Supplementary Material for "Sex Differences in Estimated Brain Metabolism in Relation to Body Growth Through Adolescence"

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METHODS:

RMR in grams of glucose per day is estimated using the piecewise linear functions defined by the Food and Agriculture Organization of the United Nations (www.fao.org/docrep/007/y5686e/y5686e07.htm Table 5.2)[1]. The function is defined by the following pseudo-code:

```
rmr(age, sex, kg) = if(sex= "male"){
                      if(age<3){
                            (59.512*kg - 30.4)
                          }else if(age<=10){
                            (22.706*kg + 504.3)
                          }else if(age<=18){
                            (17.686*kg + 658.2)
                          } else if(age<=30){
                            (15.057*kg + 692.2)
                          } else if(age<=60){
                            11.472 * kg + 873.1
                          } else{
                            11.711 * kg + 587.7
                          }
                 } else {
                      if(age<3){
                            58.317 * kg - 31.1
                          }else if(age<=10){
                            (20.315*kg + 485.9)
                          }else if(age<=18){
                            (13.384*kg + 692.6)
                          } else if(age<=30){
                            (14.818*kg + 486.6)
                          } else if(age<=60){
                            8.126*kg + 845.6
                          }
                 }/3.72
```

where 3.72 converts from kcal to grams of glucose[2].

To investigate whether %RMR and CBF in the precuneus or SFG reached maturity earlier we compared the first age after 10 when the slope of the developmental curve was zero. We used 1000 bootstrap samples to estimate the distribution of the difference and computed the probability that the difference was less than zero. Specifically, for each bootstrap sample, $b = 1, \ldots, B$, for each sex and region we computed the parameter estimate $\hat{\tau}$; the first point after age 10 the derivative of the slope of the estimated function was greater than zero,

$$\hat{\tau}_{SRb} = \min\left\{a : a > 10, \frac{d\hat{f}_{SRb}}{da} > 0\right\}$$

where $\hat{f}_{SRb}$ is the estimated nonlinear curve for sex S and region R in bootstrap sample b, and $\frac{d\hat{f}_{SRb}}{da}$ denotes the derivative of $\hat{f}_{SRb}$ evaluated at a. Then the p-value is computed as the number of times the difference in bootstrap parameter estimate for SFG is less than the parameter estimate for precuneus.

RESULTS:

Regional differences in %RMR and CBF developmental curves

To investigate the age when %RMR and CBF reached adult levels, we used the fitted %RMR curves to estimate the first age after 10 when the slope of the developmental curve was zero, indicating that %RMR and CBF stopped changing. The difference in the age the %RMR curve reached zero for precuneus and SFG was small (Males: 0; Females: -0.1) and was not significant in either sex (Males: p=0.84; Females p=0.20). For CBF, the curve reached zero slightly earlier in the precuneus for males (precuneus: 18 years; SFG: 18.3 years) and females (precuneus: 15.3 years, SFG: 15.8 years) as in Taki et al.[3], however the difference was not statistically significant.

Supplementary Tables:

Table S1:

	Males					
Age	**PNC MBG (umol/100g/min)**	**PNC BG (g/day)**	**Kuzawa BG (g/day)**	**Difference**	**PNC MBG (umol/100g/min)**	**PNC B (g/da**
8	62.7	134.5	155.5	21.0	60.3	121.4
9	61.7	133.4	148.7	15.3	58.7	118.1
10	60.2	130.5	142	11.5	56.6	113.5
11	58.1	126.1	136.9	10.8	54.1	108.2
12	55.7	120.6	134.5	13.9	51.7	102.9
13	53.2	114.7	134.4	19.7	49.8	98.2
14	50.7	108.9	134.3	25.4	48.6	94.9
15	48.6	103.8	131.6	27.8	48.2	93.1
Adult	45.6	93.8	88.8	-5.0	50.4	93.7

Estimates of mean brain glucose consumption (MBG) (umol/(100g tissue)/min and brain glucose consumption (BG; (grams glucose)/day). The difference column compares our estimates brain glucose consumption to those of [4]. Results differ by 1-30 grams. Adult resting levels are estimated by age 20 in our sample.

Table S2:

	Males			Females		
Age	**PNC %RMR**	**Kuzawa %RMR**	**Difference**	**PNC %RMR**	**Kuzawa %RMR**	**Difference**
8	43.8	51.9	8.1	40.6	50.3	9.7
9	41.3	46.5	5.2	38.7	44.9	6.2
10	38.3	41.9	3.6	35.8	41	5.2
11	34.7	38.1	3.4	32.4	38	5.6
12	31.0	35.2	4.2	28.9	36.1	7.2
13	27.3	33.1	5.8	26.1	35.2	9.1
14	24.1	31.2	7.1	24.2	34.5	10.3
15	21.5	29	7.5	23.2	33.4	10.2
Adult	19.7	19.1	-0.6	24.4	24	-0.4

Comparison of our estimates %RMR to those of [4]. Results differ by approximately 5-10%. Adult resting levels (age 20 from our estimates) match closely between the two studies.

References

1. Food and Agriculture Organization of the United Nations., United Nations University. and World Health Organization. *Human energy requirements : report of a Joint FAO/WHO/UNU Expert Consultation : Rome, 17-24 October 2001*. Rome: Food and Agricultural Organization of the United Nations, 2004, p.ix, 96 p.
2. Institute of Medicine (U.S.). Panel on Macronutrients. and Institute of Medicine (U.S.). Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids*. Washington, D.C.: National Academies Press, 2005, p.xxv, 1331 p.
3. Taki Y, Hashizume H, Sassa Y, et al. Correlation between gray matter density-adjusted brain perfusion and age using brain MR images of 202 healthy children. *Hum Brain Mapp*. 2011; 32: 1973-85.
4. Kuzawa CW, Chugani HT, Grossman LI, et al. Metabolic costs and evolutionary implications of human brain development. *Proceedings of the National Academy of Sciences of the United States of America*. 2014; 111: 13010-5.