

Human metabolic adaptations and prolonged expensive neurodevelopment: A review

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METABOLIC ADAPTATIONS

ABSTRACT

1. After weaning, human hunter-gatherer juveniles receive substantial ($\approx 3.5\text{-}7$ MJ day⁻¹), extended (≈ 15 years) and reliable (kin and nonkin food pooling) energy provision.
2. The childhood (pediatric) and the adult human brain takes a very high share of both basal metabolic rate (BMR) (child: 50-70%; adult: $\approx 20\%$) and total energy expenditure (TEE) (child: 30-50%; adult: $\approx 10\%$).
3. The pediatric brain for an extended period ($\approx 4\text{-}9$ years-of-age) consumes roughly 50% more energy than the adult one, and after this, continues during adolescence, at a high but declining rate. Within the brain, childhood cerebral gray matter has an even higher 1.9 to 2.2-fold increased energy consumption.
4. This metabolic expensiveness is due to (i) the high cost of synapse activation (74% of brain energy expenditure in humans), combined with (ii), a prolonged period of exuberance in synapse numbers (up to double the number present in adults). Cognitive development during this period associates with volumetric changes in gray matter (expansion and contraction due to metabolic related size alterations in glial cells and capillary vascularization), and in white matter (expansion due to myelination).
5. Amongst mammals, anatomically modern humans show a unique pattern in which very slow musculoskeletal body growth is followed by a marked adolescent size/stature spurt. This pattern of growth contrasts with nonhuman primates that have a sustained fast juvenile growth with only a minor period of puberty acceleration. The existence of slow childhood growth in humans has been shown to date back to 160,000 BP.
6. Human children physiologically have a limited capacity to protect the brain from plasma glucose fluctuations and other metabolic disruptions. These can arise in adults, during prolonged strenuous exercise when skeletal muscle depletes plasma glucose, and produces other metabolic disruptions upon the brain (hypoxia, hyperthermia, dehydration and hyperammonemia). These are proportional to muscle mass.
7. Children show specific adaptations to minimize such metabolic disturbances. (i) Due to slow body growth and resulting small body size, they have limited skeletal muscle mass. (ii) They show other adaptations such as an exercise specific preference for free fatty acid metabolism. (iii) While children are generally more active than adolescents and adults, they avoid physically prolonged intense exertion.
8. Childhood has a close relationship to high levels of energy provision and metabolic adaptations that support prolonged synaptic neurodevelopment.

1. INTRODUCTION

1.1. Unique human metabolic innovations

Anatomically modern humans (*Homo sapiens sapiens*) are often viewed as biologically unique in regard to possessing articulate thought, language and symbolic culture (human specific cognitive capabilities). However, humans are also unique or specialized in several less appreciated ways related to energy and glucose metabolism.

- Following weaning, human juveniles receive substantial ($\approx 3.5\text{-}7 \text{ MJ day}^{-1}$), extended (≈ 15 years) and reliable energy (kin and nonkin food pooling) provision (see fig. 1 on page 7 for the marked contrast between consumption and production between chimpanzees and hunter-gatherer forages) (Kaplan, 1994; Kaplan, Hill, Lancaster, & Hurtado, 2000).
- The childhood (pediatric) and the adult human brain takes a higher share of both basal metabolic rate (BMR) (child: 50-70%; adult: $\approx 20\%$) and total energy expenditure (TEE) (child: 30-50%; adult: $\approx 10\%$) than any other animal (see discussion below, and figs. 2-3 on page 8).
- The pediatric brain for an extended period ($\approx 4\text{-}9$ years-of-age) consumes roughly 50% more energy than the adult one, and after this, continues during adolescence, at a high but declining rate (see fig. 4 on page 29). Within the brain, childhood cerebral gray matter has an even higher 1.9- to 2.2-fold increase in energy consumption (Chugani, 1998; Chugani, Phelps, & Mazziotta, 1987).
- This metabolic expensiveness is due to:
 - i. the high cost of synapses (74% of total brain energy expenditure in humans, (Attwell & Laughlin, 2001, p. 1140)), and
 - ii. prolonged exuberance of synapses (up to double that of adults) that is needed while human neural circuits undergo connection refinement (Huttenlocher, 2002; Huttenlocher & Dabholkar, 1997) (see fig. 5 on page 30).

Cognitive development closely associates during this period with volumetric changes to gray matter (expansion and contraction due to metabolic related size alterations in glial cells and capillary vascularization), and in white matter (expansion due to myelination) (see fig. 6A and 6B on pages 33 and 34).

- The energy needed for the pediatric brain is labile in spite of the pediatric liver (just under a third of adult size) producing near adult quantities of glucose (Bier et al., 1977). Moreover, the pediatric brain is more sensitive to glucose deficiency as it shows

neurological impairment (indexed by reduced P300 amplitude) at a much higher level of low plasma glucose (4.2 mmol L^{-1}) than the adult one (3.0 mmol L^{-1}) (Jones et al., 1995, see particularly their fig 3.).

- Amongst mammals, anatomically modern humans show a unique pattern in which of slow musculoskeletal body growth following by an adolescent size/stature spurt. (Bogin, 1999a; Walker, Hill, Burger, & Hurtado, 2006). (See fig. 7 on page 43). This pattern of growth contrasts with chimpanzees and other primates that have a sustained fast juvenile growth with only a minor period of puberty growth acceleration (Hamada & Usono, 2002; Walker, Hill et al., 2006) (fig. 8 on page 54). The existence of slow childhood growth in anatomically modern humans (*Homo sapiens sapiens*) has been shown to date back to 160,000 BP using x-ray synchrotron microtomography of tooth enamel (Smith, Tafforeau et al., 2007). The same technique, however, suggests that archaic *H. sapiens* species such as Neanderthals had a different and faster juvenile growth (Ramirez Rozzi & Bermudez De Castro, 2004; Smith, Toussaint, Reid, Olejniczak, & Hublin, 2007).
- In adults, skeletal muscle (the main nonbrain glucose using tissue) during prolonged intense exercise creates in a mass proportionate manner brain impairment due to:

plasma glucose depletion (Coyle, Coggan, Hemmert, & Ivy, 1986; Nielsen, Febbraio, Ott, Krstrup, & Secher, 2007),

hypoxia (Dempsey, Hanson, & Henderson, 1984; Subudhi, Lorenz, Fulco, & Roach, 2008),

dehydration (Baker, Conroy, & Kenney, 2007; Cian, Barraud, Melin, & Raphel, 2001),

hyperthermia (Nybo, Moller, Volianitis, Nielsen, & Secher, 2002; Nybo & Nielsen, 2001; Secher, Seifert, & Van Lieshout, 2008), and

hyperammonemia (Nybo, Dalsgaard, Steensberg, Moller, & Secher, 2005).

The skeletal muscle of children during strenuous exercise is adapted to limit the possible existence of such potential metabolic disturbances upon the brain.

- (i) Due to its limited mass as result of slow growth and small body size.
- (ii) Its exertion metabolism is less anaerobic (i.e. nonoxidative glucose using) than in adults (Boisseau & Delamarche, 2000)
- (iii) Its exercise aerobic oxidization is also biased to the metabolism of free fatty acids rather than the uptake of glucose (Timmons, Bar-Or, & Riddell, 2003).
- (iv) Also while children are more active than adolescents and adults (Sigmund, De Ste Croix, Miklankova, & Fromel, 2007), they minimize engagement in prolonged intense physical exertion (Bailey et al., 1995; Gilliam, Freedson, Geenen, & Shahraray, 1981).

1.2. Outline of review

These above human specific metabolic traits are reviewed here in the context of their adaptive role in supporting the neurodevelopment of anatomically modern human cognitive capabilities. This discussion details the reasons why neurodevelopment in general, and human neurodevelopment, in particular, is metabolically expensive. It also reviews the adaptations in the child's body that minimize metabolic disruption to its neurodevelopment. The review specifically does not directly address the adaptiveness of the enhanced cognitive capacities acquired in childhood (except in regard to metabolic issues) to anatomically modern humans.

1.3. Technological innovations

Three technological advances make this review particularly opportune.

