ± 0.98	−0.20	3.53 ± 0.90	−0.38[c]	1.00 ± 0.14	0.25
Hippocampal region	20–35	34	4.41 ± 1.27	−0.01	4.41 ± 1.30	−0.07	1.01 ± 0.09	0.19
Anterior-medial temporal region	20–35	12	4.02 ± 0.82	−0.17	3.96 ± 0.87	−0.07	1.01 ± 0.09	−0.10
Occipital lobe								
Cuneus	45–65	37	6.04 ± 1.29	0.00	6.00 ± 1.30	−0.01	1.01 ± 0.11	0.04
Calcarine region	30–45	40	5.49 ± 1.27	0.14	5.53 ± 1.30	0.10	0.99 ± 0.05	0.19
Lingual region	15–30	36	4.63 ± 1.35	0.07	4.49 ± 1.45	0.13	0.97 ± 0.08	−0.22
Retrosplenial gray matter	45–70	31	5.73 ± 1.53	0.02	(Midline)	...	...	...
Caudate nucleus	35–55	40	5.42 ± 1.30	0.00	5.65 ± 1.38	−0.12	0.96 ± 0.08	...
Thalamus	40–50	37	5.48 ± 1.47	0.00	5.58 ± 1.45	0.03	0.98 ± 0.06	−0.13
Lenticular nucleus	35–55	18	5.67 ± 1.46	−0.05	5.67 ± 1.47	−0.12	1.00 ± 0.04	0.48
Insula	40–60	39	5.91 ± 1.38	−0.02	6.03 ± 1.49	−0.04	0.99 ± 0.07	0.12
Cerebellum	0–15	27	4.22 ± 1.01	−0.03	4.35 ± 1.10	−0.04	0.98 ± 0.07	0.01
Centrum semiovale	70–90	37	2.69 ± 0.69	−0.03	2.62 ± 0.61	−0.25	1.03 ± 0.17	0.31

[a]All rates expressed as means ± SDs in mg · 100 gm^{-1} · min^{-1}.
[b]Correlation with age.
[c]Statistically significant correlation ($p < 0.05$).

$rCMR_{glc}$ = regional cerebral metabolic rate for glucose.

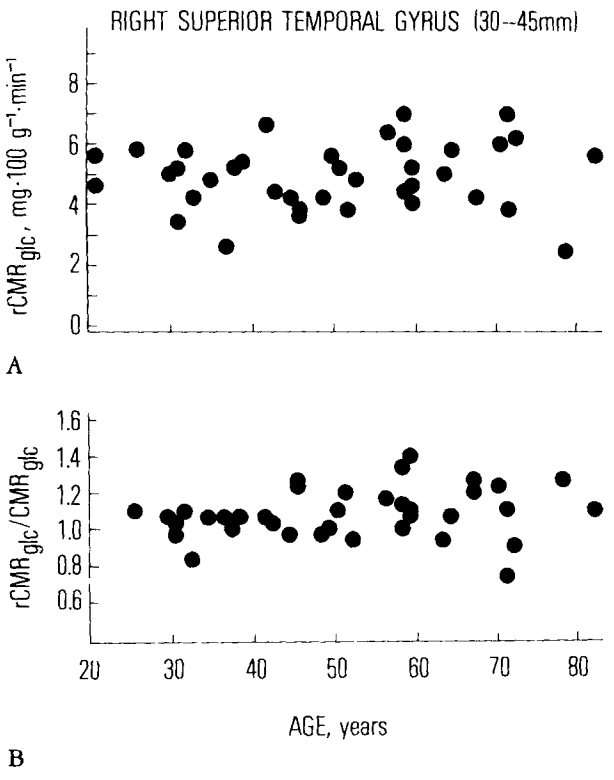

Fig 3. Relation of regional cerebral metabolic rate for glucose ($rCMR_{glc}$) *and* $rCMR_{glc}/CMR_{glc}$ *at right superior temporal gyrus to age in 40 subjects.*

gions for $rCMR_{glc}$. However, the coefficient of variation of CMR_{glc} increased significantly with age in both hemispheres. In the right hemisphere, for example, it equaled 13% in the 21- to 35-year-old group, 28.3% in the 36- to 50-year-old group, 17.1% in the 51- to 65-year-old group, and 35.3% in the 66- to 83-year-old group.

