Supporting Information

SI Materials and Methods

PET Procedure. Of the 29 children and adolescents in the PET analysis, 24 were selected to evaluate the role of PET in seizures and epilepsy, but they had mild episodes. Each had suffered transient neurological events not significantly altering neurological development on close follow-up. The remaining 5 subjects were asymptomatic, but because they had facial capillary nevi they were evaluated with PET for possible Sturge-Weber syndrome. Because PET did not disclose any hemispheric asymmetry of local cerebral metabolic rates for glucose (lCMRGlc) in any of these 5 patients it was concluded that they were normal. The older children were all attending school and performing well in classes. Of the infants studied, none had been born prematurely and all developed normally during the period of continued follow-up. These 29 children are thus reasonably representative of normal childhood development and provide a rare opportunity to measure lCMRGlc changes during normal brain development, as entirely healthy children cannot be studied with PET.

Subjects were fasted for 4 hours prior to PET. One hour prior to the study, scalp electrodes were applied in children with a history of seizures so that the electroencephalogram (EEG) could be monitored during the PET scan. Patients were injected with a low dose (5.3 MBq/kg) of 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG). Forty minutes after FDG injection, scanning of the brain was initiated using the NeuroECAT positron tomograph (CTI, Knoxville, TN) with a spatial resolution of 8.4 mm in the plane of section and a 12.4-mm slice thickness. A head holder minimized head movement during scanning. To confirm true axial positioning, 2 rectilinear images (anteroposterior and lateral views) were obtained prior to generating a standard set of 12 tomographic images parallel to the canthomeatal line. Additional details of the PET and clinical procedures are described elsewhere (1, 2).

MRI Brain Volumetry Protocol. Three-dimensional whole T_1-weighted, T_2-weighted and proton density brain images (1-2 mm-thick) at 1.5 T were acquired without sedation at six sites across the US using a 30-45 minute protocol in 402 well-screened, healthy, and typically developing participants (191 males, 211 females). Volumes were obtained with automatic tissue and regional segmentation. Total brain volume was defined as the sum of whole-brain gray matter and whole-brain white matter including the brainstem and cerebellum. Additional details of the NIH study of normal brain development have been published previously (3, 4).

Calculation and interpretation of the ratio of brain glucose/RMR and brain glucose/DER in glucose equivalents ($glucose_{rmr\%}$ and $glucose_{der\%}$). Past work has typically evaluated the relative importance of the brain to the body's overall metabolism by calculating the %RMR accounted for by the brain, with the latter calculated using N_2O-based estimates of brain energy expenditure (e.g. 5, 6). Recent work shows that a shifting, but at certain developmental stages sizeable (as high as 30%), fraction of the glucose used by the brain enters aerobic glycolysis, much of which serves as substrate for processes related to cellular and synaptic growth rather than energy metabolism (7-9). These uses of glucose are largely missing from N_2O based estimates of brain energetics, which thus underestimate the brain's true metabolic costs to the body. For the purposes of evaluating the magnitude of trade-offs between brain and body, the absolute quantity of glucose used by the brain, irrespective of its fate within the brain, is the key

variable of interest. Based upon these considerations, here we quantify the strength of brain-body substrate trade-offs as the ratio of brain glucose uptake (g/day) relative to the body's RMR ($glucose_{rmr\%}$) or relative to the body's DER ($glucose_{der\%}$), which were converted to units of daily glucose equivalents to allow direct comparison with brain glucose uptake (1 kcal RMR or DER requiring 0.2688 g glucose). Because some brain glucose is used in aerobic glycolysis rather than to meet energy needs, these ratios do not reflect the %RMR or %DER accounted for by the brain. Instead, they may be interpreted as the fraction of the body's RMR or DER that could be met by the quantity of glucose used by the brain if converted to energy via oxidative phosphorylation. Past work has shown that whole-body glucose production is tightly, linearly correlated with body size (10), suggesting that these ratios may also be interpreted as rough proxies for the % of total body glucose devoted to brain metabolism.