1.3.1. Qualitative MRI. Volumetric MRI already reveals profound maturation related changes occurring during the period of human prolonged expensive neurodevelopment. These changes correlate, moreover, to the acquisition of human specific cognitions (Lenroot & Giedd, 2006; Shaw, 2007). In the near future, this research will considerably expand with the use of new forms of MRI that allow the qualitative study of the maturation of gray and white matter (such as high b value diffusion weight (Ben Bashat et al., 2005)), proton spin-lattice relaxation time (T1) MRI (Steen, Ogg, Reddick, & Kingsley, 1997)), and longitudinal relaxation rate (Sigalovsky, Fischl, & Melcher, 2006). Also improved forms of MRI are now available for the investigation of developmental changes in white matter, for example quantitative diffusion tensor tractography MRI (Eluvathingal, Hasan, Kramer, Fletcher, & Ewing-Cobbs, 2007; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008), and fractional anisotropy and mean diffusivity tensor MRI (Schmithorst, Wilke, Dardzinski, & Holland, 2005).

1.3.2. Genomics. Human genomic research identifies metabolic genes and their up regulated expression in the adult human and primate brain as having undergone positive selection (Caceres et al., 2003; Grossman, Wildman, Schmidt, & Goodman, 2004; Haygood, Fedrigo, Hanson, Yokoyama, & Wray, 2007; Uddin et al., 2008; Uddin et al., 2004). The technical possibility now exists to extend such research to the pediatric brain as it has already been done with the fetal one (Uddin et al., 2008). The Neanderthal genome (Green et al., 2006; Noonan et al., 2006) further allows a direct DNA comparison between the genes involved in the human genome with those in Neanderthals. This raises the prospect of a paleogenomic orientated detailing of the metabolic adaptations that support human prolonged expensive neurodevelopment.

1.3.3. X-ray synchrotron microtomography of tooth enamel. The recent development of x-ray synchrotron microtomography of tooth enamel of immature fossil *Homo* (Tafforeau & Smith, 2008) permits the investigation of the evolution of early *H. sapiens sapiens* (Smith, Tafforeau et al., 2007), and Neanderthal growth trajectories (Smith, Toussaint et al., 2007).

This will allow the detailed modeling of the growth pattern differences in *Homo* species, and through this, its changing role in preadult energy metabolism.

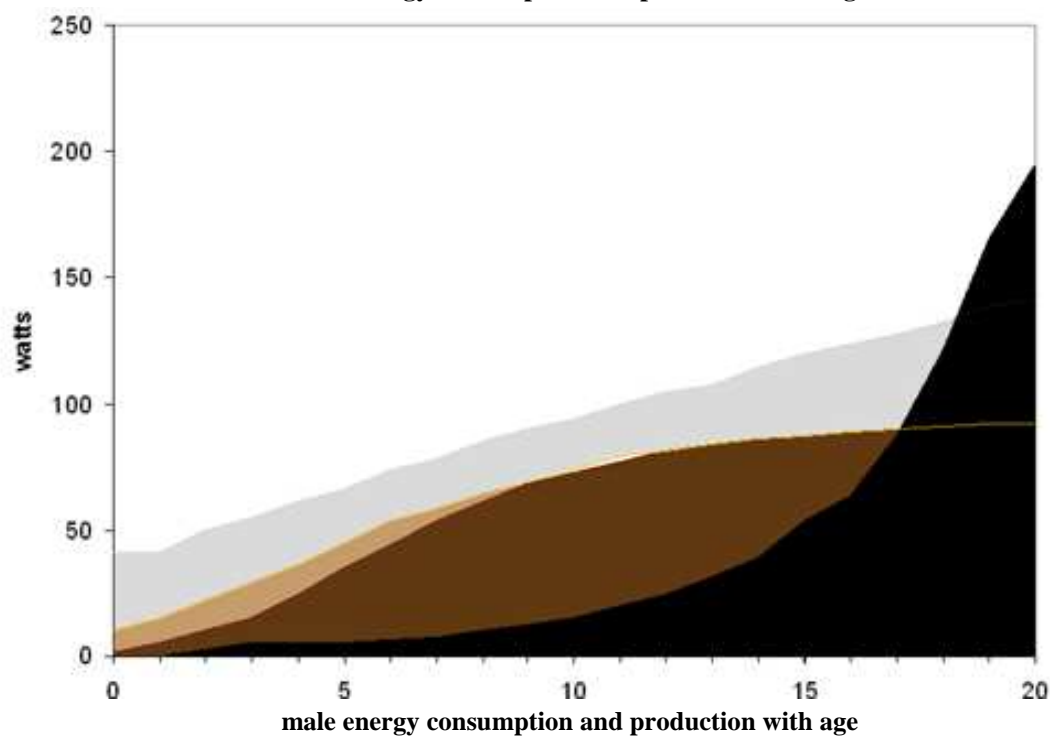
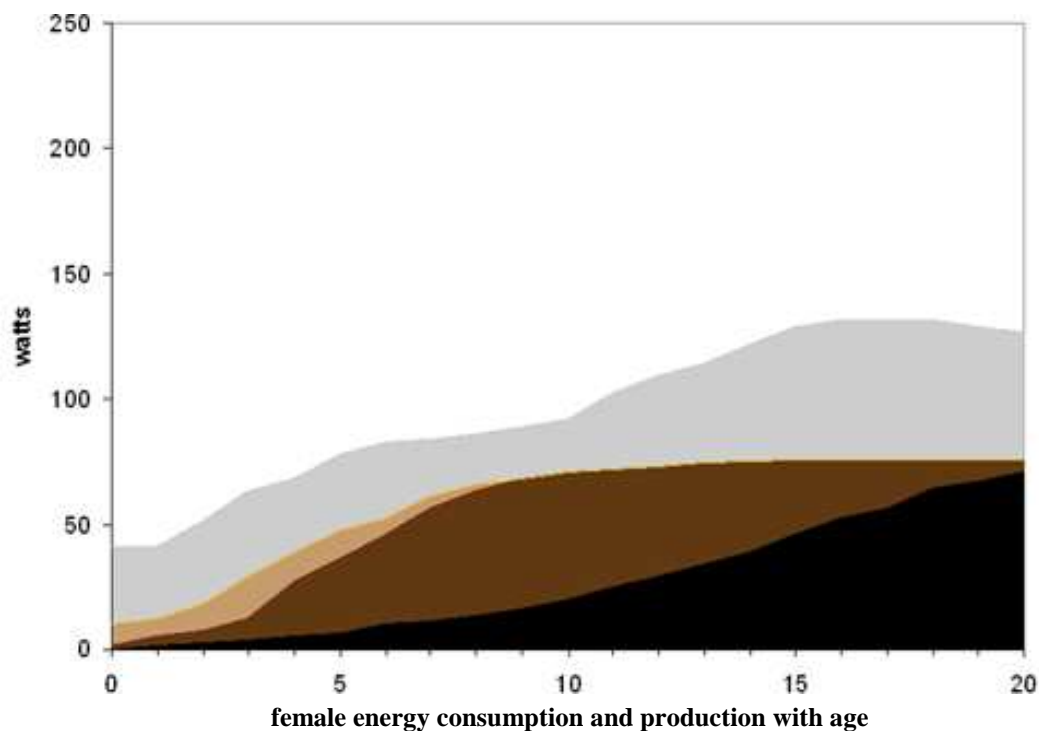
2. BRAIN EVOLUTION AND BRAIN ENERGY CONSUMPTION

The vertebrate central nervous system (CNS) is a high energy consuming organ due to the metabolic costs associated mostly with synapse junction activation: 34% in rodents (Attwell & Laughlin, 2001), and 74% in humans (Attwell & Laughlin, 2001, p. 1140). These energy demands contrast with those made by other organs in that they are to a large extent similarly high whether the brain is active or not. For example, there is a limited $\approx 12\%$ increase in total brain glucose consumption during problem solving compared to mental rest (Madsen et al., 1995). Task related local area activations are higher than this but their effect on total brain energy consumption is reduced by counterbalancing cortical area deactivations elsewhere (Raichle & Mintun, 2006; Seitz & Roland, 1992; Singh & Fawcett, 2008). In contrast, skeletal muscle can show a ≈ 2000 -fold difference between rest and maximum energy consumption, for example, when human adults jump from swat. For continuous activity, such as extending repetitively the human knee, the difference is less but a still substantial ≈ 40 -fold¹.

Further—and a major topic in this review—the energy costs of the brain are far greater per unit mass or volume of neural tissue in juveniles than in adults due to exuberant developmental synaptogenesis (about 2-fold in the human cerebral cortex).