As described in Table 3, individual lobar values for $rCMR_{glc}$ demonstrated hypotemporality rather than hyperfrontality of metabolism. Kuhl and associates [33] defined hyperfrontality as the ratio of $rCMR_{glc}$ in the superior frontal gyrus to $rCMR_{glc}$ in the superior parietal gyrus, and showed that it equaled 1.17 in young adults and declined significantly with age. In the present study the identical ratio had a mean of 1.01 and did not correlate significantly with age.

Hyperfrontality of rCBF has been reported [28, 52]. If a similar hyperfrontality of $rCMR_{glc}$ existed, it would be defined from the following ratio (see Fig 2): weighted $rCMR_{glc}$ in superior frontal gyrus (80 to 100 mm) + superior frontal gyrus (60 to 80 mm) + midfrontal gyrus (65 to 90 mm) + paracentral lobule (80 to 100 mm), divided by weighted $rCMR_{glc}$ in posterior sections of the inferior parietal gyrus (45 to 70 mm) + superior temporal gyrus (30 to 45 mm) + midtemporal gyrus (15 to 30 mm). In 33 subjects this ratio equaled 1.20 ± 0.11 (SD) at the right hemisphere and 1.17 ± 0.15 at the left and did not correlate with age at either hemisphere (r = 0.15 and 0.06, respectively).

We determined all possible partial correlations (factoring out age) between each of several metabolic variables—$rCMR_{glc}$, CMR_{glc}, and $rCMR_{glc}/CMR_{glc}$—and each of the following cognitive test results: sum of WAIS Verbal Subtest scaled scores, sum of Performance Subtest scaled scores, WAIS Full Scale IQ, Verbal IQ, Performance IQ, and the error score on the Benton Revised Visual Retention Test. Of a total of 744 partial correlations that were examined, only 37 were statistically significant at the p = 0.05 level, as might be expected by chance alone (Table 6). When correlations were found, the psychological functions were not known to be associated with the specific brain regional functions.

The anxiety score during PET scanning correlated positively and significantly with cerebral metabolism in only 3 of 150 analyses but did not correlate with differences between PET and non-PET days in heart rate, systolic or diastolic blood pressure, or concentrations of 3-OHB or AcAc.

Discussion

The present study provides much stronger evidence than our previous report [18] that cerebral metabolism, measured at rest and with reduced sensory input, is age invariant in healthy men. In 40 men virtually all correlation coefficients between absolute metabolic rates and age were small and far from statistical significance. These rates included hemispheric CMR_{glc} and $(CMR_{glc})_{gray}$, lobar $rCMR_{glc}$, and $rCMR_{glc}$ in twenty-nine pairs of bilateral and in three midline brain regions. Ratios of $rCMR_{glc}$ in gray matter of the frontal lobe to $rCMR_{glc}$ in each of the other lobes, and right/left ratios for $rCMR_{glc}$ and CMR_{glc}, generally were not related significantly to age. The few exceptions, at the inferior frontal (35 to 50 mm above the IOM line) and orbitofrontal (20 to 35 mm) gyri, may reflect a real reduction in left-sided metabolism, in view of reported focal electroencephalographic slowing over the left anterior temporal area in healthy elderly subjects [42, 56].

Q values, i.e., $rCMR_{glc}/CMR_{glc}$, had coefficients of variation about half those of the absolute metabolic rates but also did not correlate significantly with age, indicating an age invariance of relative values of resting cerebral metabolism in healthy men.