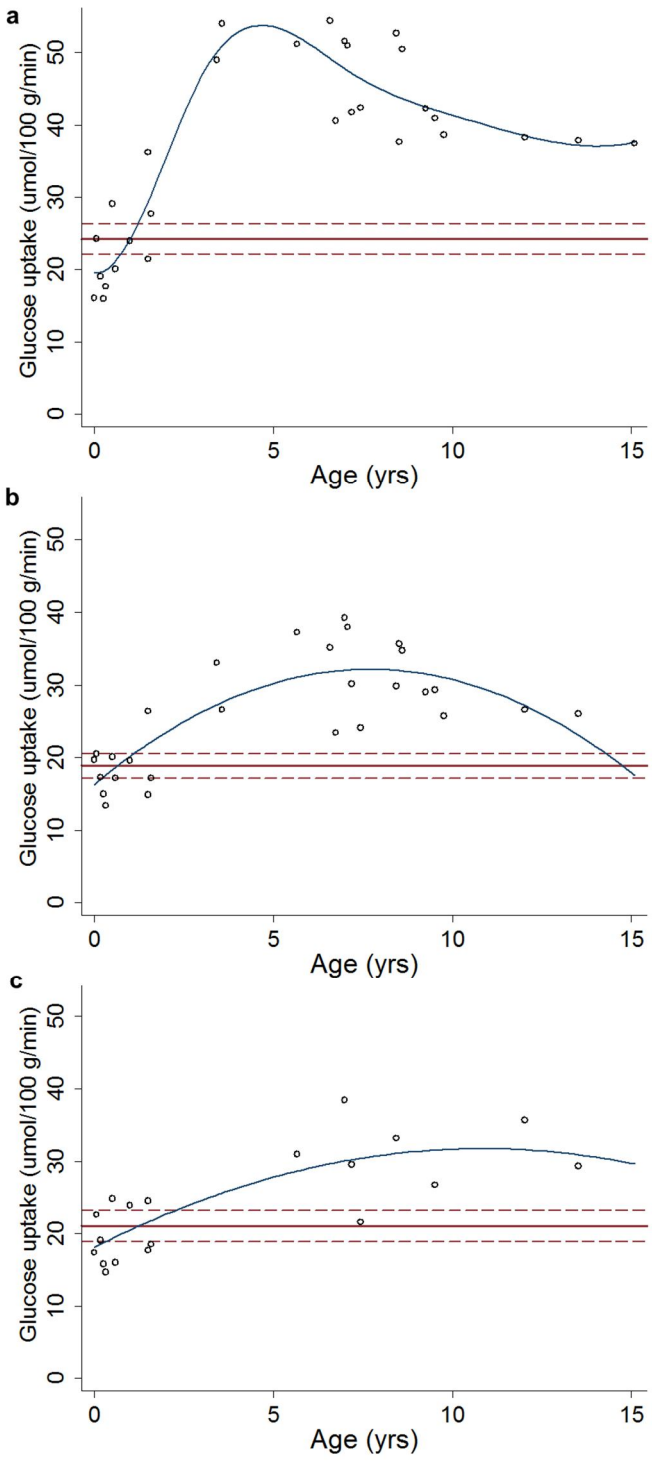

Fig. S1

PET measures of glucose uptake by brain region. **a**, Cerebrum (inclusive of gray and white matter) fit with cubic spline function (solid line). **b**, Cerebellum fit with polynomial function (solid line). **c**, Brainstem fit with quadratic function (solid line). In all panels, red horizontal lines indicate mean (solid line) and 95% CI (dotted) of glucose uptake in that brain region measured in the adult sample (n=7). All data from (2) .

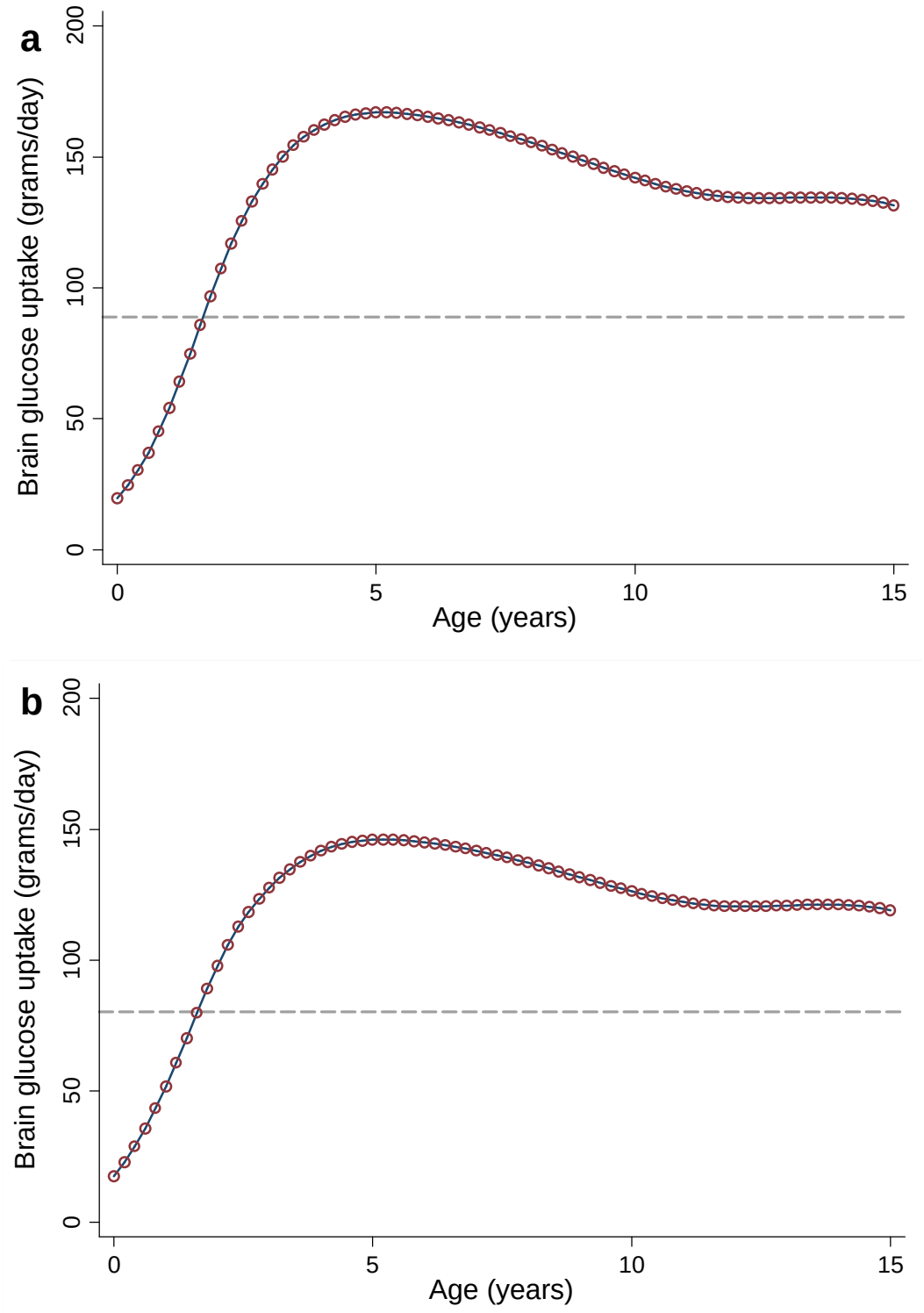

Fig. S2

Brain glucose uptake (grams/day). Daily brain glucose uptake in a) males and b) females was calculated as the sum of glucose uptake in all brain regions, estimated by multiplying PET-based measures of regional glucose uptake X predicted mass for that region on 0.2-year intervals.