The proportion of the body's basal metabolic rate (BMR) devoted to the CNS is highly conserved across mature vertebrates being 2.7-7.7% (mean 5.3%) irrespective of vertebrate class, size, and thermoregulatory status (homothermy, $5.5 \pm 0.7\%$, or ectothermy, $4.8 \pm 0.6\%$) (Mink, Blumenschine, & Adams, 1981). (The size BMR allometric function is unity (Mink et al., 1981) allowing discussion of percentages independent of body size.) In this context, it is notable that the proportion of energy allocated to the adult CNS is markedly increased in primates ($>10\%$), and particularly in modern humans (20%). Concomitant with this increase, there has been the positive selection in primates and humans upon energy related genes that have otherwise been generally conserved in vertebrate evolution, such as the electron carrier molecule cytochrome c, (Grossman et al., 2004). As Grossman and colleagues note of cytochrome c, that it, “underwent two periods of increase amino acid replacement: the first occurred early in vertebrate evolution and the second occurred at the stem of the anthropoid primates” (Grossman et al., 2004, p. 582).

1. Resting skeletal muscle has a BMR of 0.63 W kg^{-1} (Elia, 1992). An adult human male when jumping up from a swat mechanically generates 314 W kg^{-1} (Scholz, D'Aout, Bobbert, & Aerts, 2006): since muscle energy conversion is only 25% efficient, mechanical and heat production will be $\approx 1200 \text{ W kg}^{-1}$. (Interestingly, bonobos produce nearly twice as much mechanical energy in such jumps, 615 W kg^{-1} (Scholz et al., 2006).) For continuous knee extending, this consumes $0.5 \text{ mmol glucose min}^{-1} \text{ kg}^{-1}$ of muscle (Richter, Kiens, Saltin, Christensen, & Savard, 1988). Assuming complete oxidation and that this fuel is the only source of energy to the muscle, this is equivalent to $\approx 24 \text{ W kg}^{-1}$.



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Fig 1. The two panels show the energy consumption and production with filled in graph “slopes” of humans and chimpanzees. Humans are the very light gray (consumption) and the black (production) filled in graph slopes; chimpanzees, the light brown (consumption) and the dark brown (production) ones. Energy is shown in watts to be uniform with the other graphs in this review. Humans (very light gray) receive much more energy initially but chimpanzees (light brown) (which are slightly smaller) begin to catch up by 8 years-of-age but this is due to their own energy production (brown), which is not the case in humans (black). Energy production only comes to equal energy consumption for men at 18 years-of-age, while for women this is delayed until 45 years-of-age when they cease to be mothers of dependent children (off graph). Based upon human data averaged for the Ache, Hiwi, and Hadaza hunter-gathering bands and chimpanzees (Kaplan et al., 2000, fig.3).

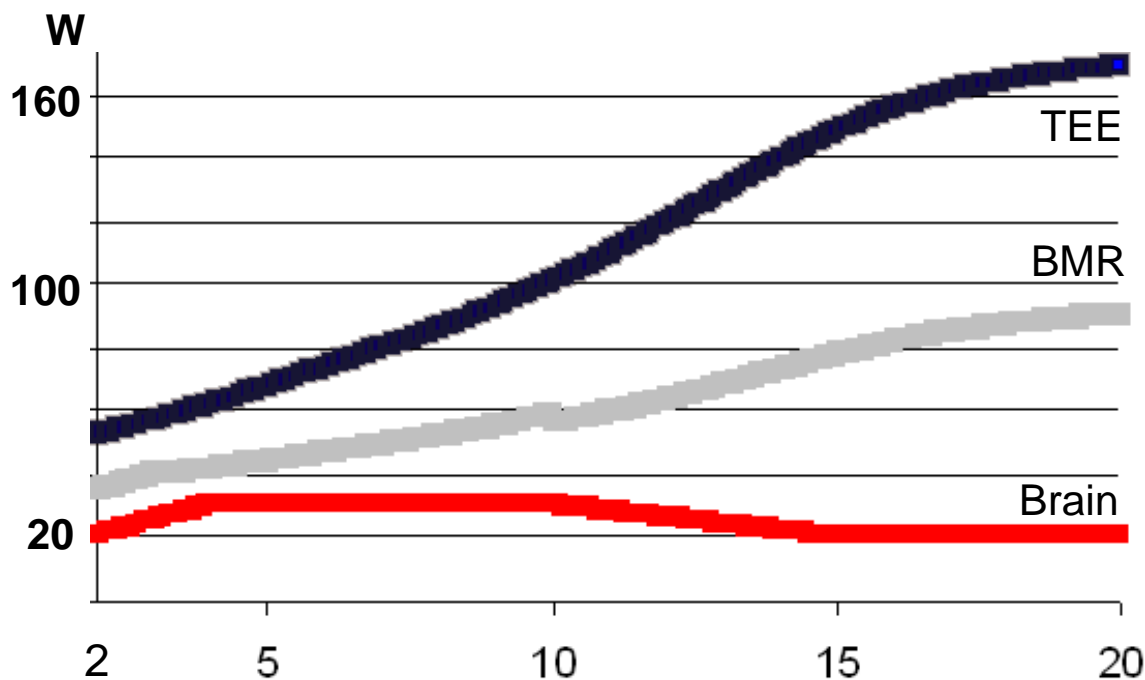
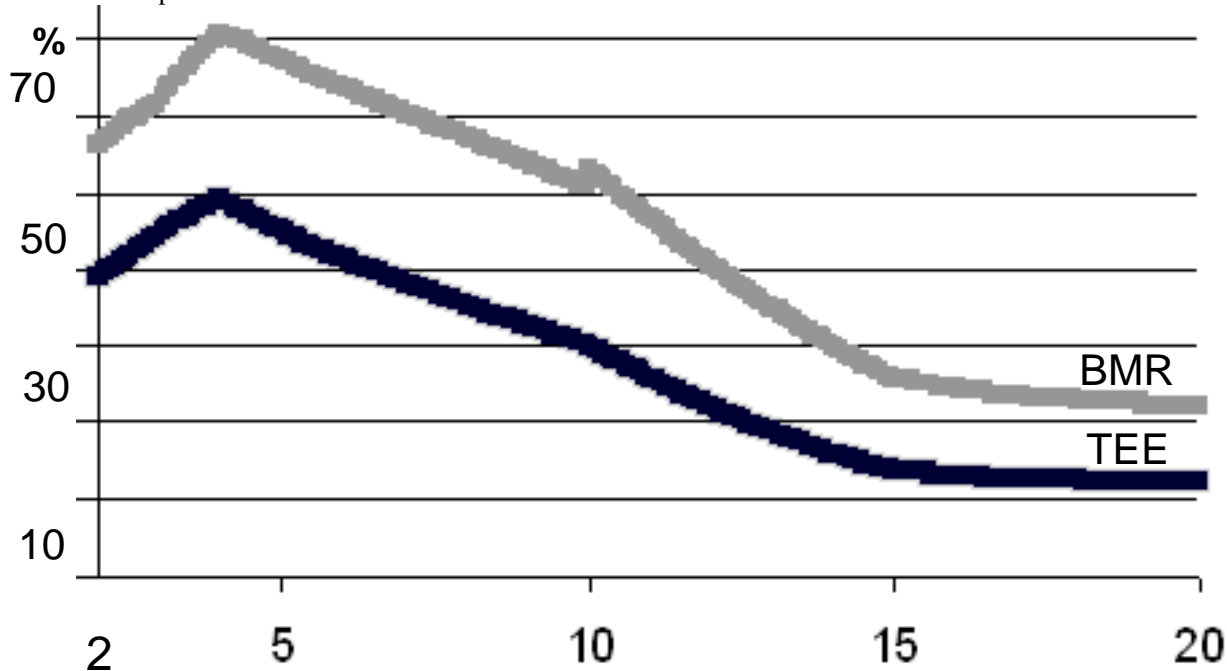


Fig. 2 The total energy expenditure (TEE) is based upon the predictive equations for boys and men in (Torun, 2005). The basal metabolic rate (BMR) is based upon the predictive equations in (Henry, 2005). The slight nonsmoothness in the BMR line around 10 years-of-age is due to two equations for different age partitions that do not exactly match at this transitional age. The brain line is based on children between 4 and 9 years-of-age having a 50% higher metabolic rate than adults, and that this smoothly declines between 10 and 15 years-of-age to adult levels. Energy is expressed in watts. Note, the energy consumption appears slightly higher than the total energy expenditure in fig. 1. However, the graph line for this in men in fig. 1 continues upwards and reaches 157 W which is in a similar range to that in fig. 2. It also, moreover, concerns hunter-gatherers from groups that tend to have smaller body sizes than those populations used to create the TEE and BMR predictive curves.