Our results agree with some recent reports [13, 20, 35] but differ from those of Kuhl and associates [33], who noted that glucose utilization is reduced in gray and white matter regions and in the brain as a whole in elderly subjects, and that hyperfrontality of $rCMR_{glc}$

Table 5. Quotients (Q Values) of Regional to Overall Cerebral Metabolic Rates for Glucose, and Their Correlations with Age, at Different Regions of Interest[a]

Brain Region	Distance Above Inferior Orbitomeatal Line (mm)	No. of Subjects	Right Side		Left Side	
			$rCMR_{glc}/CMR_{glc}$	r[b]	$rCMR_{glc}/CMR_{glc}$	r[b]
Frontal lobe						
Superior frontal gyrus	80–100	37	1.21 ± 0.16	−0.11	1.18 ± 0.16	−0.16
	60–80	38	1.21 ± 0.12	0.08	1.19 ± 0.10	−0.09
	35–60	39	1.15 ± 0.11	0.16	1.15 ± 0.11	0.04
Midfrontal gyrus	65–90	37	1.25 ± 0.16	0.02	1.27 ± 0.14	−0.10
	45–65	38	1.18 ± 0.11	−0.05	1.19 ± 0.11	−0.02
Inferior frontal gyrus	50–70	33	1.24 ± 0.10	0.16	1.25 ± 0.12	0.12
	35–50	39	1.20 ± 0.11	0.27	1.21 ± 0.11	0.05
Orbitofrontal gyrus	20–35	34	1.06 ± 0.18	0.14	1.09 ± 0.16	−0.01
Cingulate gyrus	35–70	40	1.23 ± 0.10	−0.14	(Midline)	. . .
Precentral gyrus	70–100	37	1.27 ± 0.15	−0.18	1.28 ± 0.13	−0.03
	55–70	33	1.23 ± 0.16	−0.18	1.27 ± 0.12	−0.05
Paracentral lobule	80–100	36	1.28 ± 0.13	−0.17	(Midline)	. . .
Parietal lobe						
Postcentral gyrus	70–100	37	1.21 ± 0.13	0.11	1.20 ± 0.12	0.23
	55–70	33	1.15 ± 0.13	−0.02	1.18 ± 0.14	0.18
Superior parietal gyrus	70–100	37	1.16 ± 0.16	0.08	1.17 ± 0.14	0.09
Inferior parietal gyrus	45–70	40	1.12 ± 0.11	0.03	1.15 ± 0.13	0.07
Precuneus	65–80	34	1.39 ± 0.16	0.07	1.38 ± 0.15	−0.01
Temporal lobe						
Superior temporal gyrus	30–45	40	1.08 ± 0.13	0.20	1.11 ± 0.16	0.18
Inferior and middle temporal gyri	15–30	26	0.92 ± 0.15	0.31	0.96 ± 0.19	0.28
Inferior temporal gyrus	5–15	24	0.81 ± 0.14	0.07	0.80 ± 0.15	−0.25
Hippocampal region	20–35	34	0.97 ± 0.18	−0.15	0.97 ± 0.18	−0.15
Anterior-medial temporal region	20–35	12	0.83 ± 0.14	0.49	0.82 ± 0.14	−0.43
Occipital lobe						
Cuneus	45–65	37	1.34 ± 0.18	0.20	1.33 ± 0.17	0.18
Calcarine region	30–45	40	1.20 ± 0.17	0.31	1.21 ± 0.16	0.28
Lingual region	15–30	36	1.03 ± 0.22	0.07	1.06 ± 0.24	0.15
Retrosplenial gray matter	45–70	31	1.20 ± 0.15	−0.08	(Midline)	. . .
Caudate nucleus	35–55	40	1.17 ± 0.10	−0.06	1.22 ± 0.11	−0.04
Thalamus	40–50	37	1.16 ± 0.16	−0.02	1.17 ± 0.15	0.05
Lenticular nucleus	35–55	17	1.26 ± 0.15	0.47	1.26 ± 0.13	0.34
Insula	40–60	39	1.28 ± 0.13	0.02	1.30 ± 0.12	0.08
Cerebellum	0–15	27	0.94 ± 0.19	0.15	0.96 ± 0.21	0.16
Centrum semiovale	70–90	37	0.57 ± 0.13	0.02	0.57 ± 0.14	−0.12

Footnotes as in Table 4.
CMR_{glc} = cerebral metabolic rate for glucose (weighted mean for both hemispheres); $rCMR_{glc}$ = regional cerebral metabolic rate for glucose.

occurs in younger subjects but is reduced in the elderly. The different findings may relate to differences in health screening in the two studies. Inadequate screening may allow inclusion of individuals with subclinical diseases, which occur more frequently in the elderly and would tend to reduce cerebral metabolism [12, 22, 50, 57].