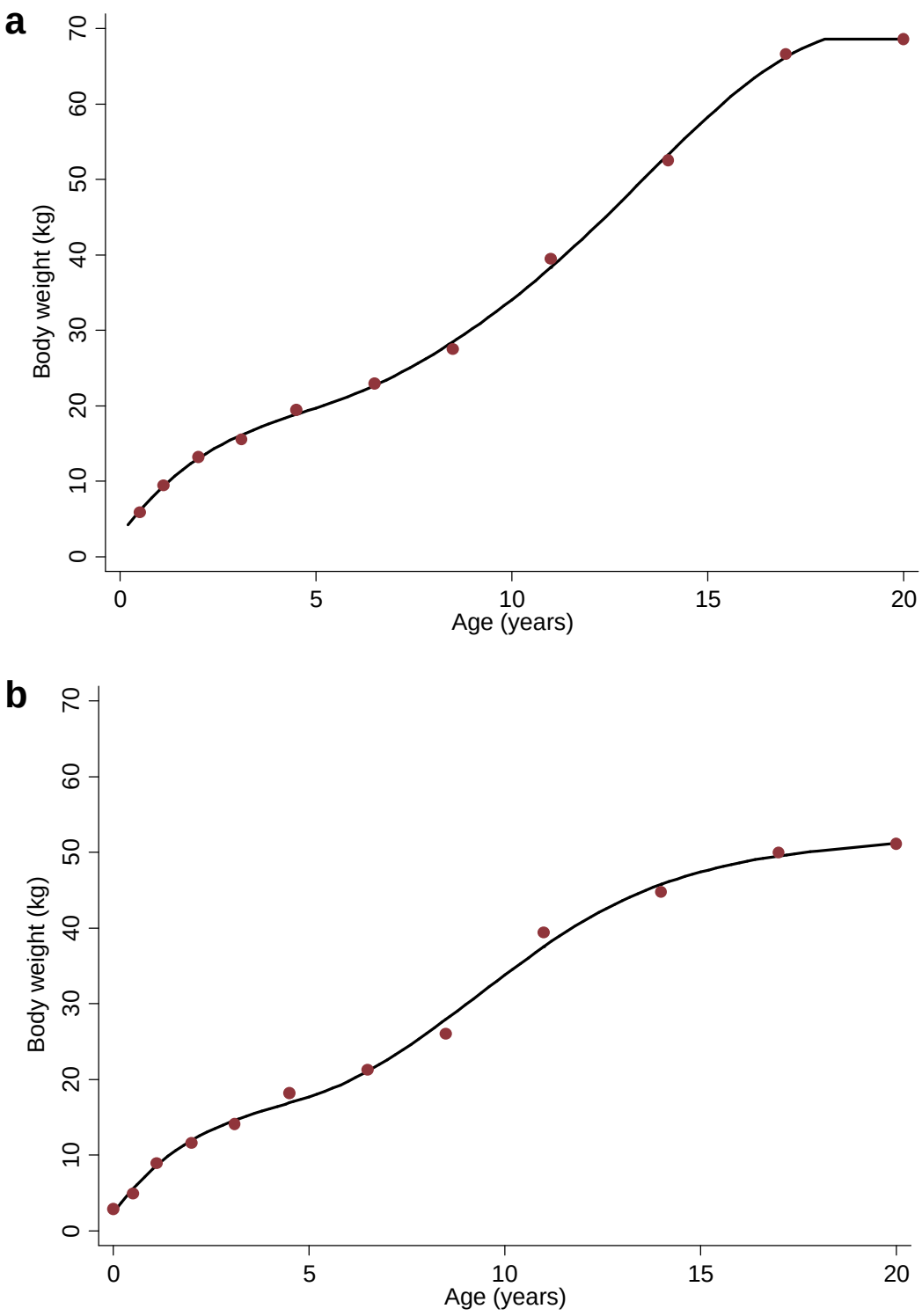

Fig. S3
Cubic spline models fit to Dekaban and Sadowsky (11) body weights. Dots are mean values for age groups (total n = 1004) reported for a) males and b) females.

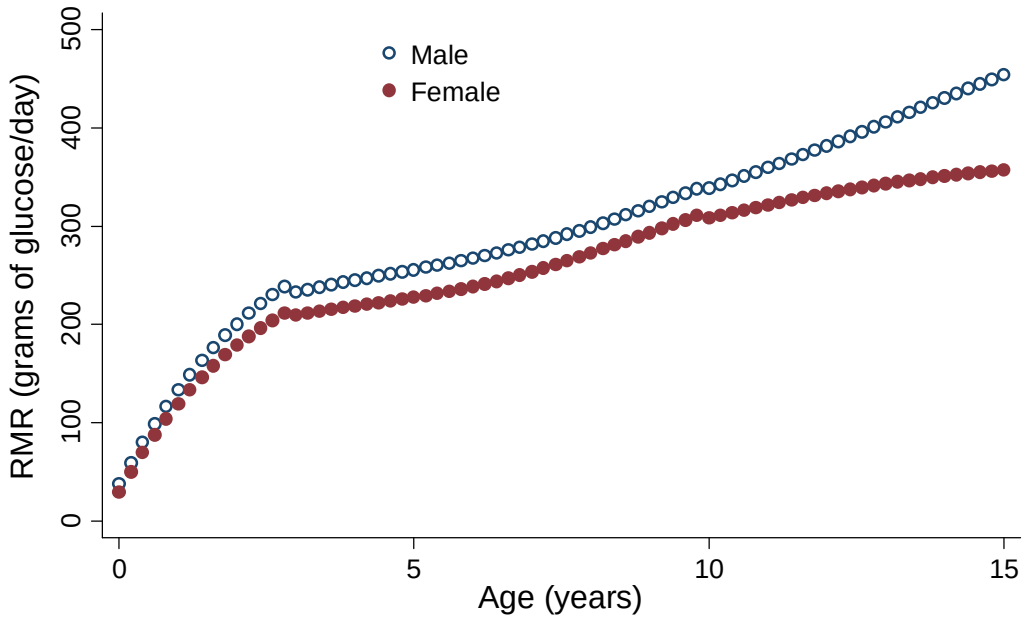

Fig. S4
Resting metabolic rate (RMR) of the body by age. Calculated from body weights predicted on 0.2-year intervals (Fig. S3) and age- and sex-specific FAO/WHO predictive equations (12) for males (open circle) and females (solid circle). Kcal converted to glucose-gram equivalents using the conversion 1 gram glucose = 3.72 Kcal. Discontinuities occur at ages (3 and 10 years) when predictive equations change.

