Intersubject Variability of Brain Glucose Metabolic Measurements in Young Normal Males

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This study evaluates intersubject variability on regional glucose metabolic values in a group of 50 healthy right-handed males between 20 and 40 yr of age. **Methods:** Brain glucose metabolism was measured using PET and 2-deoxy-2[^{18}F]fluoro-D-glucose under resting conditions and was separately assessed for subjects in their twenties (n = 34) and those in their thirties (n = 16). **Results:** Regional brain metabolic values showed significant intersubject variability with coefficients of variation (CV) that ranged between 11.1% to 15.2% (twenties) and 7.2% to 12.6% (thirties). Relative measures (regional/global) were less variable than absolute measures and the CV ranged between 4.1% to 8.3% (twenties) and 3.9% to 10% (thirties). Whereas global brain metabolic rate for subjects in their twenties was not significantly different from that of subjects in their thirties, the metabolic rate in left frontal regions was significantly lower in the older subjects. **Conclusion:** The correlations between age and absolute and relative metabolism in the left frontal region were $r = 0.438$, $p < 0.002$ and $r = 0.447$, $p < 0.001$, respectively. This study shows significant intersubject variability for regional brain metabolic values in normal controls and documents age-related decreases in frontal metabolism that occur even in relatively young adults.

Key Words: cerebral glucose metabolism; intersubject viability; PET

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The assessment of cerebral glucose metabolism with PET using the glucose analogue 2-deoxy-2[^{18}F]fluoro-D-glucose (^{18}FDG) has been shown to be an indicator of regional neuronal function in the brain. Fluorine-18-FDG PET has been used to evaluate changes in neuronal function due to neurological, psychiatric and oncological disorders. Studies have also been done to assess the effect of cognitive, perceptual and motor tasks and pharmacological challenges on ^{18}FDG PET (*1,2*).

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The increasing utilization of PET and ^{18}FDG to assess normal brain function and its disruption in neuropsychiatric disorders brings us to evaluate normal variability of these measurements within a homogenous group of subjects. Studies evaluating intrasubject variation for test-retest measures of brain glucose metabolism without interventions report less than 10% variation for absolute measures (*3–6*) and less than 1% for normalized values (relative measures).

In contrast to the low intrasubject variability, previous studies have consistently reported large intersubject variability for absolute and relative measures of glucose metabolic rate in normal subjects at rest (*4–7*). Some of this variability may be accounted for by handedness (*8,9*), gender (*8,10–12*), mental status of the subject during the scan (*13*), brain volume and cortical atrophy (*11,14*) and age (*15*). Of special interest has been the documentation of age-related changes in brain metabolism. The data from different laboratories is conflicting and complicated by small sample sizes and the use of scanners with different spatial resolutions (*15–20*). Most studies document age-related changes that are most prominent after 50 yr of age and predominantly localized in frontal cortical areas (*21,22*). However, the effects of age on young adults has not been evaluated.

The purpose of this study is to assess intersubject variability in a group of healthy right-handed male subjects with similar socioeconomical and educational backgrounds between 20 and 40 yr of age, and to assess the effects of age on brain glucose metabolism within this age range. This study also reviewed metabolic values in normal controls reported by various PET centers (Table 1) to assess the intersubject and intercenter range of variability. The results from the current study were compared with those reviewed.

MATERIALS AND METHODS

Subjects

Fifty right-handed, healthy male subjects were recruited for the study. Thirty-four subjects were in their twenties (20–29 yr) and sixteen subjects were in their thirties (30–39 yr). These subjects

TABLE 1
Summary of Brain Metabolic Values Reported by Representative Investigators of the Various PET Centers