Fig 3 The figures for TEE and BMR energy consumption in fig. 2 expressed as percentages of brain energy consumption.



2.1. Origin of the CNS share in juveniles

The immature CNS has a considerably higher energy consumption than mature CNS (discussed below in section 4). Due to this, it is usually the maternal energy support provided to the developing brain (such as during pregnancy and lactation in mammals) that determines the adult brain, and through this, its later energy needs (Martin, 1981; Martin, 1989, 1996; Martin, 2007). Thus, the high share of BMR in adult primates and humans originates in adaptations that have led them to receive a high energy supported neurodevelopment.

2.2. Primate energy provision to young

Primates as an order of mammals make an unusually high energy investment in each of their offspring: (i) gestation is prolonged, and (ii) usually a single birth. After this, postnatally infants and juveniles receive (iii) an extended period of lactation and (iv) protected and prolonged dependency (Martin, 2007). While this pattern of high investment is not unique to primates (it is found also, for example, in Cetacea, dolphins and whales), primates also provide their young with novel energy requiring forms of assistance. For example, as an order, primates, uniquely (apart from Chiroptera) have on several occasions evolved the long-duration “fur riding” carriage of their young, an energetically costly form of support provided to young by their mothers (Ross, 2001).

2.2.1. *Forage-while-with-mother*

Primates gradually wean juveniles while the young engage in foraging of their own in physical proximity to their mothers (an infant chimpanzee, starts increasingly to forage after six months, though weaning does not stop until 4 to 5 years-of-age (Hiraiwa-Hasegawa, 1990)). Lactation adapts to this as it is “on demand”. This kind of lactation contrasts with “on schedule” lactation which occurs when the offspring are not carried for long durations but deposited in nests and so regularly separated from their mothers (Martin, 2007). Fur carrying and “on demand” lactation is important since it allows offspring to stay together with their mothers while they both forage.

Foraging-while-with-mother advantages the transmission of specialized foraging related skills and knowledge such as types of food, existence of fallback foods, the location and nature of foraging sites, techniques in foraging including tool use such as nut cracking (Boesch & Boesch, 1990) and termite-fishing (Lonsdorf, 2006) (though not with instruction, (Csibra, 2007)). Chimpanzees will, for example, prevent their young eating inedible fruits, and young chimpanzees look at their mother before ingesting novel foods (Ueno & Matsuzawa, 2005). The tolerated “thief” of food by offspring from their mothers provides a means of familiarizing them with safe food (Jaeggi, van Noordwijk, & van Schaik, 2008). Male chimpanzees (a species that remains in the same group and territory as their mothers) during

food shortages visit the same foraging areas used by their mothers up to 20 years after their deaths, since these are the areas for which they have acquired, due to their association with her, their greatest foraging-related knowledge (Murray, Gilby, Mane, & Pusey, 2008). These skills allow the better exploitation of local resources, and so make adult foraging better adapted to particular local habitats.

2.2.2. *Subsidized expert skill learning*

Continued lactation while foraging with mother is also developmentally critical since it allows a juvenile to take the learning risks needed to acquire expert forager skills. While much food is readily available for direct picking, many foods require skills that involve experimental learning and deliberate practice. Gorillas, for example, feed upon leaves with powerful stings by folding their edges so the stings are innermost when ingested to prevent them hurting their lips (Byrne & Byrne, 1993). This skill requires trial and error learning to perfect (Byrne & Byrne, 1993). Another example in chimpanzees is cracking nuts with hammerstones upon anvils: this skill requires considerable practice and patience before motor coordination allow that nut shells can be broken to yield their high energy kernels intact (Boesch & Boesch, 1990). The first attempts of a novice primate forager at such a food acquisition skill are usually unsuccessful. A mother's presence therefore makes this practice possible since she can provide an alternative food—lactation—during the learning period when their attempts at a new foraging skill initially fail².

Due to this conditional nutritional support, juvenile primates can afford to experiment with foraging skills observed in others, and so allow their cultural transmission (Horner, Whiten, Flynn, & de Waal, 2006). These copied skills by reason of their higher motor coordination requirements will have before expertise develops much early failure. The provision of lactation ensures, however, that they can be learnt without compromising the juvenile's energy intake. As a result, not only can such skills culturally transmit but that juveniles grow into adults that possess the complex food foraging skills—and so the high energy acquiring ones—that can support such transmission.

2.2.3. *Social skill investment*

Fur riding carriage by enabling a juvenile to be constantly with their mother also allows them greater opportunities to acquire by observation and participation the skills needed for social interaction, cooperation and communication. These skills are particularly important to fission-fusion primates such as chimpanzees, since they make possible a band-type of social group in which varying sized foraging units are constantly and formed and reformed. This allows for the better exploitation of variably available food resources than can be made by primates that live in troop-type social groups that do not break up in this flexible resource adaptive manner

2. A link between foraging skills and resources to “waste” on learning has also been found (in regard to better “body condition”) with meerkats (Thornton, 2008).

(Chapman, Wrangham, & Chapman, 1995; Hashimoto et al., 2003). Such social interaction and cooperation skills also allow for the making, organizing and coordinating of hunting parties (Boesch & Boesch, 1989).

In summary, the increased energy investment made in young by primates closely interacts with juveniles learning superior food acquiring related skills. These skills, in turn, later on, play a critical role when they are adults in enabling them to obtain the large amounts of food energy needed to provide such high energy investment in their own offspring's cognitive development.

3. HUMAN HIGH-ENERGY FOOD PROVISIONING

3.1. Adult provision of supplementary food

Humans build upon such primate high energy investment in their young both by increasing it considerably (Robson & Kaplan, 2003), and by providing them with additional forms of energy support. This high investment greatly enhances the capacity of humans to acquire complex adult cognitions. One key innovation is that while lactation is gradually replaced with weaning foods (as in many other primates), these foods are to a large extent not gathered by the juvenile but provided by adults (including nonkin). By the age of 18, in this way, young individuals in hunter-gather bands receive 55×10^9 J, while obtaining energy that is only around a quarter of this from their own efforts (Kaplan, 1994, pp. 760-763). This practice amongst primates is unique to humans though some nonprimate animals—canids [dogs, wolves, foxes], meerkats, and birds—also return with prey fragments or regurgitate them (Macdonald, Creel, & Mills, 2004). However, this is provided by parents and alloparents that are usually related to the juveniles, and the period of support does not usually last more than a year. Human provisioning investment—both in terms of its prolonged length and its freeing immature individuals from immediate food acquisition needs—is important as it puts human juveniles in a novel evolutionary situation in regard to the metabolic support of the neurodevelopment needed to become cognitively competent adults.

3.1.1. High-energy foods and adult skills

Several factors interlink with this shift by humans to the highly prolonged adult provisioning of juveniles. One is the dietary change that has occurred in *Homo* to foods that require highly specialized adult skills. The australopith diet like that of other hominoids was predominately vegetarian (Spoonheimer et al., 2006; Teaford & Ungar, 2000), and so required few adult specific skills. But with the *Homo* diet, this changed to one that depended upon proficient complex forms of expertise since it included high-energy foods (such as meat and tubers) that were acquired by adults in wide territory, tool and socially cooperative based hunter-gathering (Foley, 2002). Further, at some stage, the energy and nutrition content of such foods was

enhanced (detoxification, increased digestibility) by adult skills in cooking (Wrangham & Conklin-Brittain, 2003; Wrangham, Jones, Laden, Pilbeam, & Conklin-Brittain, 1999).

3.2. Group food pooling behavior

A further key behavioral innovation—because it radically changes the reliability of energy provision and its support for juveniles and mothers—is group food pooling behavior (Kaplan & Hill, 1985). Food pooling is distinct to the limited food sharing occasionally found in nonhuman primates as it is not necessarily linked to direct reciprocity, tolerated thief, nor focused upon kin (these issues are reviewed in Gurven, 2004; Kaplan & Hill, 1985). In studies of extant human hunter-gatherers, group food pooling behavior, moreover, has been found to occur in regard to a substantial proportion of high energy foods (Kaplan & Hill, 1985). In contrast, nonhuman primates such as chimpanzees show no similar behavior failing to provide food to other nonkin group members when it could be done at a very low cost to themselves (Silk et al., 2005; Vonk et al., 2008).