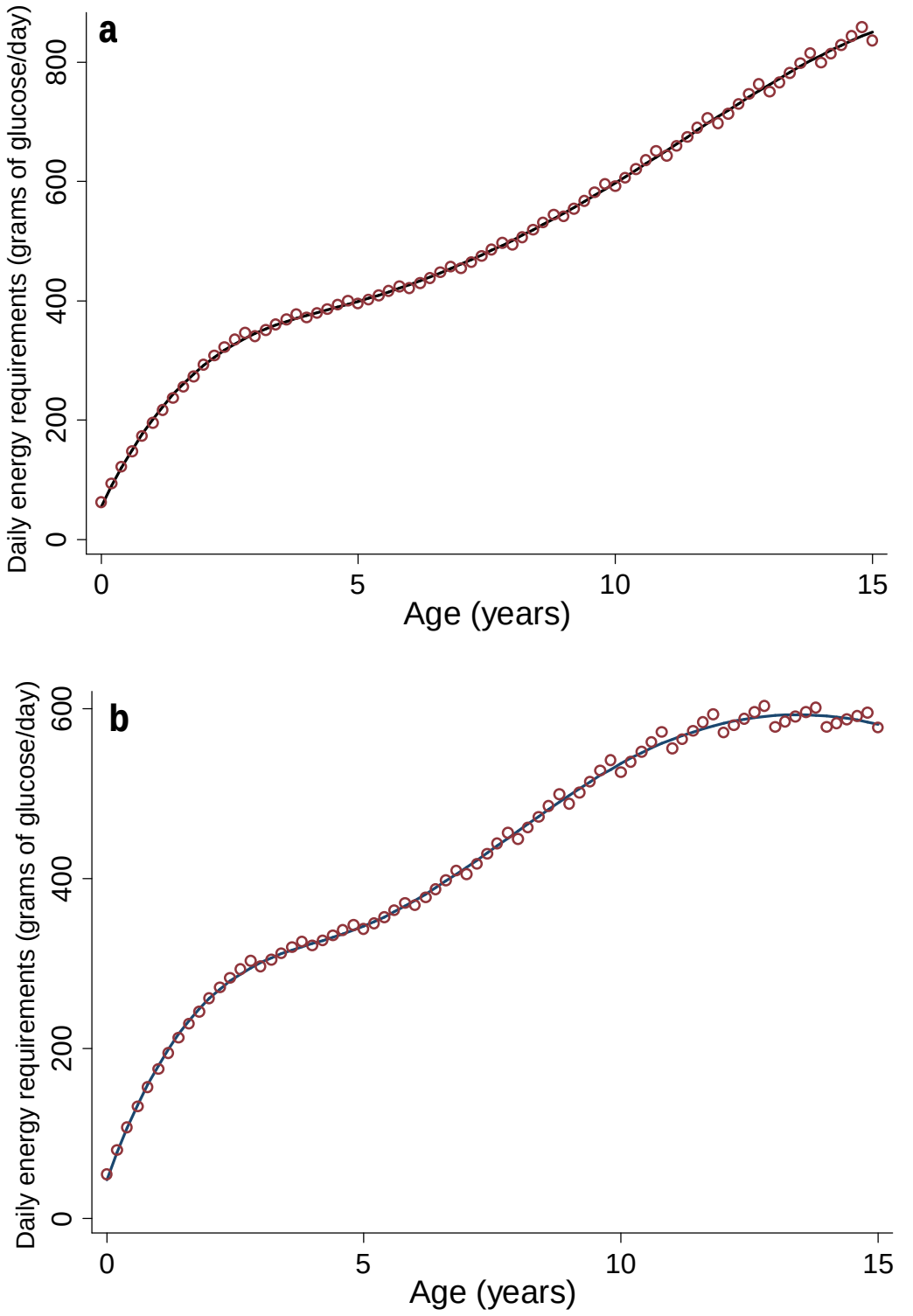

Fig. S5

Daily energy expenditure (DER) of the body by age in males (a) and females (b). Calculated from body weights predicted on 0.2-year intervals (Fig. S3) and age- and sex-specific FAO/WHO predictive equations (12). Kcal converted to glucose-gram equivalents using the conversion 1 gram glucose = 3.72 Kcal.