Year	PET center	Age range (yr)	Age mean	No. of subjects	PET scanner	Resol	Plane	Scan time (min)	Eyes	Ears	sti	ROI	μmole/100g/min	CV	Ref
1979	U Penn	24–26	25.0 ± 1.4	2M	Mark IV	17	4	?	+	–	–	8	32.2 ± 4.3	13.28	64
1985	U Penn	19–30	?	6M	PETT V	16.5	14	30–70	+	–	–	2	31.5 ± 2.1	6.54	27
1987	U Penn	?	27.1 ± 8.6	8M	PETT V	16.5	14	40–70	+	–	–	?	21.3 ± 3.3	15.63	3
1987	U Penn	18–39	23.9 ± 4.8	14M	PETT V	16.5	14	40–70	+	–	–	1	20.2 ± 3.8	18.63	13
1988	U Penn	18–30	?	8M	PETT V	16.5	14	45–65	+	–	–	14	31.1 ± 5.5	17.54	65
1988	U Penn	?	25.7 ± 6.2	17M, 1F	PETT V	16.5	14	40–70	+	–	–	40	21.5 ± 3.9	17.77	66
1989	U Penn	27–73	57.0 ± ?	12M	PETT V	16.5	14	40–70	+	–	–	1	26.9 ± 4.0	15.04	67
1991	U Penn	20–31	?	7M	PETT V	16.5	14	40–70	–	–	–	1	34.3 ± 5.2	15.26	68
1980	UCLA	?	?	13M/F	ORTEC ECAT II	16	1	70–90	+	–	–	5	40.9 ± 7.4	18.09	50
1980	UCLA	21–35	23.0 ± ?	8M	ORTEC ECAT II	16	6	40–82	+	–	–	5	37.5 ± 4.5	12.10	69
1982	UCLA	18–78	?	17M, 23F	ORTEC ECAT II	16	6	40–82	+	–	–	6	26.1 ± 6.1	23.37	16
1981	UCLA	21–27	?	7M/F	ORTEC ECAT II	16	6	40–82	–	–	–	5	37.0 ± 8.5	23.01	70
1983	UCLA	?	?	16M/F	ORTEC ECAT II	16	7	40–140	+	–	–	7	24.0 ± 5.6	23.46	71
1983	UCLA	18–32	24.8 ± 6.4	4M	CTI NeuroECAT	11	12	40–60	–	–	–	50	29.6 ± 6.6	22.18	32
1983	UCLA	53–68	60.5 ± 6.5	4M/F	CTI NeuroECAT	11	12	40–60	–	–	–	50	29.4 ± 1.5	5.07	32
1987	UCLA	?	?	7M	CTI NeuroECAT	11	12	40–60	+	–	–	?	23.2 ± 2.1	9.18	11
1987	UCLA	?	?	7F	CTI NeuroECAT	11	12	40–60	+	–	–	?	28.0 ± 4.3	15.40	11
1988	UCLA	23–66	39.8 ± 12.3	5M, 5F	CTI NeuroECAT	11	12	40–60	–	–	–	?	26.6 ± 6.8	25.46	72
1984	UC Irvine	?	31.1 ± 10.5	13M, 6F	ORTEC ECAT II	17	7	50–70	–	–	+	24	24.4 ± 7.5	30.74	73
1990	UC Irvine	?	26.2 ± 8.1	14M, 4F	CTI NeuroECAT	8	9	45–100	+	–	+	24	21.6 ± 5.5	25.46	74
1986	U Michigan	25–65	37.0 ± 3.0	14M/F	TCC PC4600A	11	20	30–75	–	–	–	1	38.8 ± 9.8	25.35	75
1988	U Michigan	46–71	60.0 ± 8.0	13M, 8F	TCC PC4600A	11	20	30–75	–	–	–	96	33.2 ± 5.2	15.46	76
1988	U Michigan	?	49.0 ± 13.0	14M, 16F	TCC PC4600A	11	20	30–75	–	–	–	5	31.5 ± 5.7	18.06	77
1988	U Michigan	18–58	36.0 ± 12.0	10M, 14F	TCC PC4600A	11	20	30–75	–	–	–	80	32.1 ± 5.7	17.76	51
1990	U Michigan	22–53	36.0 ± ?	5M, 7F	TCC PC4600A	11	20	30–75	–	–	–	?	34.1 ± 7.5	21.99	78
1990	U Michigan	25–46	36.0 ± ?	4M, 6F	CTI NeuroECAT	11	12	40–60	+	–	–	72	23.8 ± 3.3	13.79	79
1988	U Louvain	?	?	5M	CTI ECAT III	15	6	30–90	–	–	+	6	43.5 ± 4.2	9.66	80
1989	U Louvain	?	66.2 ± 8.1	21M	ORTEC ECAT II	17	7	45–140	–	+	–	59	25.6 ± 7.0	27.51	81
1990	U Louvain	21–24	?	13M	CTI ECAT III	15	1	30–40	–	+	–	1	47.9 ± 10.8	22.55	82
1990	U Louvain	?	55.6 ± 14.5	16M/F	CTI ECAT III	15	1	30–40	–	–	–	1	50.5 ± 6.1	12.08	38
1990	U Louvain	?	25.6 ± 7.7	39M/F	CTI ECAT III	15	1	30–40	–	–	–	1	51.2 ± 7.6	14.84	39
1990	U Liege	22–30	25.1 ± 3.1	9M	CTI NeuroECAT	11	9	45–100	–	–	–	89	29.5 ± 3.9	13.08	6
1991	U Liege	?	25.8 ± 4.3	14M/F	CTI NeuroECAT	11	12	45–100	–	–	–	89	30.3 ± 8.2	27.21	21
1991	U Liege	?	60.1 ± 3.4	11M/F	CTI NeuroECAT	11	12	45–100	–	–	–	89	26.8 ± 7.6	28.57	21
1990	U Chicago	19–31	?	9M	PETT VI	12	7	45–60	?	?	?	?	36.0 ± 3.0	8.33	83
1991	U Chicago	21–29	24.5 ± ?	8M	PETT VI	12	7	45–60	+	–	+	14	45.1 ± 3.3	7.39	84
1983	NIA	21–33	27.5 ± ?	10M	ORTEC ECAT II	17	7	45–140	–	+	–	23	26.7 ± 1.3	4.90	33
1983	NIA	45–55	49.1 ± ?	8M	ORTEC ECAT II	17	7	45–140	–	+	–	23	22.7 ± 1.8	7.93	33
1983	NIA	21–83	50.8 ± 4.0	21M	ORTEC ECAT II	17	7	45–140	–	+	–	61	29.9 ± 8.6	28.70	16
1984	NIA	21–83	50.0 ± 17.0	40M	ORTEC ECAT II	17	7	45–140	–	+	–	61	28.9 ± 6.6	22.84	15
1985	NIA	45–83	63.4 ± ?	26M	ORTEC ECAT II	17	7	45–140	–	+	–	61	25.0 ± 6.4	25.26	85
1987	NIA	45–83	66.0 ± 8.1	21M	ORTEC ECAT II	17	7	45–140	–	+	–	61	25.6 ± 7.0	27.51	34
1988	NIA	18–39	27.0 ± 6.6	14M	ORTEC ECAT II	17	7	45–140	–	–	–	61	28.5 ± 3.3	11.69	86
1990	NIA	20–35	?	22M, 2F	ORTEC ECAT II	17	7	45–140	–	+	–	61	33.0 ± 5.6	16.80	87

