Notes to the video on my PNAS "Skeletal muscle-induced hypoglycemia risk, not life history energy trade-off, links high child brain glucose use to slow body growth" (2014)

Reply to Kuzawa et al's reply to the above.

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1. General comment

There is substantial agreement between us. I do not doubt their data nor its importance. Nor do I question that body growth can trade-off with metabolic expenditure—much of biology is shaped by this and other energy related trade-offs.

My question is whether this is the dominant and determining factor in explaining the link between human slow growth and the prolonged expensive neuromaturation of our species. The issues, however, are complex while covering diverse areas of biology from evolutionary theory to paediatric diabetes medicine. The question is also researchable—providing that there is communication—which is missing—between these separated and presently isolated fields of science.

The topic is important. If we can understand the link between growth and neuromaturation in our species, we can understand whether there is or is not a difference in neuromaturation between us and other members of the Homo genus such as Neanderthals. Same sized brains but different neuromaturation could explain why only one Homo species—our own—presently exists. It is also important since a greater appreciation of the vulnerability of human children to extreme energy needs might change our attitude to the 300 million children that go to bed hungry every day. Human origins—see my "Human neuromaturation, juvenile extreme energy liability, and adult cognition/cooperation" tie closely to the unique behavior of our species to nutritionally support *all* children (other species limit this—if it occurs—to those of the dominant female). Maybe in our origins—but not presently in living humans—witness our tolerance of childhood hunger. While this is a separate issue, the paper "Human neuromaturation, juvenile extreme energy liability, and adult cognition/cooperation" is a pair to my "Human metabolic adaptations and prolonged expensive neurodevelopment: A review" that details the high vulnerability of the childhood brain. Note citations to research below if they lack full adjacent reference have full ones in the second paper.

2. A small error on my part

In my piece, I make an error by considering the energy expenditure of a child upon tissue growth—but only given their actual slow growth rate. But, of course, the question is not what they actually expend but what they would expend if they had a nonslowed rate of growth.

But this does not make a substantial difference to the conclusion that slowing growth does not save much in terms of energy expenditure upon tissue growth. A child of five (the age of slowest body mass gain) using the author's data for males (in their supplementary materials) weighs 19.7 kg and in this year puts on 1.7 kg—8.63% change. What would it put on if its growth—we will take the most extreme case—was the highest it was capable of such during the adolescent growth spurt? The authors figures suggest this is maximal at 13 years-of-age when a male child weighs 48.2 kg and puts on 5.2 kg—10.79% change. (In my reply I use the case of a four-year-old which has a slight faster rate of growth, by their data, 18.0 kg, 1.8 kg, and 10%). What these figures show is that while humans change their rate of growth this is not so much as might be thought (the adolescent growth spurt is more a height spurt than a weight one).

3. The problem of growth expenditure accounts

Bigger bodies expend more. And children they note expend less than adolescents and adults. What they ignore is that body mass of an individual is not the only factor determining how much that energy that individual expends in exercise. As I point out children partition their exercise expenditure differently to adolescents and adults by avoiding long intense periods of exertion while engaging in more low and moderate exercise. If energy expenditure was such an important factor, why more low and moderate exercise? Why not reduce all forms of exercise related energy expenditure?

4. More details upon skeletal muscle brain glucose competition

The reason for this partition is that while low and moderate exercise use energy, they do not draw upon plasma glucose, and so do not put skeletal muscle in competition with the brain. Intense sustained exercise however does. As put by the follow quote: "the bulk of muscles .. constitute a menace to the brain, owing to their great mass and the fact that they never return glucose to the blood" Guanyu Wang 2014 Raison d'être of insulin resistance: the adjustable threshold hypothesis. J. R. Soc. Interface 11: 20140892. http://dx.doi.org/10.1098/rsif.2014.0892 The problem faced by the child's brain is not only acquiring the energy needed to fuel its energy expensive neuromaturation but also ensuring that its brain's glucose supply is not threatened by other body organs—notably its skeletal muscle.

The situation has been put by Delamarche and colleagues "Even at rest, it would appear to be difficult for children to maintain blood glucose concentration at a steady level; an immaturity of their glucoregulatory system would seem to be likely,

therefore causing a delay in an adequate response to any stimulus to hypoglycemia like prolonged exercise." (Delamarche et al., 1992, p. 71). (Full references to this and following citations can be found in my "Human metabolic adaptations and prolonged expensive neurodevelopment: A review")

The child glucose homeostasis exists on a knife edge: the half life rate of turnover of plasma glucose in a 15 kg child is 26 minutes, but 78 minutes in an 80 kg adult.