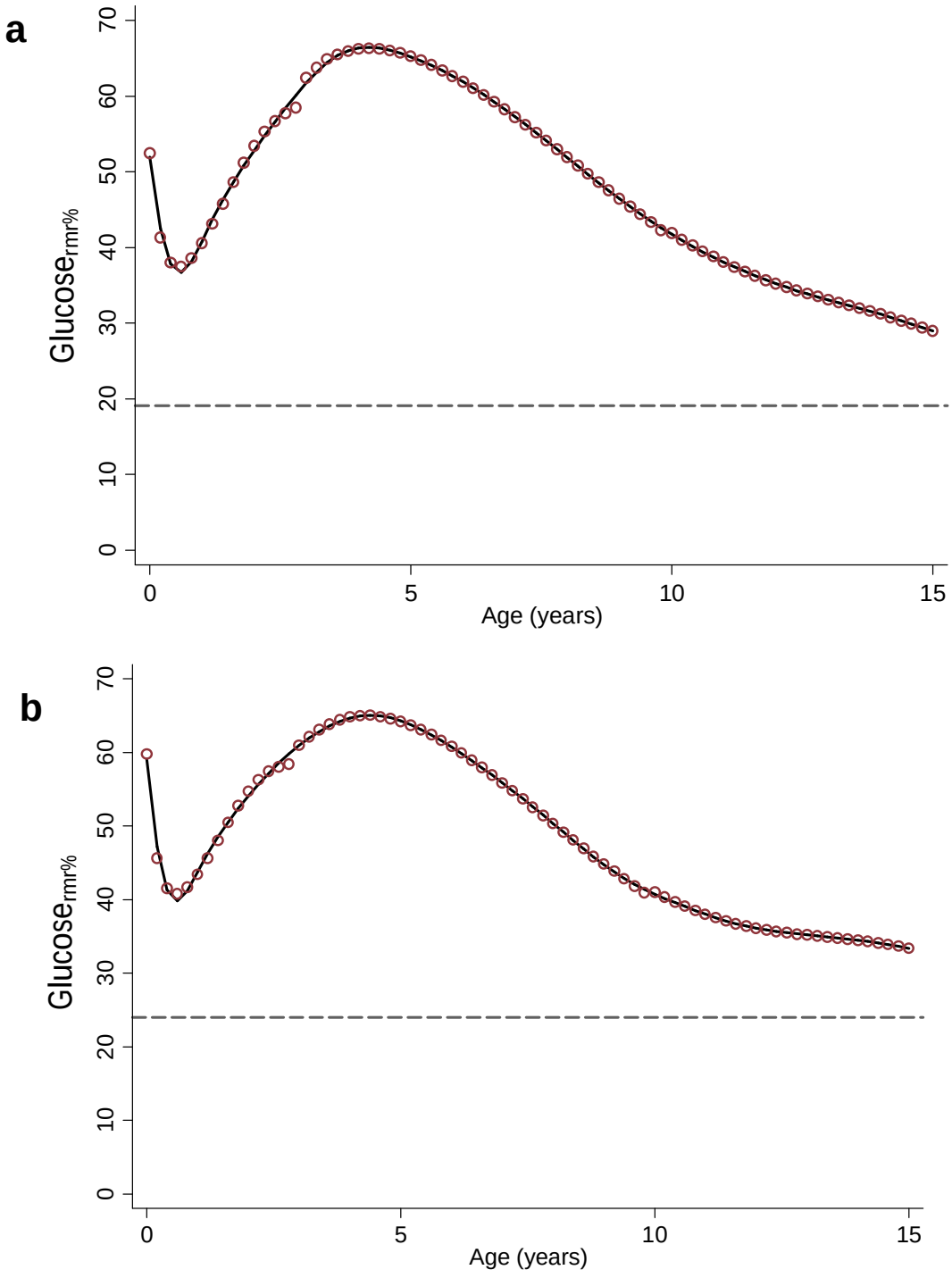

Fig. S6
Cubic spline fit to glucose$_{rmr\%}$ by age on 0.2-year intervals in a) males and b) females. Dashed line is adult value.

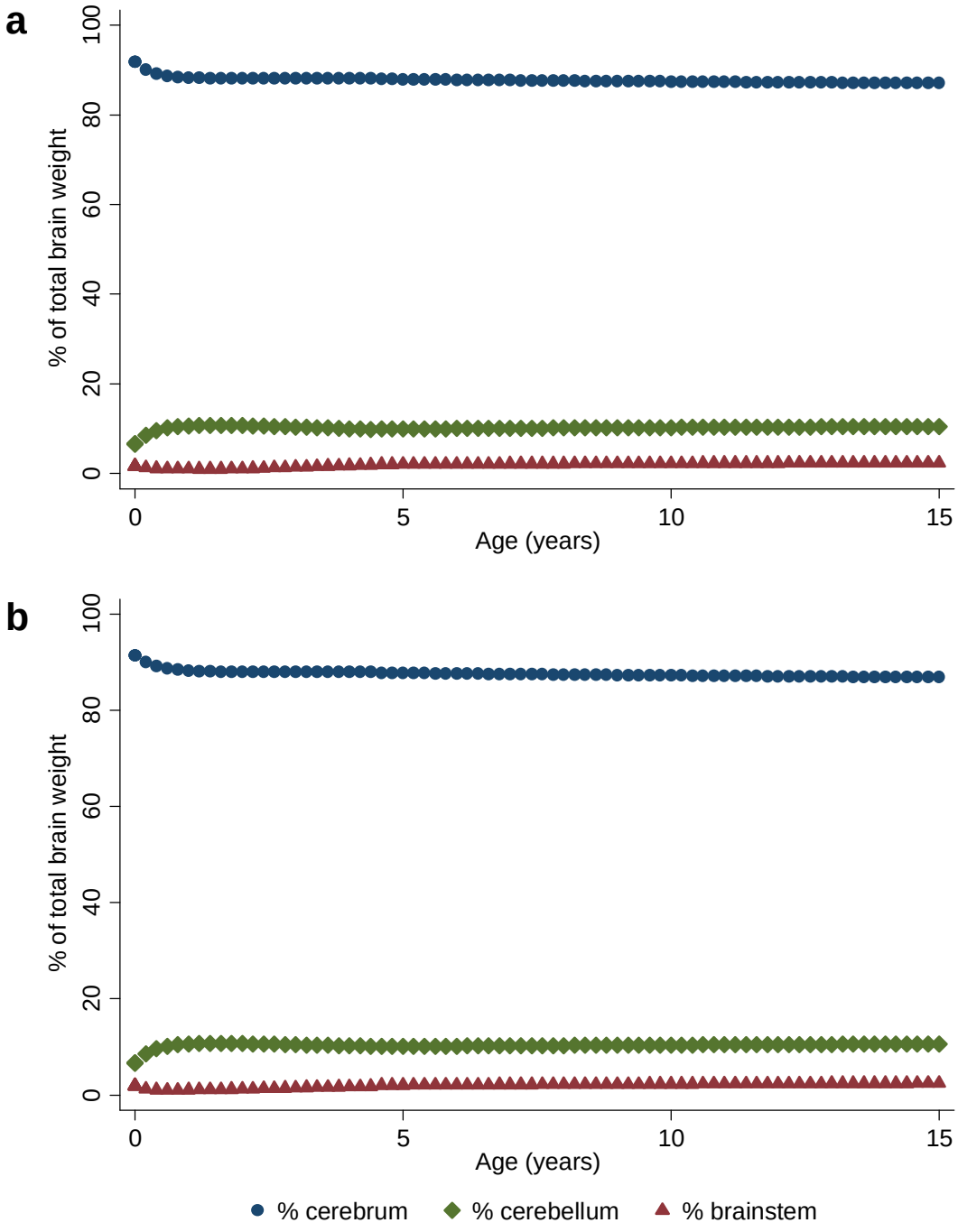

Fig. S7
Percentage of total brain weight accounted for by cerebrum, cerebellum and brainstem by age, in males (a) and females (b).