We chose to study an exceptionally screened population rather than a representative sample of the general population, so as to determine optimal relations between age and metabolism distinct from the influence of disease. The rigid health screening probably accounts for the positive correlation between IQ and age in our sample, because IQ by definition is age

Table 6. Statistically Significant Correlations between Psychological Test Scores and Metabolism

Psychological Test	Significantly Correlated Variable	Brain Region[a]	Partial Correlation (age excluded)
BENTON REVISED VISUAL RETENTION TEST			
Error score	$rCMR_{glc}$	L inferior frontal gyrus (50–70 mm)	−0.34
		R inferior frontal gyrus (50–70 mm)	−0.45
		R superior parietal gyrus (70–100 mm)	−0.43
	$rCMR_{glc}/CMR_{glc}$	R superior temporal gyrus (15–30 mm)	0.44
		R midtemporal gyrus (15–30 mm)	0.45
		R anterior-medial temporal region (20–35 mm)	0.36
WECHSLER ADULT INTELLIGENCE SCALE			
Verbal scale score	$rCMR_{glc}/CMR_{glc}$	L postcentral gyrus (55–70 mm)	0.44
Performance IQ		R precentral gyrus (70–100 mm)	−0.36
		L postcentral gyrus (55–70 mm)	0.39
		L superior parietal gyrus (70–100 mm)	−0.38
		R superior parietal gyrus (70–100 mm)	−0.38
Full Scale IQ		L postcentral gyrus (55–70 mm)	0.37

[a]Values in parentheses indicate distance above inferior orbitomeatal line in millimeters.

L = left; R = right; other abbreviations as in Table 5.

invariant in representative so-called normal populations [5, 63]. Factors related to higher IQ may provide a biological advantage toward health and longevity [25, 29, 51]. Careful screening also explains the statistically nonsignificant correlation between blood pressure and age in our subjects; a significant positive relation exists in the general population [59].

In an earlier report [18] we suggested that published age declines in CMR_{glc} or $rCMR_{glc}$ in subjects allowed sensory stimulation may have been due to reduced visual and auditory acuities [24, 43, 64]. Visual and auditory deprivation even in young subjects can reduce $rCMR_{glc}$ by up to 40% in many brain regions [37, 38]. However, recent studies of $CMRO_2$ with PET in subjects without explicit sensory deprivation also indicate that cerebral metabolism is age invariant [20], suggesting that differences among reports more likely reflect different health screening criteria than different sensory conditions.

Weighted CMR_{glc} in the 40 healthy men in this study equaled 4.67 mg · 100 gm^{-1} · min^{-1} at the left hemisphere and 4.60 mg · 100 gm^{-1} · min^{-1} at the right. These values are somewhat lower than those determined directly in healthy young men (6.0 mg · 100 gm^{-1} · min^{-1}) and in healthy subjects 20 to 50 years of age (5.3 mg · 100 gm^{-1} · min^{-1}), but they approximate a mean of 4.6 mg · 100 gm^{-1} · min^{-1} found in healthy elderly subjects [12, 22]. In several studies with PET and ^{18}FDG, CMR_{glc} has been reported to be between 5.4 and 5.8 mg · 100 gm^{-1} · min^{-1} [27, 37, 48]. However, Kuhl and associates [33] recently reported a mean of 4.7 mg · 100 gm^{-1} · min^{-1} in normal healthy subjects between 18 and 79 years of age, and de Leon and colleagues [13] reported a mean of 3.71 mg · 100 gm^{-1} · min^{-1} in healthy subjects of a wide age range.