A child weighing 15 kg (roughly the age of 3 years and 6 months) has a circulating plasma that contains a total of 18.8 mmol (3.4 g) of glucose. In a child weighing 30 kg (roughly the age of 9 years and four months) it is 37.4 mmol, and for an 80 kg adult, it is 100 mmol (Haymond & Sunehag, 1999, table 1). The quantity of glucose at any particular time in plasma in children is thus very limited—18.8 mmol (3.4 g) of glucose is equivalent in weight to about three smartie sweets/ M&Ms, or all the dissolved types of sugar in two tablespoons of Coca Cola.

Children aged 8.5-11 upon exercising show a drop in plasma glucose levels (Delamarche et al., 1994). After 18 minutes of 60% VO 2max exertion on an ergometer, plasma glucose dropped in such children from 3.75-3.78 mmol l-1 to 3.1-3.4 mmol l-1 (Delamarche et al., 1994). This drop does not occur in adults.

In adults, active physical exertion by skeletal muscle extracts plasma glucose (after muscle glycogen stores are depleted) in a glucose concentration dependent manner (Rose & Richter, 2005). This can significantly extract plasma glucose, for instance, the muscle working repetitive knee extending draws 0.5 mmol kg-1min-1 (Richter et al., 1988). Hepatic output of glucose can increase to compensate in adults five-fold to make up for this depletion during exercise (Wahren, Felig, Ahlborg, & Jorfeldt, 1971), and usually provides a much higher level of plasma glucose (Howlett, Febbraio, & Hargreaves,1999). However, this increase can be insufficient in intense exercise to keep up with prolonged glucose utilization from plasma (replacing only a third to two thirds) (Nielsen et al., 2007). As a result, strenuous prolonged exercise can dramatically reduce plasma glucose levels (ergometer cycling: pretest, 4.3 mmol L-1, 3 hours, 2.5 mmol L-1(Coyle et al., 1986). That this is due to a limited capacity to replace glucose is demonstrated by the fact that there is no drop if exercisers take a glucose polymer supplement every 20 minutes (Coyle et al., 1986)).

Intense physical exercise in children, even given their small bodies and other glucose minimizing adaptations, will to some extent extract plasma glucose in competition to the brain. It is therefore notable that research upon exercise in children finds that they do not do the intense exercise that would deplete plasma glucose. Children engage in much more general exercise than adults (Sigmund et al., 2007)—perhaps linked to stimulating motor and cognition learning—but such exercise is not as intense in terms of heart rate increase (Gilliam et al., 1981) and tempo (Bailey et al., 1995) as that in adults. "Over a 12-h day, subjects spent a mean of 22.3 min in high-intense activities, but the median duration of an intense activity event was very short—just 3 s. No bout of intense activity lasting 10 consecutive mins was ever recorded, and 95% of intense activity events lasted less than 15 s." (Bailey et al., 1995, children 6-10 years-of-age,

activities include periods in sport practice, dance, and swimming, p. 1038). Moreover, the total energy expenditure of children (8-11 years-of-age) engaged in a full out 30 seconds on a cycle ergometer is lower in power output than in adults (19-29 yearsof-age), even when adjusted for lower body mass (8.4 vs. 13.8 W kg -1), and fat free body mass (9.5 vs. 16 W kg -1) (Delamarche et al., 1994, table 1).

Though the brain can partially use nonglucose fuels (see appendix 9), low levels of plasma glucose limit brain functioning, and do so at much higher levels (as shown in effects upon the latency of theP300 wave) than those that cause physiological signs of hypoglycemia such as confusion, faintness or anxiety (De Feo et al., 1988). The adult brain, moreover, when faced with a hypoglycemic drop in plasma glucose (2.5 mmol L -1) adapts by a task specific shifting of cerebral blood to compensate for impaired function (Rosenthal et al., 2001). For example, in finger tapping, there are hemodynamic declines in many right hemisphere motor areas but also increases such as in the left hemisphere frontal pole. In a four-choice reaction time task, there are decreases in motor and visual areas and increases in the left parietal areas involved in planning (Rosenthal et al., 2001). This shifting of brain area activations could well be less developed in children and so potentially more disruptive. Consistent with this, drops in plasma glucose are known to particularly effect children: in artificially induced hypoglycemia, reductions in the amplitude of the P300 auditory evoked brain potentials occur in children at higher blood glucose levels (4.2 mmol L -1) than cause such disruptions in adults (3.0 mmol L -1) (Jones et al., 1995).