1987	NIA	21–83	?	49M	ORTEC ECAT II	17	7	45–140	–	+	–	18	26.4 ± 6.0	22.57	88
1990	NIA	21–38	28.5 ± 4.9	17M	Scandi PC1024-7B	6	14	45–65	–	+	–	201	36.8 ± 5.8	15.88	12
1990	NIA	21–38	28.7 ± 5.5	15F	Scandi PC1024-7B	6	14	45–65	–	+	–	201	37.0 ± 5.9	13.13	12
1990	NIA	22–38	29.5 ± 4.5	9M, 4F	Scandi PC1024-7B	6	14	45–65	–	+	–	201	47.7 ± 6.5	13.62	89
1991	NIA	55–90	68.0 ± 10.0	12M, 18F	Scandi PC1024-7B	6	14	45–65	–	+	–	201	34.0 ± 4.4	13.02	90
1992	NIA	21–38	28.9 ± 5.1	18M	Scandi PC1024-7B	6	14	45–55	–	+	–	65	36.1 ± 6.0	16.64	43
1992	NIA	21–38	28.7 ± 5.5	15F	Scandi PC1024-7B	6	14	45–55	–	+	–	65	36.9 ± 4.9	13.33	43
1984	NINCDS	52–66	59.0 ± 1.7	4M, 4F	ORTEC ECAT II	17	7	30–125	–	+	–	63	41.1 ± 2.7	6.49	91
1989	NIMH	?	32.9 ± 12.2	15M, 12F	ORTEC ECAT II	17	7	35–130	–	–	–	60	39.1 ± 8.3	21.23	92
1989	NIMH	?	35.5 ± 11.3	18M, 12F	Scandi PC1024-7B	6	28	45–75	–	–	+	60	53.8 ± 7.9	14.67	93
1990	NIMH	?	33.3 ± 9.8	16M, 14F	Scandi PC1024-7B	6	28	45–75	–	–	+	60	55.6 ± 6.9	12.39	94
1989	NIMH	21–42	31.7 ± 6.6	9M, 9F	Scandi PC1024-7B	6	14	45–65	–	–	–	201	35.9 ± 5.0	13.85	95
1991	NIMH	21–43	32.8 ± 7.0	20F	Scandi PC1024-7B	8	3	40–55	+	–	–	?	34.6 ± 5.2	15.01	96
1990	NIMH	?	36.3 ± 11.7	28M, 22F	Scandi PC1024-7B	6	28	45–75	–	–	+	60	53.8 ± 9.2	17.06	97
1984	Max-Planck	28–38	?	7M	Scandi PC 384	8	7	35–40	–	–	–	10	38.1 ± 3.0	20.70	7
1985	Max-Planck	28–38	?	7M/F	Scandi PC 384	8	7	35–40	–	–	–	28	37.5 ± 5.3	14.13	98
1991	Max-Planck	?	62.5 ± 7.4	6M, 3F	Scandi PC 384	8	14	30–50	+	–	–	?	31.7 ± 4.3	13.69	99
1984	NYU/BNL	?	26.1 ± 5.1	15M/F	PETT III	17	1	30–50	–	–	–	12	20.0 ± 3.2	15.80	18
1984	NYU/BNL	?	66.6 ± 7.6	22M/F	PETT III	17	1	30–50	–	–	–	12	20.5 ± 3.1	15.20	18
1985	NYU/BNL	?	27.0 ± 4.0	8M	PETT VI	12	7	35–52	+	+	–	1	33.3 ± 1.0	3.00	100
1991	BNL	23–59	32.0 ± 12.0	17M	PETT VI	9	7	35–43	+	–	–	1	29.5 ± 3.3	11.11	101
1992	BNL	23–59	32.0 ± 10.0	18M	CTI 931	6	15	35–55	+	–	–	1	38.4 ± 3.0	7.81	102
1986	McGill U	?	63.0 ± 6.0	7M/F	Therascan 3128	19	3	40–45	+	–	–	98	43.3 ± 9.0	20.78	35
1988	McGill U	18–32	25.0 ± ?	10M, 10F	Therascan 3128	12	12	40–96	+	–	–	30	45.4 ± 7.7	16.96	5
1989	McGill U	31–44	38.0 ± 6.2	4M	Therascan 3128	19	3	40–45	+	–	–	82	29.0 ± 2.0	6.90	103
1989	McMaster U	22–38	27.6 ± 4.8	10M	single ring	8	16	45–75	–	–	–	108	31.0 ± 6.9	22.27	104
1986	RI-B&BV/Akita	26–35	?	7M	Headtome III	9.8	5	60–70	?	?	?	24	36.3 ± 3.0	8.26	105
1987	Mt Sinai/Miami	61–80	71.6 ± ?	4M, 5F	PETT V	15	7	30–60	–	–	–	59	36.0 ± 8.5	23.64	106
1989	Mt Sinai/Miami	?	70.3 ± 6.1	36M/F	PETT V	15	7	30–50	–	–	–	67	37.1 ± 8.2	22.06	36
1989	Mt Sinai/Miami	28–73	50.8 ± 21.0	6M, 2F	PETT V	15	7	30–50	–	–	–	35	38.2 ± 4.4	11.43	9
1989	Mt Sinai/Miami	23–69	40.0 ± 20.1	4M, 4F	PETT V	15	7	30–50	–	–	–	35	45.9 ± 16.9	26.04	9
1991	Mt Sinai/Miami	?	30.5 ± 8.5	15M	PETT V	15	7	30–60	–	–	–	67	38.2 ± 11.5	30.00	37
1987	Sloan-Kettering	?	27.0 ± 5.0	12M, 6F	Positron PC4600	10	5	45–55	–	+	–	24	35.5 ± 4.4	11.58	107
1988	Hammersmith H	23–53	34.0 ± 10.5	5M, 2F	ORTEC ECAT II	16	1	45–55	–	–	–	2	27.4 ± 2.4	8.76	108
1988	Tohoku U	52–71	62.0 ± 6.0	4M, 3F	ORTEC ECAT II	16	3	40–70	–	–	–	18	28.2 ± 5.5	19.23	109
1989	LBL/UC Berkeley	?	63.0 ± 3.0	2M, 5F	Donner 280	8	3	40–55	+	–	–	?	34.6 ± 5.2	15.01	110
1991	LBL/UC Davis	62–80	69.4 ± 7.7	7M/F	PET600	2.6	1	35–50	+	–	–	1	68.0 ± 5.6	8.24	111
1989	NRC/Julich	?	?	11M/F	PC4069	5	?	?	?	?	?	?	55.5 ± 12.2	21.98	112
1990	Hopital d'Orsay	?	38.0 ± 11	6M, 4F	LETI TTV01	13	7	?	–	–	–	70	35.0 ± 7.0	20.28	113
1990	Johns Hopkins U	?	43.0 ± 17	6M/F	CTI NeuroECAT	8	12	45–60	+	–	–	70	53.0 ± 15.3	28.87	114
1991	Johns Hopkins U	?	26.7 ± ?	12M	CTI NeuroECAT	8	12	45–60	–	+	–	24	48.2 ± 6.4	13.27	115
1992	Johns Hopkins U	22–40	?	12M	CTI NeuroECAT	8	12	45–60	+	–	?	24	47.0 ± 3.3	13.80	54
1991	Case Western U	18–40	?	4M/F	Scandi SP3000	?	7	?	+	–	–	?	28.9 ± 6.0	20.75	116