The increased coefficient of variation of $rCMR_{glc}$ that we find in elderly subjects has not been reported previously, although a number of physiological variables (e.g., auditory thresholds, creatinine clearance) and psychological test scores (Benton Visual Retention Test, Raven Progressive Matrices Test) also demonstrate increased variance in the elderly (see Table 2) [24, 26, 41, 54]. This phenomenon may reflect early disease in presumably healthy subjects [11].

The bilateral symmetry of $rCMR_{glc}$ is in accord with the observed bilateral symmetry of CBF as measured under roughly comparable experimental conditions (eyes covered in a darkened room) [52], and of $rCMR_{glc}$ as measured during visual and auditory deprivation [49], although another report suggests left-greater-than-right metabolism with sensory deprivation [37]. CBF becomes asymmetrical in response to auditory stimulation, left-sided values being elevated following speech and right-sided values being elevated following indiscriminate noise [40].

The ratio of superior frontal $rCMR_{glc}$ to superior parietal $rCMR_{glc}$, defined as hyperfrontality by Kuhl and associates [33] and reported by those authors to be reduced in the elderly, is not correlated with age in our study. The lobar pattern of $rCMR_{glc}$ represents hypotemporality of cerebral metabolism rather than hyperfrontality (see Table 3), because $rCMR_{glc}$ in frontal areas is not measurably higher than that in parietal and occipital areas. Even hypotemporality may be artifactual and may arise from attenuation correction er-

rors associated with the greater thickness of skull bone surrounding the temporal lobe. $rCMR_{glc}$ in the temporal cortex of the awake rhesus monkey is not less than that in other cortical areas [30].

As pointed out by Kety [32], CMR_{glc} and CBF are rates per gram of tissue and do not distinguish between cellular and extracellular or individually active metabolic units. The constancy of cerebral metabolism with age, despite reported age reductions in neuronal number and changes in neurochemical markers in the human brain [2, 7, 10, 11, 14, 17, 32], suggests that compensatory mechanisms, perhaps related to plasticity and redundancy of neuronal networks, can maintain resting cerebral functional activity in the senescent brain [11, 45, 47].

Kety [31] noted in a single subject that CBF was markedly elevated during extreme anxiety, but later studies could not confirm a relation between CBF and anxiety [55, 58]. We do not find a significant correlation between anxiety and cerebral metabolism during PET scanning, but we have observed that anxiety is lower in the elderly, possibly because of an increased ability of older subjects to cope with novel stressful situations. One recent report does indicate that right-sided CMR_{glc} is elevated by 15% in anxious compared with less anxious subjects undergoing PET scanning [48].

Elevated blood concentrations of 3-OHB and AcAc for the group as a whole on the PET compared with the non-PET day could reflect stress-induced increases in plasma norepinephrine and epinephrine during PET scanning and mobilization of free fatty acids for ketogenesis [8, 9, 60]. Net blood concentrations of the ketone bodies in both cases are within normal limits [53], however, and not sufficiently high to replace more than 2% of glucose consumed by the brain for oxidative metabolism [23]. The reduced arterial carbon dioxide tension and elevated arterial pH in our older subjects suggest respiratory alkalosis, but measures of anxiety during PET scanning did not correlate with these laboratory findings.

Our findings of age decrements in the sum of WAIS Performance Subtest scaled scores and in the error score of the Benton Revised Visual Retention Test agree with many previous reports [1, 5, 6, 36]. Furthermore, nonsignificant correlations between cognitive scores and regional cerebral metabolic rates agree with and extend the report of Birren and colleagues [4] that significant relations are absent in healthy subjects between intelligence and global measures of cerebral metabolism. Significant relations have been reported for CBF, however, but only when patients with probable cerebral disease were included in the studies [4, 15, 61]. Thus, some cerebral disease may be necessary to reduce intellectual function and resting cerebral metabolism concurrently.

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