Group food pooling behavior minimizes differences in the individual capacity to acquire food resources. Importantly, it also makes food availability more reliable for any individual band member since it buffers them against daily variability in their own foraging success (Kaplan & Hill, 1985). This is crucial to survival since the high-energy foods exploited by human foragers cannot on a daily basis be relied upon as they are environmentally patchy.

A consequence of food pooling is that hunter-gatherer foragers lack within group variations in body mass index and percent body fat (except those linked to gender), and exist in what anthropologists call “nutritional homogeneity” (Sherry & Marlowe, 2007). Moreover, this equal access to resources across the forager band has the effect of equalizing the growth of its children irrespective of the advantages possessed by their parents: in foragers, “kin groups, some more powerful than others either in influence or in sheer number, were not able to gain superior access to resource and then divert them to their own children” (Daper & Howell, 2005, p. 280). This situation contrasts with wild hominoids such as chimpanzee that show marked individual differences, particularly as juveniles, in mass related to their own or their mother’s ability to acquire foods, together with their mother’s dominance status (Pusey, Oehlert, Williams, & Goodall, 2005).

3.3. Human physiological adaptations and food pooling behavior

Group food pooling behavior radically changes the metabolic situation of mothers that due to them being pregnant or caring for dependents cannot obtain by themselves sufficient food for their needs. Human mothers receive substantial additional energy intake ($\approx 3.5 \text{ MJ day}^{-1}$) (Kaplan et al., 2000, fig. 3) that more than adequately covers the cost of pregnancy (325 MJ total; for the first, second and third trimesters: 0.4 MJ day^{-1} , 1.2 MJ day^{-1} , 1.9 MJ day^{-1}), and lactation (2.6 MJ day^{-1}) (Butte & King, 2005; Sellen, 2007). This provisioning has effected

human physiology: human neonates have a birth weight that is roughly twice that of primates of similar size and length of gestations (humans: 3.4 kg, 267 days; chimpanzees, 1.7 kg, 235 days; orangutans, 250 days, 1.7 kg; gorillas, 2.1 kg, 260 days) (Martin, 1989). They also provide more energy early in lactation: a human infant by the age of two has gained 25% more of its adult weight (12.7 kg of 70.6 kg) than a chimpanzee by this age (12.6 kg of 59.5 kg). This difference can be seen in Fig. 1 on page 7 in the different neonatal energy consumption by chimpanzees and hunter-gatherer humans³.

Another factor, due to bipedality and lack of body hair, is that human mothers have to physically hand carry their very young infants. This makes such mothers more dependent upon support as infant carrying (without a sling) limits their ability to gather foods. It is also energetically costly (Wall-Scheffler, Geiger, & Steudel-Numbers, 2007).

3.3.1. Energy banking

The extra weight gain in human juveniles is physiologically novel in that it provides for tissue energy banking. The above noted greater weight of the human newborn is due to increases in adipose tissue (15% at birth) in the last trimester (Kuzawa, 1998). It also underlies 2 year-old infants' rapid weight gain since this is mostly not growth in skeleton and muscle but adipose tissue (70% of its growth expenditure (Kuzawa, 1998)). Energy banking tissue as result makes up to 25% of body weight in 18-month-olds (compared to 15% in 5 and 10 year-olds, 11% male adults, 20% female adults) (Kuzawa, 1998). Given the energy involved, this energy banking by fetuses and infants depends upon the existence of high energy provision during pregnancy and lactation from their mothers, and so in turn, the existence of the energy support that they receive from group food pooling behavior. (See Appendix 1 for the evolutionary importance of energy banking).

This human energy banking generally enhances survival since mortality in primates occurs mostly during the first year of life.

- Human infants are particularly vulnerable as they cannot forage foods if food stuffs are not supplied to them—such energy banks ensure that even if adults fail to obtain food due to temporary problems (famine, poor weather, illness) that they can survive such periods.
- Another problem specific to humans is the greater vulnerability of human infants compared to other primate infants to such energy shortages due to the exceptionally high energy consumption (relative to the rest of their bodies) of their

3. The graphs in fig. 1 based on food acquisitions and distribution budgets in Ache, Hiwi and Hadza seem to overestimate slightly the intake of infants and children, while underestimating them for adolescents when compared to energy provision given in lactation and estimates of age related TEE based on modern populations. The source of discrepancy is not clear but it could relate to assumption(?) that “children begin at a consumption level of 0.3 of a standard consumer” (Kaplan et al., 2000, notes to fig. 3).

very large brains (Kuzawa, 1998; Leonard, Robertson, Snodgrass, & Kuzawa, 2003) (see figs. 2 and 3).

- A major cause of early death is the very high energy demands of illness: every 1 degree C rise in body temperature increases BMR by 13%; infections can raise resting metabolic rate by 15-30%, and cause 15-30% loss in body weight (Lochmiller & Deerenberg, 2000). Energy banking could be crucial to provide the energy capital needed to afford fever heat losses that in humans are exuberated in their cost due to the lack of insulating body fur and sweat based thermoregulation.

3.3.2. *Deciduous dentition and child appropriate food*

Human children spend two to three years after they have weaned (2.3-3.2 years-of-age) (Marlowe, 2006; Robson, van Schaik, & Hawkes, 2006) without adult dentition (acquired 5.5-6 years-of-age). As a result, instead of lactation, they rely in this critical period (in which they start high energy neurodevelopment) upon food ingested with deciduous dentition (in place by 24 months) that has thin enamel and short roots, and so is easily broken and worn. Thus, for two to three years, unlike other primates that receive a much longer lactation, they are totally dependent upon ingesting high energy adult foods for which they as juvenile primates are not evolved, and for which they have inappropriate teeth (Bogin 1997; Kennedy, 2005). Further, their digestive tracts cannot not always absorb adult foods (Bogin 1997). This requires that adults not only provision them but that they also can select and prepare juvenile appropriate foods. This adult provisioning contrasts markedly with the occasional nonlactational support given to chimpanzee and ape juveniles where mothers rarely give food, or allow it to be “thieved” (Jaeggi et al., 2008; Nishida & Turner, 1996). Such nutritional support is even limited when it is begged and whimpered for by the dependent juvenile: “only food scraps are given and difficult-to-process food rather than easy-to-process food is more likely to be taken” (Nishida & Turner, 1996). As noted above, its function might be less nutritional than to provide juveniles with information about what foods are safe to eat (Jaeggi et al., 2008).

3.3.3. *Children and energy provisioning*

Human juveniles continue to receive substantial ($\approx 3.5-7$ MJ/day) and prolonged (≈ 15 years) energy support (Kaplan et al., 2000), following the end of weaning (2.3-3.2 years-of-age in hunter-gatherer forgers: (Marlowe, 2006; Robson et al., 2006)).

This provisioning makes human infant survival after the age of one largely independent of the continued survival of its mother (Sear, Steele, McGregor, & Mace, 2002). (Before the age of one, a child’s survival links not only to nutritional support but the antibodies—and so enhanced immunity—obtained from its mother’s milk). It also—the topic of the sections 4, 5 and 6 of this review—could allow for humans to have an especially extended period of synapse exuberance and so metabolically expensive neurodevelopment with a consequent capability to learn complex cognitions.

3.4. Energy banking as evidence for ancient food pooling behavior

The existence of energy banking adaptations in fetuses and infants, as noted above, depends upon mothers obtaining increased energy intake from human food pooling behavior. This is theoretically important since the food pooling behavior seen in contemporary human foragers (Kaplan & Hill, 1985) potentially could have originated more recently than the Middle Paleolithic when the first anatomically modern humans evolved. All the researched contemporary, or near-contemporary hunter-gatherer bands have (i) been subject to contact with nearby agrarian communities, and/or (ii) depend upon Upper Paleolithic technologies such as the bow and arrow. These might have changed their behavioral profile. However, the existence of physiological adaptations that link to food pooling behavior argue that such behavior must have also been in existence when the adipose tissue composition biology of modern humans arose, and so present, at least, by the period of the first early anatomically modern human hunter-gatherers, 160,000-200,000 BP.

4. ENERGY COSTS OF BRAIN DEVELOPMENT

4.1. Adaptive cost space of brain development

Modern human brains, in addition to the extensive metabolic support noted above, have cognitive capacities that are distinct to those found in other animals. This raises the question of the opportunities that arose to acquire complex cognitive capabilities when energy intake is removed as a limiting factor upon neurodevelopment.

Three factors seem particularly pertinent for review, of which the first two are discussed immediately below. The third is given special treatment in sections 5 and 6.