? = data not provided; M/F = gender not indicated; resol = spatial resolution (mm); plane = number of axial slices obtained; eyes + = eyes open; eyes – = eyes closed; ears + = ears plugged; ears – = ears unplugged; sti + = with stimulation; sti – = without stimulation; ROI = number of ROIs taken to obtain global metabolic value; μmole/100g/min = mean values for global cerebral glucose metabolic rate; CV = coefficient of variation of global metabolic rate (s.d./mean value); and Ref = reference.

This table presents only PET studies reported with mean values for global metabolic rate. Most of the studies in this table use the model of Sokoloff and associates' (Sokoloff et al. 1977; Phelps et al. 1979; Huang et al. 1980).

were students and/or employees of our institutions and had received at least 12 yr of education. Each subject received a complete physical, neurological and psychiatric examinations and a series of laboratory tests (hematological profile, blood chemistry, urinalysis and urine toxicology) as part of their evaluation. Subjects with a history of neurological, psychiatric, metabolic, endocrinologic disease, alcoholism, drug abuse or head injury were excluded from the investigation. Subjects were asked if they were right- or left-handed; only right-handed individuals were included. Any over-the-counter medications were discontinued in all subjects at least 7 days prior to the PET study. The studies of younger and older subjects were performed interleaved over a 3-yr period.

Consent was obtained from each participant after the nature of experiment was fully explained. The informed consent forms and protocols were previously approved by the Committee for the Protection of Human Subjects of New York University, the Institutional Review Boards of Northport Veterans Administration Medical Center and Human Subjects Research Committee of Brookhaven National Laboratory, New York.

PET Scanning

Subjects were asked to refrain from smoking, eating or drinking coffee for at least 4 hr prior to the study. The subjects were placed in the scanner with their eyes open and their ears unplugged in a dimly lit room with minimal noise. Two intravenous lines were inserted and maintained with saline and heparin. Arterialization was achieved by warming the hand to 48°C using a heating box designed for this purpose. Arterialized blood was obtained from a catheter placed in a dorsal vein. The other catheter was in the antecubital region of the opposite arm for tracer injection.

For each study, the subjects were injected with 5–6 mCi of 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}FDG). Synthesis of ^{18}FDG was achieved as described by Hamacher et al. (*23*). The amount of labeled mannose of the final product was < 2% (purity > 98%).

PET was performed using a Computer Technology Incorporated (Knoxville, TN) model 931 tomography system (6 × 6 mm in plane resolution FWHM) which provides 15 contiguous axial planes of 6.5 mm each. An individualized headholder was used to position the subjects with the aid of two orthogonal laser beams. The gantry was placed parallel to the canthomeatal line. After recording a 5-min blank scan and a 5-min transmission scan for photon attenuation correction, a 20-min emission scan was obtained beginning 35 min after injection of ^{18}FDG. Arterialized venous blood samples were obtained to measure plasma radioactivity and plasma glucose concentration. Metabolic images were computed using an extension of Sokoloff and associate's model (*24–26*). The operational equation, lumped constant (L.C. = 0.52) and rate constants (k1 = 0.095, k2 = 0.125, k3 = 0.069, k4 = 0.0055) were as described previously (*27*).