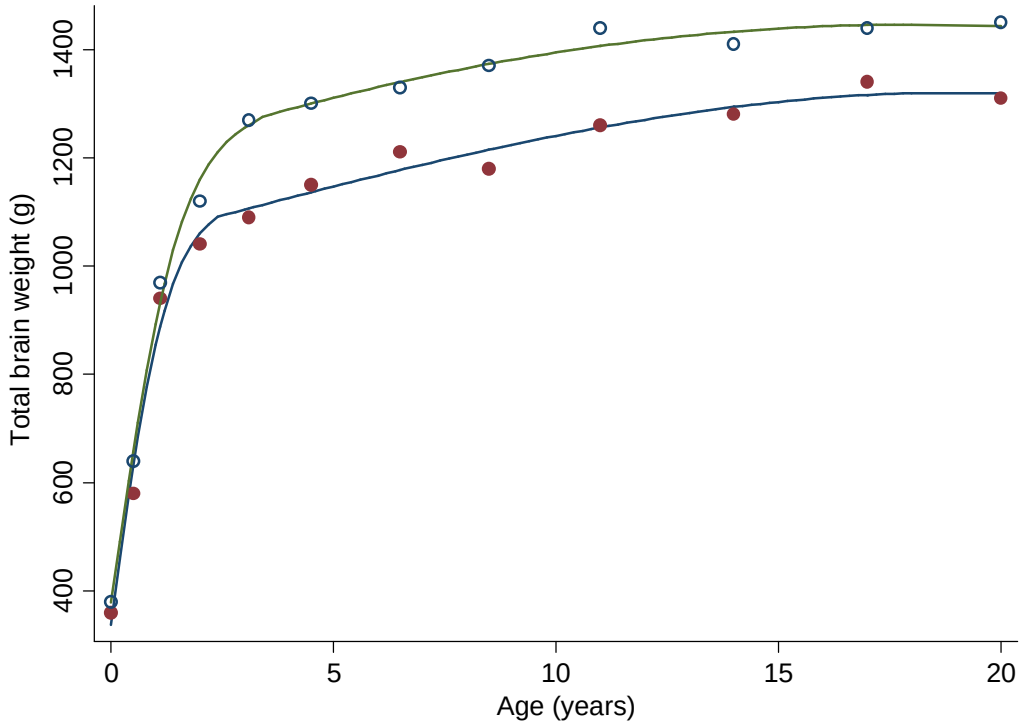

Fig. S8
Model fit to Dekaban and Sadowsky (11) total brain weights. Dots are mean values for age groups (total n = 1004) reported for males (open circles) and females (solid circles).