5. The conflict of brawn and brain is not just depleting plasma glucose.

Intense exertion has other impacts upon the brain such as the availability of oxygen. The brain's functional integrity is as sensitive to the availability of oxygen as it is to glucose (Ames, 2000). Moreover, the body in activity increases oxygen availability to the brain, but like with glucose, if exercise is strenuous, this can turn into a reduction (Dempsey et al., 1984; Subudhi et al., 2008). Extra oxygen, like extra glucose, also appears to enhance cognition (Chung et al., 2006; Scholey, Moss, Neave, & Wesnes, 1999) such as reaction times and word memory (Scholey et al., 1999), and verbal cognition (Chung et al., 2006), but see negative findings for working and long-term memory (Andersson, Berggren, Gronkvist, Magnusson, & Svensson, 2002). Reduced oxygen both by experiment and by high altitude (as with reduced glucose) can impair cognitive performance (Bartholomew et al., 1999; Virues-Ortega, Buela-Casal, Garrido, & Alcazar, 2004). Children that have interrupted oxygen intake during sleep due to obstructive sleep apnea syndrome show increased compensatory cerebral blood flow (Hill et al., 2006), and slightly impaired daytime cognitions such as in processing speed and visual attention (Hill et al., 2006), and in memory tasks (Kennedy et al., 2004). One odd and inexplicable but potentially theoretically important finding that needs replication is that neonates whose brains receive additional oxygen due to extracorporeal membrane oxygenation show enhanced performance IQ when 5 to 8 years-of-age (Ikle et al., 1999).

Like with glucose, strenuous exercise can compromise the oxygen availability to the brain (Dempsey et al., 1984; Subudhi et al., 2008). This might be due to

hyperventilation lowering carbon dioxide tension and impairing of the autoregulation of the cerebral blood flow (Nybo & Rasmussen, 2007), or the existence of diffusion limits upon hemoglobin's oxygen-binding in the lungs due to the short transit times of pulmonary circulation (Dempsey et al., 1984). Such impairment upon the brain can be relieved by increased availability of oxygen (Subudhi et al., 2008). Children, it should be noted have small lungs (vital capacity of a five year-old: 1 L, an adult male: 5 L) (International Commission on Radiological Protection, 2002), and low cardiac output (the cardiac output of a five year-old: 3.4 L min^{-1}, an adult male: 6.5 L min^{-1}) (International Commission on Radiological Protection, 2002). This will limit the ability of children compared to adults to support the combined oxygen needs of both the brain and activated high muscle mass.

Strenuous exercise can effect the brain in regard to other less well research factors including:

- autoregulation of its blood supply (Ogoh et al., 2005), particularly in warm environments (Watson, Shirreffs, & Maughan, 2005)

- hyperthermia that lowers cerebral blood flow (Nybo et al., 2002; Nybo & Nielsen, 2001), and raises brain temperature (Secher et al., 2008).

- the accumulation of ammonia in the brain produced by purine nucleotide deamination and amino acid catabolism of myofibrils in exercised muscles (Nybo et al., 2005).

These metabolic consequences, moreover, can exacerbate each other's negative neurological effects. For example, the uptake of ammonia by the brain is greater with glucose depletion (CSF ammonia levels: rest, below 2 μmol min^{-1} detection level; following 3 hours exercise with glucose supplementation, 5.3 μmol min^{-1}, without glucose supplementation, 16.1 μmol min^{-1}) (Nybo et al., 2005). The effects of dehydration are greater and happen at a lower threshold in hot environments (Maughan et al., 2007).

6. Children are adapted to minimize skeletal muscle brain conflict

A suite of adaptations exist that reduce the above noted capacity of skeletal muscle to deplete plasma glucose, and as a result, the capacity of intense prolonged exercise to disrupt the glucose supply to the pediatric brain.

- During high-intensity exercise, the muscles of children have a more oxidative than glycolytic (lactate producing but glucose substrate dependent) metabolism (Boisseau & Delamarche, 2000; Eriksson, Karlsson, & Saltin, 1971; Hebestreit, Meyer, Htay, Heigenhauser, & Bar-Or, 1996; Kaczor, Ziolkowski, Popinigis, & Tarnopolsky, 2005; Zanconato, Buchthal, Barstow, & Cooper, 1993). Children, for example, show lower levels of lactate following exhaustive exercise than adults (Eriksson et al., 1971; Hebestreit et al., 1996; Kaczor et al., 2005). They

also show less increase than adults in H+ concentration (acidosis) after exercise to exhaustion (Hebestreit et al., 1996; Zanconato et al., 1993).