Image Analysis

Images were analyzed using a template of 115 nonoverlapping regions of interest (ROIs) as described previously (*28*). To minimize errors in the metabolic values due to partial volume effects, small ROIs (average: 0.7 cm^3 for cortical structures and 1.2 cm^3 for the basal ganglia, paracentral lobules, hippocampal gyrus, orbital-frontal gyri and cerebellum) were used. The absolute size and orientation of the ROI for a given brain structure were held constant for all the subjects. Placement of regions was determined by reference to an atlas of human axial tomography (*29*). The 115 ROIs were grouped into 13 composite cortical, subcortical and cerebellar regions which represented the average of ROIs from different plains corresponding to the same anatomical structure.

TABLE 2
Coefficient of Variation of Absolute and Relative Metabolic Rates in Subjects in Their Twenties and Thirties

Region	Absolute values		Relative values	
	20s	30s	20s	30s
Right frontal cortex	13.31	9.23	4.64	4.39
Left frontal cortex	13.04	9.32	4.15	4.28
Orbitofrontal gyri	13.42	12.61	5.32	8.84
Cingulate gyri	13.67	10.08	5.23	5.67
Right parietal cortex	13.29	10.36	6.43	5.18
Left parietal cortex	13.20	8.83	4.99	4.14
Right temporal cortex	11.09	7.22	4.54	3.98
Left temporal cortex	11.15	7.71	5.01	5.36
Right occipital cortex	14.23	9.58	7.20	5.73
Left occipital cortex	15.22	8.40	7.56	5.54
Thalamus	12.52	11.18	6.29	10.01
Basal ganglia	11.15	10.10	5.89	6.77
Cerebellum	12.09	9.46	8.31	6.86

In addition, a measure of whole-brain glucose metabolism was obtained by averaging the values from the pixels located in the brain tissue component of the brain images. The outer boundary of the brain which separates cortex from cerebrospinal fluid was computed using threshold methodology. All of the pixels within this outer boundary including gray matter, white matter and ventricles for the 15 slices were averaged.

Absolute metabolic rates and relative metabolic rates (the regional absolute rate divided by the whole-brain metabolic rate) of the age groups were evaluated with the Student's t-test. The relationship between age and regional brain glucose metabolism was assessed using Pearson product moment correlation analysis. We used the Bonferroni correction as cited by Haiz (*30*) to correct for multiple comparisons. Bonferroni corrections were calculated for 13 composite brain regions and a separate correction was made for the absolute and relative measures. This set the level of significance to $p < 0.004$.

RESULTS

Fluorine-18-FDG-PET measures of absolute whole-brain glucose metabolic rates in the 20–29-yr-old subjects (n = 34) ranged between 31.7 and 53.5 μmole/100g/min (mean 39.5 ± 4.7 μmole/100g/min, CV 12.0%) and in the 30–39-yr-old subjects (n = 16) it ranged between 30.5 and 40.4 μmole/100g/min (mean 35.9 ± 2.9 μmole/100g/min, CV 8.0%). This measure did not differ significantly between the subjects in the two age groups. Regional absolute measures were more variable than the global measures with CV ranging from 11.1% to 15.2% in subjects in their twenties and 7.2% to 12.6% for subjects in their thirties (Table 2). Relative measures of regional metabolic values were less variable than absolute measures with CV ranging from 4.1% to 8.3% in subjects in their twenties and 3.9% to 10% in those in their thirties.

Comparison of ^{18}FDG-PET measures of regional absolute glucose metabolic rates between these groups revealed significant age-related differences in right and left frontal, orbitofrontal, cingulate, right and left temporal, right oc-

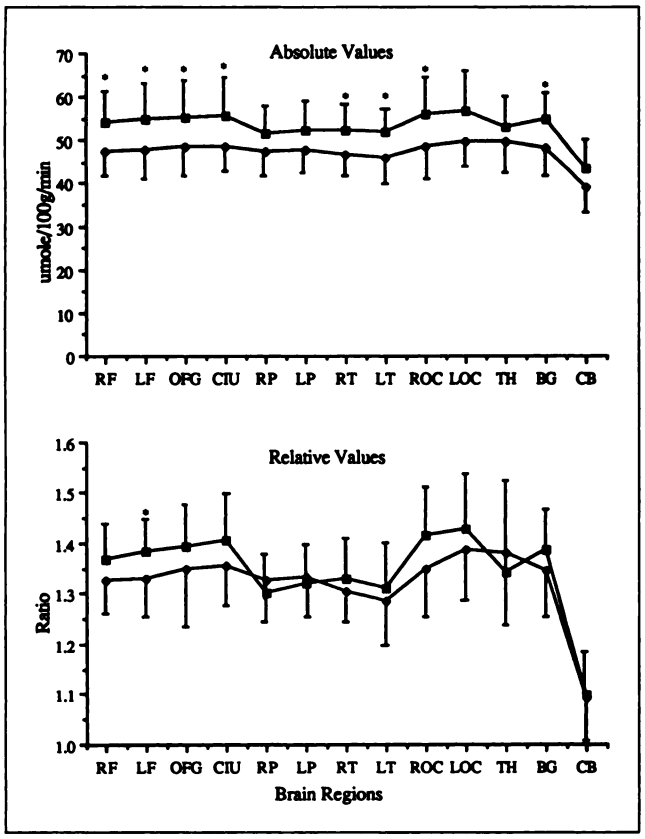

FIGURE 1. Absolute and relative glucose metabolic rates in brain regions of the 20–29-yr-old (□) and 30–39-yr-old (○) groups. Regions with significantly decreased metabolic rate were identified with * ($p < 0.004$). RF = right frontal cortex; LF = left frontal cortex; OFG = orbitofrontal gyri; CIU = cingulate gyrus; RP = right parietal cortex; LP = left parietal cortex; RT = right temporal cortex; LT = left temporal cortex; ROC = right occipital cortex; LOC = left occipital cortex; TH = thalamus; BG = basal ganglia; and CB = cerebellum.