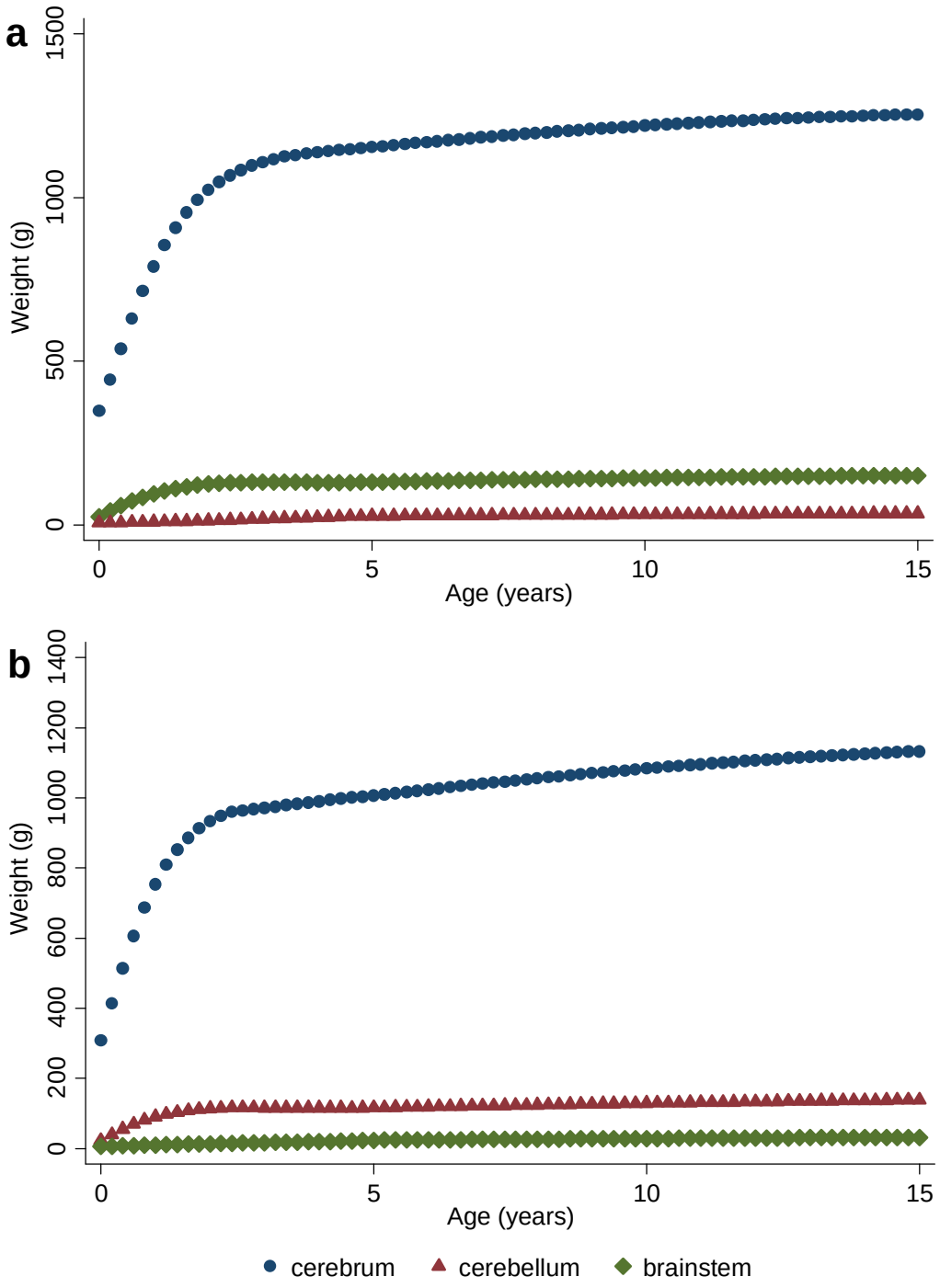

Fig. S9
Weights of cerebrum, cerebellum and brainstem by age. Calculated by multiplying %TBW for that region X TBW (Fig. S3) on 0.2-year intervals, separately in a) males and b) females.

Table S1
Predicted values at 1-year intervals in males

Age	Body weight (kg)	*dw/dt* (kg/yr)	RMR (kcal/day)	DER (kcal/day)	TBW (g)	Cerebrum weight (g)	Cerebellar weight (g)	Brainstem weight (g)	Brain glucose uptake (g/day)	Glucose (%RMR)	Glucose (%DER)
0	2.8	7.0	139.4	206.7	378.1	347.0	24.8	6.3	19.7	52.5%	35.4%
1	8.8	5.0	496.0	747.4	893.0	789.2	94.6	9.2	54.1	40.6%	26.9%
2	13.0	3.5	745.8	1087.2	1159.8	1023.3	124.1	12.4	107.2	53.5%	36.7%
3	15.9	2.4	865.5	1284.4	1255.8	1107.9	130.0	17.8	145.3	62.5%	42.1%
4	18.0	1.8	912.4	1397.2	1289.2	1137.4	129.0	22.8	162.4	66.2%	43.2%
5	19.7	1.7	951.6	1483.9	1310.6	1153.3	130.4	26.9	167.0	65.3%	41.9%
6	21.6	2.1	994.2	1588.4	1330.5	1169.3	133.4	27.9	165.4	61.9%	38.7%
7	24.0	2.6	1048.1	1715.8	1348.9	1183.9	136.2	28.8	161.3	57.3%	35.0%
8	26.9	3.1	1113.5	1864.7	1365.6	1197.2	138.7	29.7	155.5	51.9%	31.0%
9	30.2	3.6	1190.2	2033.7	1380.8	1209.2	141.1	30.5	148.7	46.5%	27.2%
10	34.1	4.1	1261.1	2221.5	1394.4	1219.8	143.2	31.3	142.0	41.9%	23.8%
11	38.4	4.5	1337.1	2425.4	1406.4	1229.2	145.2	32.0	136.9	38.1%	21.0%
12	43.1	4.9	1420.6	2634.9	1416.8	1237.2	146.9	32.7	134.5	35.2%	19.0%
13	48.2	5.2	1510.5	2836.6	1425.7	1243.9	148.5	33.3	134.4	33.1%	17.6%
14	53.3	5.1	1601.9	3017.1	1432.9	1249.3	149.8	33.9	134.3	31.2%	16.6%
15	58.3	4.7	1689.4	3162.9	1438.6	1253.4	150.9	34.4	131.6	29.0%	15.5%
Adult	68.6	-	1727.6	3023.2	1450.0	1259.7	154.2	36.2	88.8	19.1%	10.9%

dw/dt = first derivative of spline function relating body weight to age; RMR = resting metabolic rate; TBW = total brain weight.
Glucose (%RMR) and Glucose (%DER), respectively, equal the ratios of brain glucose uptake (g/day) divided by RMR or DER (in gram-equivalents and assuming 1 g glucose = 3.72 kcal) x 100. These ratios indicate the % of the body's total resting metabolic rate (inclusive of maintenance), or total daily energy requirements (inclusive of maintenance, activity and growth), that could be met if brain glucose was converted to energy via oxidative phosphorylation.

Table S2
Predicted values at 1-year intervals in females

Age	Body weight (kg)	*dw/dt* (kg/yr)	RMR (kcal/day)	DER (kcal/day)	TBW (g)	Cerebrum mass (g)	Cerebellar mass (g)	Brainstem mass (g)	Brain glucose uptake (g/day)	Glucose (%RMR)	Glucose (%DER)
0	2.4	6.9	109.1	168.6	337.2	308.4	22.3	6.4	17.5	59.8%	38.7%
1	8.1	4.7	443.8	668.2	854.8	755.0	90.5	9.3	51.8	43.4%	28.8%
2	11.9	3.0	665.6	963.6	1059.8	933.3	113.4	13.1	97.9	54.7%	37.8%
3	14.4	2.0	778.6	1120.2	1104.2	972.1	115.6	16.5	127.6	61.0%	42.4%
4	16.1	1.6	813.7	1203.5	1125.7	991.1	115.3	19.4	141.7	64.8%	43.8%
5	17.7	1.7	845.8	1279.2	1146.8	1007.1	116.1	23.6	146.0	64.2%	42.5%
6	19.8	2.4	887.1	1392.9	1167.3	1023.8	118.9	24.6	145.0	60.8%	38.7%
7	22.6	3.2	944.7	1537.3	1187.0	1039.8	121.6	25.6	141.9	55.9%	34.3%
8	26.1	3.7	1014.9	1696.0	1205.9	1055.2	124.2	26.5	137.2	50.3%	30.1%
9	29.9	3.9	1092.4	1852.8	1223.8	1069.7	126.7	27.4	131.7	44.9%	26.4%
10	33.8	3.9	1145.8	1991.5	1240.5	1083.2	129.1	28.3	126.3	41.0%	23.6%
11	37.6	3.6	1196.2	2097.5	1256.0	1095.7	131.3	29.1	122.2	38.0%	21.7%
12	40.9	3.1	1241.1	2167.2	1270.2	1107.1	133.3	29.8	120.5	36.1%	20.7%
13	43.6	2.4	1277.6	2201.1	1282.9	1117.1	135.2	30.5	120.9	35.2%	20.4%
14	45.8	1.9	1306.3	2200.0	1293.9	1125.8	136.9	31.2	121.2	34.5%	20.5%
15	47.4	1.4	1328.3	2163.4	1303.2	1133.1	138.4	31.8	119.1	33.4%	20.5%
Adult	51.1	-	1243.4	1989.5	1310.0	1135.2	141.3	33.4	80.2	24.0%	15.0%