- This oxidative metabolism during exercise is more from free fatty acids rather than glucose suggesting a shift in the Randle cycle of competition between glucose and fat oxidation (Randle, 1998). Fatty acids contribute 35.5% in a child vs. 19% in an adult of energy in the last half hour of an hour's cycling exercise at 70% of Vo_{2peak} (Timmons et al., 2003). Significantly, this is specific to exercise: metabolism during rest is more biased towards fatty acids at the expense of glucose oxidation in *adolescents* rather than in prepuberty children and adults (Hannon, Janosky, & Arslanian, 2006). This exercise increase in the use of fatty acids (Delamarche et al., 1992) correlates with a drop in glucose blood levels in children (Delamarche et al., 1994).

- Children might have muscles optimized for less intense exercise (Ratel, Duche, & Williams, 2006): there are reports of a shift in the proportion of fibers from type I (slow-twitch oxidative and use fatty acids over glucose as fuel) to type II (fast-twitch oxidative-glycolytic that utilize glucose) in autopsy sampled vastus lateralis muscle (65% at 5 years-of-age to 50% at 20 years-of-age (Lexell, Sjostrom, Nordlund, & Taylor, 1992); 54% 6-10 years-of-age to 47%, 10-15 years-of-age, 42%, 15-20 years-of-age (Oertel, 1988)). However, contrary findings exist (Bell, MacDougall, Billeter, & Howald, 1980), and opinions differ. Martin and colleagues (2003) argue they are consistent with the qualitative differences that they find between prepuberty and puberty muscle performance. This conclusion is also supported by Boisseau and Delamarche in their review of anaerobic metabolism during exercise in children (2000).

- Children have a different body composition of skeletal muscle mass to adults.

    - The soft tissue component of children's limbs before the last stage of puberty (Tanner pubertal stage 5) has a smaller proportion of skeletal muscles (56%) relative to other components (skin, connective tissue, lean portion of adipose tissue) than in adults (59%) (Kim et al., 2006).

    - The skeletal muscle mass scales to height^2 (Heymsfield et al., 2007), thus a young person's muscle mass could be expected to increase most dramatically with the height spurt that occurs in adolescence.

    - The research literature of reported total body weight across physical maturation together with weight changes for actual (rather than proxy) measures of skeletal muscle mass (particularly in the appendicular limbs that are responsible in intense exercise for depleting plasma glucose) is limited. However, the figures that do exist suggest that the percentage of the body that is skeletal muscle mass increases with age. The predictive equations for skeletal mass in adults, for example, overestimate skeletal mass in children below Tanner stage 5 (Kim et al., 2006).

The below weights are illustrative (data from International Commission on Radiological Protection, 2002). Since adipose tissue (fat) contributes such a large but gender and age variable contribution to total human body mass, the percentage is given minus this body component. The weights are in kilograms. Note the definition of adipose tissue is different from that cited earlier by Kuzawa, and "excludes essential body fat. [But] includes interstitial fat and yellow bone marrow" (International Commission on Radiological Protection, 2002, p. 76).

Age	body	fat	body - fat	muscle	Muscle % (body – fat)
5	19	3.6	15.4	5.6	36%
10	32	6	26	11	42%
♂15	56	9	45	20	44%
♀15	53	14	39	17	44%
♂adult	75	14.5	60.5	29	48%
♀adult	60	18	42	17.5	42%

- Humans generally have less skeletal muscle as a percentage of body composition than other primates, and though the data is limited to rhesus macaques, it would appear that while children have less skeletal muscle than adult humans: nonhuman juveniles (range 38.8-46.8%) show similar skeletal mass to nonhuman adults (range 39.6-52.6%) (Grand, 1977b). Note, these percentages underestimate the human nonhuman primate muscle mass difference since they do not factor out the body composition element that is fur and skin which is considerably higher in nonhuman primates (12.4 to 15%) (Grand, 1977a, 1977b; Zihlman, 1984) than in humans (3.8-4.5%) (International Commission on Radiological Protection, 2002).

- As noted above, children in spite of engaging in more physical activity than adolescents and adults (Sigmund et al., 2007), do not engage in prolonged intense physical activity (Bailey et al., 1995; Gilliam et al., 1981). Further, that when they engage in maximum exertion, it is not so powerful as that of adolescents and adults, even taking account of their smaller body and lean mass size (Delamarche et al., 1994, table 1).