- (i) The total size of the immature brain compared to that of the body both physically (mass, volume), and in terms of its cell numbers. This is important since a larger brain relative to the body, *ceteris paribus*, will cause it to have greater percentage energy needs.
- (ii) The extent to which the immature brain per unit volume or mass due to the nature of its postnatal neurodevelopment has an increased metabolic cost compared to the adult brain. Several contributing factors exist here, notably the degree to which its synapses are exuberant in numbers compared to that in adults, and the energy inefficiency of axons prior to their full adult myelination. These factors increase the expense of supporting an immature brain in addition to that created by its large size relative to that of the immature body.

- (iii) The degree to which the period of metabolically expensive neurodevelopment is extended. Is it a few months, or is it stretched over something like a decade? This is important because the longer expensive neurodevelopment is prolonged, the more its evolutionary existence will depend upon new forms of energy provision arising that can support juveniles for such a protracted period.

4.2. Absolute and relative size of the immature brain

Unlike other body organs, the brain does not scale up through cell addition during development but is formed in the fetus with most of its adult cell mass of neurons (and to a lesser extent also that of its glial support cells). In humans, the peak of neuron production is 15-20 weeks gestation, and that of glial cells from 30 weeks to end of first year (Dobbing, 1970, fig 2). No significant numbers of new neurons (Bhardwaj et al., 2006; Gould, 2007) are created after birth, though there is a continual turnover in glial cells (Bhardwaj et al., 2006). This initial cell mass is created (like that of many tissues including the neurodevelopment of the spinal cord and periphery nervous system) with an initial exuberance of components (neurons, axons, synaptic junctions) that with maturation gets eliminated and pruned (Hua & Smith, 2004; Purves & Lichtman, 1980). Around 70% of the brain's initial neurons (Rabinowicz, de Courten-Myers, Petetot, Xi, & de los Reyes, 1996), and a roughly equal percentage of axons (LaMantia & Rakic, 1990) are in this way mostly removed by the time of birth. Thus, the early immature brain may have three to four times more neurons than the adult brain, even though the immature brain takes up a smaller volume than the adult one.

Brain maturation leads to brain volume expansion:

- (i) In the cerebral gray matter, this is due to increased space being occupied by the dendritic arbors upon which synapses exist, and the microvascular capillaries and glial cells from which synapses gain metabolic support. These make up a substantial component of gray matter. Every 1 mm³ of gray matter, for example, contains, 4 m of capillaries (Kreczmanski et al., 2005). In the human cerebral cortex, depending upon layer, roughly half to two glial cells exist for every neuron (Gittins & Harrison, 2004). Apart from neuropil, gray matter in nonelderly adults is 3.8-8.6% blood (Leenders et al., 1990). The volume of human gray matter has a maturational inverted U shape: it initially expands due to synapse exuberance, and then, as this gets pruned and eliminated it shrinks—these volume changes link primarily to ones in metabolic supporting glial cells and capillaries (see section 4.6);
- (ii) In the cerebral white matter, volume expands due to increased myelination of its axons as the circuit connections between networks become better differentiated and integrated. White matter is in nonelderly adults 1.7-3.6% blood (Leenders et al., 1990). White matter has a delayed expansion relative to gray matter, and in

adolescence, its pattern of increase is broadly inverse to that of gray matter (Lebel et al., 2008)⁴.

While expanding overall the size of the brain, these two maturational changes do not increase its use of energy (indeed, they reduce it—decline in gray matter volume links to decreases in synaptic numbers, and so the size of their capillary/glial cell energy support; increased myelination makes axonal transmission more energy efficient).

The relative size of the brain to the body also reflects the concomitant but separately determined size increase that occurs in the rest of the body. Due to the initial large size of the immature brain (even if it is smaller than in the adult), the brain body ratio starts off high after birth and then decreases, usually abruptly (Kobayashi, 1963). The peculiar pattern of juvenile body growth that characterizes anatomically modern humans is discussed in section 8.

4.3. Metabolic cost of the immature brain

4.3.1. *Two neurodevelopmental stages with different costs and opportunities for adaptive innovation*

Compounding the high juvenile/ adult brain body ratio is that the immature brain consumes more energy per unit volume/weight than the adult brain. These neurodevelopmental costs can be divided broadly into those linked (i) to a predominantly embryo/fetus neuron and axon formation stage, and those linked (ii) to a predominantly postnatal infant/juvenile synapse junction proliferation and refinement stage. These two stages pose different evolutionary adaptive challenges, first, in regard to the energy costs that must be supported, and, second, in regard to their inheritable and environmental adaptively as to their adult cognitive capacities. In what follows, discussion mainly refers to the development of the cerebral hemispheres due to their predominance in primates (they make up 80% of the adult human brain (Filipek, Richelme, Kennedy, & Caviness, 1994)).

4.3.2. *Neuron and axon excess/elimination timetable*

The costs of the initial formation stage concern the energy needed to create the brain's initial overproduction of neurons and axons. This cost is proportional to adult brain size as this determines the number of cell numbers with which the brain is created. Since neurons (Rabinowicz et al., 1996) and axons (LaMantia & Rakic, 1990) are mostly eliminated before birth, or shortly postnatally, the expense of this stage is largely borne by the mother during pregnancy, and to a lesser extent during lactation. The sequence of developmental events that this involves occurs, moreover, within a highly conserved timetable across different mammalian species (Clancy, Darlington, & Finlay, 2001; Darlington, Dunlop, & Finlay,

4. One factor here is that by the time of adolescence, the cranial sutures of the skull have started to fuse constraining total brain to a fixed volume.

1999). This leaves two main variables at this stage open to evolutionary change. First, variation in the duration of the timetable of these developmental events (Clancy et al., 2001; Darlington et al., 1999). Second, the degree to which the initial embryonic neural precursor cells proliferate into neurons and glial cells of the brain, and so determine the eventual size of the brain (Chenn & Walsh, 2002).

4.4. Synaptic neurodevelopment

The postnatal stage concerns neurodevelopmental changes in gray and white matter. In the gray matter, these changes relate to the refinement of neural networks. These networks mainly consist of axons that link to synapses located on dendritic arbors. Each neuron has ≈ 12 mm of dendrite arbor, that when mature, can express up to $\approx 30,000$ synapses (Megias, Emri, Freund, & Gulyas, 2001). The diameter of the space in which the arbor extends can in humans be 1.0 mm (Elston et al., 2006, p. 33). The arbor also can reach up and down through the six cerebral cortex layers (about 3.1 mm) (Hutton, De Vita, Ashburner, Deichmann, & Turner, 2008). The neuron's soma exists in a particular layer that determines how its axon connections link with the synapses and dendrites of other neurons elsewhere in the brain. These connections can range from those to nearby mini- and macro- column groups (Casanova & Tillquist, 2008), to those with other parts of the cerebral cortex, or the subcortical brain, and in some cases, the spinal cord. White matter changes concern the myelination of the axons, and concern predominately the connections that link neural networks in different cortical areas.

4.5. Synaptogenesis and synapse elimination

Synapses are initially exuberant like neurons and axons. For example, the auditory cortex might have 29.4 synapses on each micrometer (μm) of dendrite in the newborn, but this quickly rises to an exuberant 55.7 synapses μm^{-1} in a 3.5 year-old, and then reduces in a 19 year-old, to 24.0 synapses μm^{-1} (Huttenlocher & Dabholkar, 1997, table 2) (see also fig. 5. on page 30, for changes in visual and prefrontal cortex synapse numbers).

However, while neurons and axons are created during one period and then with few exceptions fixed and subject only to later reduction, that of synapses is dynamic as they are constantly created and eliminated. This happens, moreover, within homeostatically determined set points that are open (unlike the evolutionarily conserved sequence that timetables the development of neurons and axons) to be adaptively modified by diverse genetic and environmental factors.

4.5.1. Synapse dynamic turnover within set points

$\approx 7\%$ of the adult macaque visual cortex synaptic boutons found on axons change each week, (Stettler, Yamahachi, Li, Denk, & Gilbert, 2006), and in the somatosensory cortex of 5-10 week-old mice, 17% dendritic spines change day to day; 23% last two to three days, and

50% last more than 30 days (Trachtenberg et al., 2002)⁵. However, other research suggests lower rates of change i.e. 87.5% of dendritic spines remaining after 3 weeks (Majewska, Newton, & Sur, 2006). Grutzendler and colleagues (2002) also estimates a half-life greater than 13 months for dendritic spines in adult mice. Accompanying such changes to synapses can be ones to the small side branches that arise from axons (Stettler et al., 2006, fig. 7), though these are more stable with 95% unchanged over one week (Majewska et al., 2006).