dw/dt = first derivative of spline function relating body weight to age; RMR = resting metabolic rate; TBW = total brain weight.
Glucose (%RMR) and Glucose (%DER), respectively, equal the ratios of brain glucose uptake (g/day) divided by RMR or DER (in gram-equivalents and assuming 1 g glucose = 3.72 kcal) x 100. These ratios indicate the % of the body's total resting metabolic rate (inclusive of maintenance), or total daily energy requirements (inclusive of maintenance, activity and growth), that could be met if brain glucose was converted to energy via oxidative phosphorylation.

Table S3

Regional brain weights as a percentage of total brain weight (TBW) from birth to 4.6 years. Separate male and female values were used when reported, augmented by % TBW-estimates derived from studies of pooled male-female samples (italics). CBM = cerebellum. Volumetric data from 4.6 years to adulthood from a normative MRI series described elsewhere (4).

	Females			Males			
Age (yr)	**% Cerebrum**	**% CBM**	**% Brainstem**	**% Cerebrum**	**% CBM**	**% brainstem**	**Source**
0.00		*6.5%*			*6.5%*		(13)
0.00		*6.7%*	*1.3%*		*6.7%*	*1.3%*	(14)
0.00	91.5%	6.9%	1.7%	91.8%	6.6%	1.6%	Centre for Developing Brain, King's College, UK
0.00		*6.4%*			*6.4%*		(15)
0.00	*89.8%*	*8.9%*	*1.3%*	*89.8%*	*8.9%*	*1.3%*	(16)
0.00	*88.8%*	*10.1%*	*1.1%*	*88.8%*	*10.1%*	*1.1%*	(16)
0.00	*88.6%*	*10.4%*	*1.1%*	*88.6%*	*10.4%*	*1.1%*	(16)
1.00		*10.8%*			*10.8%*		(15)
2.00		*10.7%*			*10.7%*		(15)
4.60	87.9%	10.1%	2.0%	88.1%	9.8%	2.0%	(4)

1. Chugani HT (1996) Neuroimaging of developmental nonlinearity and developmental pathologies. *Developmental Neuroimaging: Mapping the Development of Brain and Behavior*, eds Thatcher R, Lyon G, Rumsey J, & Krasnegor N (Academic Press, San Diego), pp 187-195.
2. Chugani HT, Phelps ME, & Mazziotta JC (1987) Positron emission tomography study of human brain functional development. *Ann Neurol* 22(4):487-497.
3. Evans AC (2006) The NIH MRI study of normal brain development. *Neuroimage* 30(1):184-202.
4. Brain Development Cooperative Group (2012) Total and regional brain volumes in a population-based normative sample from 4 to 18 years: the NIH MRI Study of Normal Brain Development. *Cereb Cort* 22(1):1-12.
5. Holliday MA (1971) Metabolic rate and organ size during growth from infancy to maturity and during late gastation and early infancy. *Pediatrics* 47(1):Suppl 2:169-179.
6. Kennedy C & Sokoloff L (1957) An adaptation of the nitrous oxide method to the study of the cerebral circulation in children; normal values for cerebral blood flow and cerebral metabolic rate in childhood. *J Clin Invest* 36(7):1130-1137.
7. Goyal MS, Hawrylycz M, Miller JA, Snyder AZ, & Raichle ME (2014) Aerobic glycolysis in the human brain is associated with development and neotenous gene expression. *Cell Metab* 19(1):49-57.
8. Bauernfeind AL, *et al.* (2014) Aerobic glycolysis in the primate brain: reconsidering the implications for growth and maintenance. *Brain Struct Funct* 219(4):1149-1167.
9. Lunt SY & Vander Heiden MG (2011) Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. *Annu Rev Cell Dev Biol* 27:441-464.
10. Bier DM, *et al.* (1977) Measurement of "true" glucose production rates in infancy and childhood with 6,6-dideuteroglucose. *Diabetes* 26(11):1016-1023.
11. Dekaban AS & Sadowsky D (1978) Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. *Ann Neurology* 4(4):345-356.
12. Food and Agriculture Organization & World Health Organization. (2004) *Human Energy Requirements: Report of a Joint FAO/WHO/UNU Expert Consultation* (Food and Agricultural Organization of the United Nations, Rome).
13. Limperopoulos C, *et al.* (2005) Late gestation cerebellar growth is rapid and impeded by premature birth. *Pediatrics* 115(3):688-695.
14. Gousias IS, *et al.* (2012) Magnetic resonance imaging of the newborn brain: manual segmentation of labelled atlases in term-born and preterm infants. *Neuroimage* 62(3):1499-1509.

15. Knickmeyer RC, *et al.* (2008) A structural MRI study of human brain development from birth to 2 years. *J Neurosci* 28(47):12176-12182.
16. Choe MS, *et al.* (2013) Regional Infant Brain Development: An MRI-Based Morphometric Analysis in 3 to 13 Month Olds. *Cereb Cort* 23(9):2100-2117.