- Research upon muscle reflexes and maximum voluntary contraction in children and adults suggests that children compared to adults have less voluntary ability to activate their motorneurons (Paasuke, Ereline, & Gapeyeva, 2000). This conclusion is also supported by research upon maximum sustained contraction and surface electromyography (Halin, Germain, Bercier, Kapitaniak, & Buttelli, 2003). Children would thus seem to place a neurological ceiling upon the potential muscle force—and so possible glucose extraction—that might otherwise be musculoskeletally available to them.

One effect of these adaptations is that children recover more quickly from exhaustive exercise than adults (Ratel et al., 2006) as their musculoskeletal exertion is not so intense, so productive of lactate, nor so disruptive of glucose availability.

Children in spite of these adaptations remain more vulnerable to exercise glucose extraction than adults. For example, during exercise children more readily substitute external glucose for endogenous glucose (52.3%) than adults (31.3%) (Timmons et al., 2003). Further, the preferential use of free fatty acids (Timmons et al., 2003) is related to problems in generating sufficient replacement glucose: upon starting exercise children show a drop in plasma glucose and an adrenomedullary counter-reaction of epinephrine that is not normally found in adults (Delamarche et al., 1994; Delamarche et al., 1992).

7 Life history vs homeostasis explanations

My theory contrasts with Kuzawa and colleagues in being a homeostasis rather than a life history one. As such the processes it concerns operate on a second or perhaps minute timescale rather than the months and years across of those that might underlie life history trade-offs.

It also differs in that it identifies—or at least makes explicit—the existence of processes that can be directly investigated. I have not detailed the complex—very complex—system of hormonal and neural processes that underlie the control of glucose and energy metabolism and expenditure. These require a major review and are still only partially understood. For example, what is the function of insulin? Guanyu Wang in his 2014 Raison d'être of insulin resistance: the adjustable threshold hypothesis. J. R. Soc. Interface 11: 20140892. http://dx.doi.org/10.1098/rsif.2014.0892 offers a very different account to the standard one. And the regulation is not just hormonal—the hepatic vagus, for example, is required for the glucoregulatory effect of glucagon (see Mighiu et al, 2013, "Hypothalamic glucagon signaling inhibits hepatic glucose production", Nature Medicine, 19, 766–772.)

Putting these processes into the picture, of course, is important—particularly for interpreting the faster growth of Neanderthals. Two situations are possible. It might be that a brain that uses more glucose directly has by this an effect (without any particular selection) upon glucoregulation such that this causes body growth to slow—or it may need some further selection to refine the link. In the first case selection for more prolonged neuromaturation in our species would cause us to have slower growth by the mere fact of such prolongation. In the second, there might be a need for further evolution so that expensive neuromaturation could be permitted to happen by changes in how the body grows. There is another question: what causes the prolongation of expensive neuromaturation? Is there some inherited genetic factor which causes synapses to maintain a longer period of exuberance or could it be that something in the learning environment—vocal language perhaps?— that causes greater neural stimulation and that this in turn maintains such exuberance?

8. Future research

The situation today is much like that image in the video of Einstein looking in the side mirror while driving a car and having a blind spot where the science of the child Einstein and his brain and neuromaturation is hidden. While there is much research upon child metabolism and its homeostasis thanks to the clinical importance of treating paediatric diabetes, in terms of a general synthesise with human evolution, the situation is one of a Cinderella awaiting her funding prince. To change things is why I made response to Kuzawa.

One reason is the need to use radioactive tracers. MRI can create detailed images of the young brain but what metabolically is happening still remains off limits. Or does it? There are hints that alternatives to radioactive tracers might exist. One is the use of hypercapnia, hyperoxia and combined hyperoxia/hypercapnia manipulations such as discussed in Gauthier et al, 2012 "Absolute quantification of resting oxygen metabolism and metabolic reactivity during functional activation using QUO2 MRI" NeuroImage, 63,1353–1363.

If so, such techniques, or modifications of them might be used to provide scientific "sight" into what is presently blind to scientists. We need a targeted funding to further such development—not just because the science and the questions are interesting, but because what is presently hidden, could when revealed, change our attitudes to children—particularly those we allow each night to go hungry. Their brains are, after all, human brains—what are we—the more privileged members of the human species—allowing to happen to them? If we knew, rather than say the "right words", we might actually act.