Terms here, however, are relative: such synapse and axon side branch “stability” is markedly unstable compared to the changes that happen in the timetabled development of axons and neurons.

From an evolutionary perspective, this aspect of synapse neurodevelopment is important since the homeostatic set points of synaptogenesis and elimination are variable in regard to input learning stimulation (see below), and neuroregulatory hormones such as leptin (O'Malley et al., 2007) and estradiol (Sato, Akaishi, Matsuki, Ohno, & Nakazawa, 2007; Woolley & McEwen, 1992), and neurotrophins such as BDNF (Sato et al., 2007). This makes synapse neurodevelopment (unlike that of neurons, and to a lesser extent axons) particularly open to both genetic and environmental adaptation.

4.5.2. *Synaptogenesis and environmental adaptation*

Enriched environments increase synapses by around 25% with cortex thickness expanding by up to 3.3-7% (Diamond, Krech, & Rosenzweig, 1964; Diamond et al., 1966).

Increases in synapse numbers are linked to such environmental events as eye opening (Bates, Thal, Finlay, & Clancy, 2003, p 557; Lu & Constantine-Paton, 2004), and opportunities to acquire challenging motor skills (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990). They also link to the richness of environmental stimulation, immediately following birth (Schapiro & Vukovich, 1970), after weaning (Bennett, Diamond, Krech, & Rosenzweig, 1964; Diamond et al., 1964; Diamond et al., 1966), and in maturity (Briones, Klintsova, & Greenough, 2004). Consistent with a strong environment influence (albeit upon a genetically determined developmental plan (Bourgeois, Jastreboff, & Rakic, 1989)), eye opening in mice, in its associated increase in synapse numbers is earlier by two days (12 rather than 14 postnatal days) following birth in visually rich environments (Cancedda et al., 2004). Though this research has been mostly upon rodents, similar environmental adaptation occurs in primates (Kozorovitskiy et al., 2005). Such stimulation effects not only pyramidal neurons but also stellate ones (Greenough & Volkmar, 1973). In the mature brain, the numbers of synapses increase after “acrobatic” skill learning in the rat cerebellar cortex (Black et al., 1990), and also following skill acquisition when such learning is consolidated in the rat cerebral cortex (Kleim et al., 2004).

5. The receptor complex of a synapse consists of a bouton on the axon, and a spine on the receiving dendrite, and these individual components are usually counted in proxy to synapses as a whole.

When synapse numbers increase in adults, they can remain high even when the adults are returned to improvised environment for 30 days (Briones et al., 2004) suggesting that such increases in synapse numbers need not always be confined to the immature brain nor temporary. However, the rate of synapse replacement has been observed generally to reduce with maturation (Holtmaat et al., 2005; Zuo, Lin, Chang, & Gan, 2005).

How far similar environmental stimulation effects occur in the human brain is unknown. One clue that they do is that MRI detects localized gray matter expansion after people learn complex tasks such as mirror reading (in this case in the right occipital cortex) (Ilg et al., 2008), three-ball juggling (bilateral mid-temporal area and left posterior intraparietal sulcus) (Draganski et al., 2004), and when medical students intensively revise for exams (bilaterally in the posterior and lateral parietal cortex) (Draganski et al., 2006). As will be reviewed below (section 4.9), theoretically such changes in gray matter volume can be expected to link to changes in synapse numbers due to the increased numbers of glial cells and the expanded capillary vascularization needed to support their increased energy consumption.

4.5.3. Dendritic arbor complexity

The neurodevelopment of dendritic arbors upon which synapses form and neural networks are wired can vary in the complexity with which their branches away from the neuron body divide up into further small branches, and these in turn into further “distal” 3rd and 4th order ones. Additionally, dendrites can vary in respect of the length of these various “distal” branches. Both can be effected by the environment. Higher-order dendritic branch complexity is increased in enriched environments (Greenough & Volkmar, 1973; Volkmar & Greenough, 1972), as can the length of distal branches in young animals (Wallace, Kilman, Withers, & Greenough, 1992). A link also has been found between educational level and greater dendritic branch complexity (Jacobs, Schall, & Scheibel, 1993). This suggests that not only synapse numbers but also the arbor morphology upon which they are located (and so their role in neural computation) can be subject to environmental adaptation.

4.5.4. Genetic adaptation upon synapse numbers and arbors

Though synapse numbers are effected by experience and closely associate with learning, this seems to apply mainly to the later stages of synapse neurodevelopment as the initial surge in synapse production linked to eye opening is not effected by early caesarian delivery (Bourgeois et al., 1989). There is also evidence that genetically determined constraints exist that differ between cortical areas (Majewska et al., 2006). The synaptic development of areas with different phylogenic origins also differs as the dendritic branching in the cortex areas handling the integrative stages of cognition (that arise late in phylogeny) is more complex and has greater density than that in sensory areas (earlier phylogeny) (Elston, Benavides-Piccione, & DeFelipe, 2001; Elston et al., 2006; Jacobs et al., 2001). Such phylogenic differences have

also been found in the complexity of cortical volume changes during development (Shaw et al., 2008).

Branch complexity and synapse numbers has changed markedly during primate evolution consistent with genetic factors effecting their development. A measure of peak branching complexity is quantified in marmoset prefrontal cortex as 25.5, but in macaques as 32.4, and in humans as 43.5 (Elston et al., 2001). Synaptic numbers per μm of dendrites likewise has changed during primate evolution in the prefrontal cortex: marmoset, 20.6, macaque, 24.0 and humans 32.5 (Elston et al., 2001), as has total numbers per prefrontal neuron (for basal branches only—distal ones were not measurable in humans): marmoset, 3,983; macaque, 8,766, and humans, 15,138 (Elston et al., 2006). This suggests that synapse numbers have also been subject to strong adaptive evolution.

4.5.5. Other synapse linked modifications

When synapses increase in numbers after environmental enrichment, they show other changes: the direct apposition area of glial cells with synapses expands (Jones & Greenough, 1996), the density of synaptic contact zone is greater, and the synapses tend to be very large (Sirevaag & Greenough, 1985). Moreover, the volume of glial cell nuclei for each synapse is also higher. This suggests that with increase in synapse numbers, there is also increased concomitant synapse activation (Sirevaag & Greenough, 1987). Another change with this activation is an increase in spine and synapse turnover (Trachtenberg et al., 2002).

Such changes are paralleled by a diverse changes related to LTP (long term potentiation). For example, the number of spines per bouton can vary, and the activation threshold of synapses can be modified by intracellular trafficking of plasticity-related proteins that “tag” them (Barco, Lopez de Armentia, & Alarcon, 2008). Synapses can change from silent to active and back again through changes in NMDA receptors (Adesnik, Li, Doring, Pleasure, & Nicoll, 2008). Synaptic activation can change the receptors present in synapses (Krueger & Fitzsimonds, 2006), the rates of synaptic vesicle recycling that enhance the probability of transmitter release (Krueger & Fitzsimonds, 2006), and the nonlinear compartmented electrical strength potentiation properties of dendritic branches created by diverse voltage-dependent ion channels (at least 17 types exist (Poirazi, Brannon, & Mel, 2003, p. 998)) in its membranes (Losonczy, Makara, & Magee, 2008). Spine morphology can vary in size (length 0.2-2.0 μm), and in shape (thin, stubby, sessile, mushroom, branched, heads with “thorny excrescences”) (Sorra & Harris, 2000).

4.5.6. Synapse changes and information processing

These synapse related changes are fundamental as they act to “rewire” the neural networks that form between neurons, and so refine and adjust their information processing (Chklovskii, Mel, & Svoboda, 2004; Le Be & Markram, 2006). This rewriting occurs in an enormous

developmental “space” in which neural networks can be modified to acquire cognitive capabilities. Each neuron without significant growth of axonal or dendritic arbors (such as generally is the case when mature) allows rewiring changes of 3-4 bits per synapse and so $\approx 9 \times 10^4$ bits (Chklovskii et al., 2004). With the growth of new axonal and dendritic branches (as when the neuron is developing), this rewiring could be 23 bits per synapse and so $\approx 6 \times 10^5$ bits per dendritic arbor (Chklovskii et al., 2004). Changes at the receptor such as in presynaptic calcium buffers that do not need rewiring can also enable such information processes to temporarily store large amounts of information in the patterns of synapse strengths, (Mongillo, Barak, & Tsodyks, 2008). The informational storage capacity of each neuron’s arbor has been modeled as being as high as 2.7×10^4 bits (Poirazi & Mel, 2001).