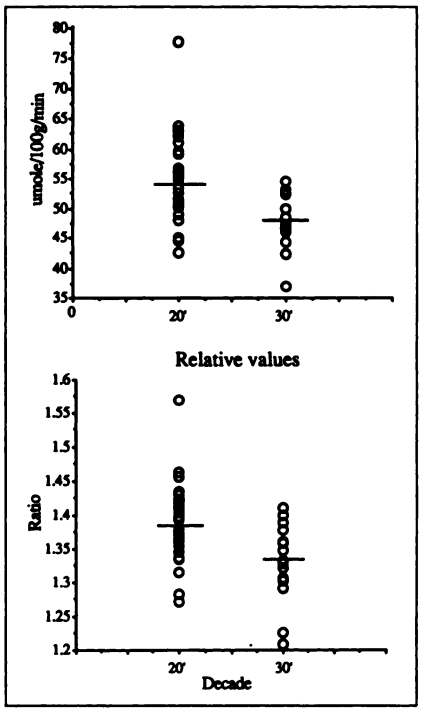

FIGURE 2. Distribution of left frontal metabolic rates of each subject in two decades. There was considerable overlapping between both groups. Transverse bars (—) represent mean values of the metabolic rates.

cipital region and basal ganglia values. These measures were significantly lower in 30–39-yr-old subjects as compared with the same measures in 20–29-yr-old subjects (Fig. 1). Comparison of relative glucose metabolic rate measurements indicated lower relative glucose metabolic rates only in left frontal regions in 30–39-yr-old subjects, compared with 20–29-yr-old subjects ($p \leq 0.003$).

Figure 2 shows the individual absolute and relative metabolic values for left frontal regions in both groups. Although the differences were significant, there was considerable overlap between groups. Correlation between age and absolute and relative metabolic rates of brain regions demonstrated a significant correlation of age and regional metabolic rates in left frontal regions (Table 3). To determine which of the left frontal regions was most affected by age, we obtained separate correlations for superior, middle and inferior frontal regions. Glucose metabolic rates in the left superior region showed the most age-related variability among the left frontal regions studied (absolute: $r = 0.438$, $p \leq 0.002$; relative: $r = 0.447$, $p \leq 0.001$) as shown in Figure 3.

DISCUSSION

This study documents wide intersubject variability for global and regional brain metabolic values (values ranging from 31.7 to 53.5 μmole/100g/min in subjects in their twenties and 30.5 to 40.4 μmole/100g/min in subjects in their thirties). Similar intersubject variability has been noticed by many investigators. The range of the variability in regional brain metabolic values reported by various PET centers can be seen from the data in Table 1. This table only includes those studies for which global absolute metabolic rates were reported. By inspecting this table, one also detects a wide range for values of whole-brain metabolic rates across different PET centers which range from

TABLE 3
Correlations Between Age and Absolute and Relative Metabolic Rates

Region	Absolute values		Relative values	
	r	p	r	p
Right frontal cortex	0.347	ns	0.291	ns
Left frontal cortex	0.397	0.004	0.464	0.0007
Orbitofrontal gyri	0.363	ns	0.286	ns
Cingulate gyri	0.353	ns	0.299	ns
Right parietal cortex	0.178	ns	0.178	ns
Left parietal cortex	0.202	ns	0.179	ns
Right temporal cortex	0.378	ns	0.212	ns
Left temporal cortex	0.378	ns	0.212	ns
Right occipital cortex	0.390	ns	0.329	ns
Left occipital cortex	0.313	ns	0.168	ns
Thalamus	0.163	ns	0.199	ns
Basal ganglia	0.348	ns	0.138	ns
Cerebellum	0.227	ns	0.077	ns

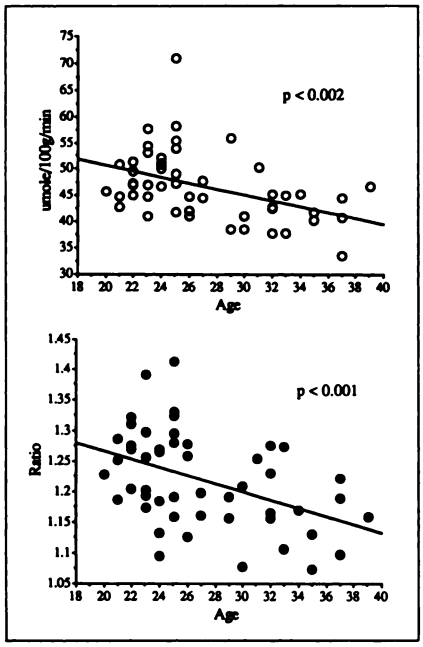

FIGURE 3. Glucose metabolic rates of left superior frontal regions versus age. There were significantly decreased absolute and relative metabolic rates with increments of age (yr).

20 to 68 μmole/100g/min. We have reported the frequency (number of articles) at which different global metabolic rates are reported (Fig. 4). The most frequently reported values are between 25 and 40 μmole/100g/min.

Variable Factors

From an inspection of Table 1, one can see that certain factors can be identified which appear to contribute to the wide variability in metabolic values.

Spatial Resolution of PET. The PET center reporting the highest metabolic values (Lawrence Berkeley Laboratory) is the one that has the PET camera with the best spatial resolution (FWHM = 2.6 mm). Analysis of values within a given center performed with cameras with different spatial resolutions also shows that their values obtained with the PET cameras with the best spatial resolution are always higher.

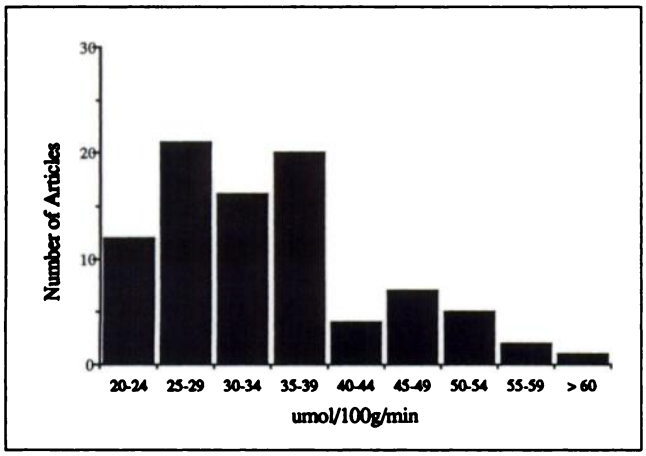

FIGURE 4. Distribution of mean absolute global metabolism reported in the articles indicated in Table 1.

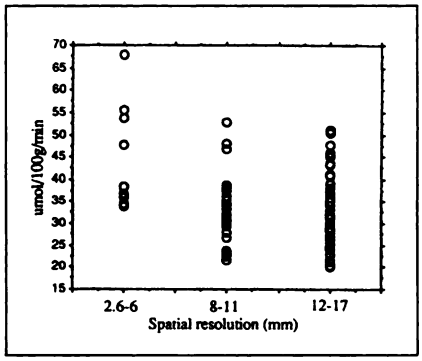

FIGURE 5. Distribution of mean global metabolic rates from Table 1 as a function of the spatial resolution of the PET instrument utilized.

In fact, a study from the National Institute on Aging (*31*) evaluated difference in regional metabolic values for seven subjects tested on two different cameras with different spatial resolutions and reported higher global metabolic values when studying the subjects with the higher resolution instrument (PC1024-7B: FWHM = 6 mm, 46.4 ± 5.9 μmole/100g/min) than with the lower resolution instrument (ECAT II: FWHM = 17 mm, 30.0 ± 4.4 μmole/100g/min). In Figure 5, we have shown the mean metabolic values reported for the various studies in Table 1 as a function of the spatial resolution of the PET scanner. This figure shows that studies reporting mean global values of less than 30 μmole/100g/min were done with scanners having 8–17 mm resolution. Whereas studies reporting on values higher than 54 μmole/100g/min were done with scanners having a 2.6–6 mm resolution.

Age. The effects of aging on brain glucose metabolism have been studied by several investigators. These studies have failed to show an effect of aging on whole-brain metabolism (Table 1). In general, studies from the same PET center reporting on groups of subjects of different ages scanned on the same instrument do not show differences in global measures {notice the values from the following paired studies: Hawkins et al. 1983 (*32*); Schwartz et al. 1983 (*33*) versus Horwitz et al. 1987 (*34*); de Leon et al. 1984 (*18*); Evans et al. 1986 (*35*) versus Tyler et al. 1988 (*5*); Duara et al. 1989 (*36*) versus Pascal et al. 1991 (*37*); and De Volder et al. 1990 (*38,39*)}. In contrast, studies have reported a decline in frontal metabolism with age (*21,22*). Our data are consistent with these findings and, in addition, showed that such changes are detected in relatively young adults. It is also consistent with brain morphological studies using MRI (*40*), which documents age-related decreases in cortical volume in young adults. Unfortunately no MR images were obtained for the subjects in this investigation which precluded the evaluation of the relation between possible age-related changes in morphology and changes in metabolism. The functional significance of the changes in left frontal metabolism with age needs to be further evaluated. In particular, since neuropsychological studies have shown a decline in certain cognitive abilities (e.g., delayed recall memory) in subjects in their thirties (*41,42*). Despite the significant differences in left frontal metabolism between the two groups, most of the 30-yr-old

subjects had values which overlapped with those of the 20-yr-olds (Fig. 2). This overlap suggests biological variability in the rate at which age-related changes affect regional brain metabolic activity. Factors contributing to the rate of decline in frontal metabolism with aging probably relate to both genetic and environmental factors.

Gender. PET studies of gender effects on brain glucose metabolism have been controversial. While two studies showed higher metabolism in women than in men (*10,11*), other studies have found no gender differences in brain metabolism (*12,43*). Human studies have also shown higher cerebral blood flow rates in females than in males (*8,44,45*). The relevance of hormones on brain glucose metabolism is demonstrated by autoradiographic studies which show that administration of high doses of estrogen increase brain glucose metabolism in ovariectomized adult rats (*46*) and by studies reporting variation of brain metabolic rates throughout the menstrual cycle with highest rates occurring during proestrus and metestrus (*47*).

Study Conditions. The conditions at which the studies are performed have been shown to affect whole-brain metabolic rates. For example, cerebral glucose metabolism is lower when subjects are scanned with eyes closed and ears plugged (21.8 ± 5.7 μmole/100g/min) than when they are scanned with only eyes closed (38.3 ± 8.5 μmole/100g/min) or ears plugged (26.1 ± 4.1 μmole/100g/min) (*48*). Unfortunately, it is difficult to determine from the latter study the extent to which the variability reflects the conditions of the scan, since the measures were done in different individuals.

Timing of ^{18}FDG Scans. As long as the constraints imposed by Sokoloff's model are met, the timing of data acquisition should not affect the metabolic values within 60 min. This factor was recently evaluated in a study which measured metabolic values when scans were performed at different times after tracer administration. The study showed no differences in metabolism in scans done between 30 and 40 min and those between 45 and 55 min (*49*). However, after 60 min, dephosphorylation of deoxyglucose-6-phosphate becomes significant and correction for k4 is required (*50,26*).

Lumped Constant. Unfortunately, for most studies the value of the lumped constant utilized was not reported. The lumped constant probably explains part of the variability in metabolic values across the different PET centers. The values typically used for the lumped constant are either 0.42 (*26*) or 0.52 (*51*). This alone can result in a difference of approximately 25% in calculated glucose metabolism. Furthermore, differences in lumped constant values with aging have been demonstrated in animal studies (*52*) and could confound the comparison across subjects of different ages.

Whole-Brain Metabolic Rate Calculation. The method of determining the whole-brain metabolic rate also differs among centers. Some report average values obtained from gray matter ROIs, others average gray and white matter ROIs, while some groups average over all brain slices, and therefore also include cerebrospinal fluid space (Table 1).

Mental State of the Subjects. It has been demonstrated that the level of anxiety during the PET procedure can affect the cerebral blood flow and metabolic value (*13*). The extent to which other mental states such as sadness, happiness and restlessness can affect metabolism needs to be investigated.

Miscellaneous. There are several other sources of potential intercenter variability:

1. Measured versus calculated attenuation correction: The measured attenuation correction for each subject may increase error during repositioning. The calculated attenuation correction adds a systematic over- or underestimation factor to the value of the imaged parameter in each PET slice due to variation of head size and positioning (*53*).
2. Method of obtaining the blood time-activity curve: The use of an arterial catheter tends to provide more reliable blood sampling in comparison to the use of arterialized venous blood, especially if the method is not carefully implemented. However, it has been shown that arterialized venous blood curves give as accurate a representation of the glucose metabolic rate as the rate determined with a true arterial sample (*54*).
3. Method of defining ROIs: The selection of a ROI can affect measures as a function of the following variables: (1) selection of ROI on PET images as opposed to MR images (*55*); (2) use of geometric versus irregular ROIs (*56*); (3) size of the ROIs (*56*); (4) use of a template versus individual tailored ROIs; (5) use of single versus multiple slices to define a given ROI.
4. Use of caffeine and nicotine: Animal studies, as well as human imaging studies, have demonstrated that caffeine and nicotine change cerebral blood flow and brain glucose metabolism (*57–59*). The effect of withdrawal from these substances prior to the study in a heavy user could bring metabolic changes (*60,61*). At Brookhaven National Laboratory, subjects are instructed to abstain from using these substances for at least 4 hr prior to the PET scan. However, instructions to volunteers differ among centers and could account for some of the variability.
5. Time of day when studies are performed: The influences of circadian rhythms on glucose metabolic rate have been reported (*4*).

Biological Variability Among Individuals

Even though several factors have been identified that contribute to variability, an important contributor to intersubject variability is biological variability which could be affected among others by ethnic, socioeconomic and demographic factors. This variability probably reflects the particular neurochemical characteristics of the brain of an individual (*49,62*). Investigation of that variability is of importance to identify brain metabolic activity changes

associated with neurological and psychiatric illness. Though we have only dealt with brain metabolism variability under baseline conditions, it is expected that intersubject variability will be observed in activation studies and pharmacological challenge studies (with respect to the magnitude of the response and the pattern of the response).

CONCLUSION

This study shows significant variability in subjects between 20 and 40 yr of age. Age contributes to this variability but other factors are probably also involved in the differences in regional brain glucose metabolism between subjects. Similar intersubject variability has previously been reported and is accentuated when comparisons are made between subjects tested in different centers. This variability should be taken into account when constructing databases of brain images (*63*) for subjects scanned in different instruments and in different experimental conditions.

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EDITORIAL

What Are the Sources of Error in Measuring and Calculating Cerebral Metabolic Rates with Fluorine-18-Fluorodeoxyglucose and PET?

In this issue of the *Journal of Nuclear Medicine*, Wang et al. describe significant intersubject variability of cerebral metabolic rates for glucose (CMRgluc) in young normal males as measured with PET and ^{18}FDG (*1*). This is an issue of major concern for both research and clinical applications of this important imaging methodology. Sensitivity and specificity of a test is heavily dependent on the degree of variability and the amount of overlap in the measured values between healthy control subjects and patients.

The first method to measure cerebral metabolic rate was introduced by Kety and Schmidt in 1948 and was used to investigate various neuropsychiatric disorders (*2,3*). However, it was soon realized that in subjects with diseases outside the central nervous

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