In the present neuroscience *terra incognita*, a large number of synapse neurodevelopmental unknowns exists. Recently, it has been found that some dendrites but not others allow currents to back propagate from the soma (Zhou, Yan, Wuskell, Loew, & Antic, 2008)—a variable trait that in its arbor distribution will profoundly change a neuron’s information processing. The speech and language disorder gene FOXP2 when expressed heterozygously in mice impairs synaptic LTD (Groszer et al., 2008), suggesting a synapse related link to complex cognitions. Thus, a diversity of synapse related phenomena exist concomitant with exuberant synaptogenesis that in unknown ways determine childhood neural network development, and so cognitive maturation.

4.6. Synapses and brain metabolism

A strong link exists between the energy consumption of the brain during the period of its most intense cognitive development, and the period of its greatest absolute number of synapses. For example, the energy demands per 100g of the human cerebral hemispheres between birth and one year of age is 87% of that of the human adult (Chugani et al., 1987, table 2), which corresponds to their limited number of synapses (Huttenlocher, 2002; Huttenlocher & Dabholkar, 1997), and the limited learning done at this age by the neonate brain. However, the energy demands per 100g of the human cerebral hemispheres between the ages of 3 and 8, and those of 9 and 15, during which children are most engaged in intense learning, jumps respectively to 198% and 162% (Chugani et al., 1987, table 2), and this parallels an increase at these ages in synapse numbers (Glantz, Gilmore, Hamer, Lieberman, & Jarskog, 2007; Huttenlocher, 2002; Huttenlocher & Dabholkar, 1997) (see figs. 4 and 5).

Both mitochondria and glial cells are directly involved in the energy provision to synapses and neurons, while increased capillary density by increasing glucose and oxygen supply associates with their increased metabolism (Borowsky & Collins, 1989). When synapses numbers increase in enriched environments, the area directly between glial cells and synapses goes up to 19% (Jones & Greenough, 1996), and the synapses that exist tend to be big (Sirevaag & Greenough, 1985): “In addition to having larger synaptic contacts.. EC [environment complex] rats exhibited a population of very large synapses not seen at all in the IC [isolated

condition] in layer IV” (Sirevaag & Greenough, 1985, p. 216). Moreover, the volume of glial cell nuclei for each synapse is also higher by 37.5%. Environmental enrichment produced in one study a 23.1% increase in dendrite length that was associated with wider capillaries (4.35 μm compared to 4.15 μm in controls), and shorter distance between any part of the neuropil and a capillary (27.6 μm compared to 34.6 μm) (Sirevaag & Greenough, 1987). The mean volume of mitochondria per neuron was also 20% greater (1599 μm^3 compared to 1280 μm^3), and the volume of glial cell nuclei for each neuron was 63% higher (Sirevaag & Greenough, 1987).

The cortex in animals exposed to enriched environments are thicker by up to 3.3-7%, and this associates with an increase in glial cell numbers per neuron of 12-14% (Diamond et al., 1964; Diamond et al., 1966). Such energy related changes are also reflected in volumetric measures of human gray matter. The subgenual part of Brodmann’s area 24 is reduced in size in those with bipolar disorder (controls: 214.7 mm^2 gray matter, major depressive disorder, MDD: 177.9 mm^2), and this correlates with reduced glial cell numbers (controls: 8.43×10^6 glial cells; MDD, 3.90×10^6) but not reduced neuron numbers (controls: 5.24×10^6 neurons; MDD, 5.97×10^6) (Ongur, Drevets, & Price, 1998). PET also finds both reduced blood flow and reduced metabolism in this area in such individuals (Drevets et al., 1997)

The impact of such learning/metabolic changes could be bigger in humans than in experimental animals. In rodents, action potential propagation (47%) rather than synapse activation (34%) takes the larger share of the brain energy consumption (Attwell & Laughlin, 2001). In humans, due to greater synapse numbers per neuron, the synapse component is estimated to increase to 74% (Attwell & Laughlin, 2001, p. 1140). Consistent with this, in larger brained animals such as cats, synapse processes are more important than transmission ones as oxygen consumption by neurons couples with synapse activity rather than the generation of axon spikes (Viswanathan & Freeman, 2007).

4.7. Non-neurodevelopment learning costs

The energy costs associated with juvenile neurodevelopment, it should be observed, do not only concern those happening in the brain as they can also involve the increased physical activity needed to encounter learning experience. Rats in enriched environments engage in more activity (Bennett et al., 1964), and IQ in a human at 11 years-of-age links to the degree to which they as a child at 3 years-of-age sought stimulation (Raine, Reynolds, Venables, & Mednick, 2002). Human children also show much higher levels of *moderate* physical activity than adolescents and adults (Sigmund et al., 2007), and so at this period gain extensive motor and other opportunities for learning. Importantly—a topic discussed at length in section 8—they do this, however, while also avoiding prolonged strenuous physical activity (Bailey et al., 1995; Gilliam et al., 1981).

4.8. Myelination

Myelination makes axon transmission more efficient: for the passage of each spike, a 0.5 μm unmyelinated axon costs about 12-fold more in energy than when that spike is passed through a myelinated one (S. S. Wang et al., 2008).

Less is understood about how white matter expansion due to myelination links to information processing. Unmyelinated axons conduct impulses at 0.5 to 10 m s^{-1} whereas myelinated do so up to 150 m s^{-1} . Spikes communicated by unmyelinated axons are as a result effected by delays and imprecision as they cross the brain (S. S. Wang et al., 2008). It has been suggested that unmyelinated axons, for this reason, might transmit information through their firing rate rather than precise spike timing (S. S. Wang et al., 2008). One problem is that myelination must be selective since widening all axons by myelination would cause an unsupportable increase in white matter volume. 2500 0.2 μm wide unmyelinated axons can fit into the space of a single 10 μm wide myelinated one. Thus, extreme selectivity must exist in regard to which connections get and receive the most myelination.

It is reasonable to suppose that efficiency and speed of information communication between gray matter neural circuits effects the development and capabilities of cognition. Supporting this is the finding that the maturation of white matter in terms of an increased density and orderly packing of fiber tracts indexed by fractional anisotropy (FA) in diffusion tensor MRI links to higher IQ (Schmithorst et al., 2005). In the human hippocampus, high FA in its white matter links to a person's ability to navigate and orientate (Iaria, Lanyon, Fox, Giaschi, & Barton, 2008).

A further indication of the importance of myelination is suggested by the substantial changes that occur in the white matter of those humans that are born blind (Lui et al., 2007; Noppeney, Friston, Ashburner, Frackowiak, & Price, 2005; Ptito, Schneider, Paulson, & Kupers, 2008), and of adult cats with retinal lesions (Darian-Smith & Gilbert, 1994). In the latter, axonal sprouting of long-range connections occurs with a "remodeling" of the visual cortex (Darian-Smith & Gilbert, 1994). Those born blind consistent with profound axon change show on a macro level significant white matter changes (Lui et al., 2007; Noppeney et al., 2005; Ptito et al., 2008). For example, they have an enlargement of the occipito-fronto fasciculus, the superior longitudinal fasciculus, and the genu of the corpus callosum (Ptito et al., 2008). Moreover, these are concomitant to profound nongenetic changes in the functioning of their "visual" cortex neural networks that is reflected in them engaging in nonvisual functions, including human specific ones such as semantics and syntax (Amedi, Raz, Pianka, Malach, & Zohary, 2003; Burton, Snyder, Diamond, & Raichle, 2002; Roder, Stock, Bien, Neville, & Rosler, 2002) (review Skoyles submitted). This suggests that myelination—like synaptogenesis—is critically linked to the processes of acquiring cognitive capacities.

While occurring concurrently with changes in synapses numbers, the trajectory of myelination change seems to differ in that it can extend for a much longer period, a situation reflected in the continued expansion in white matter volume into the third decade (Lebel et al., 2008; Sowell et al., 2003, fig. 6).

4.9. Evolutionary opportunities to modify and enhance cognition through synaptogenesis

Above, it has been shown that synapse neurodevelopment is radically distinct from that of neurons and axons as it is not part of a conserved productive and elimination timetable (Clancy et al., 2001). Indeed, it has been observed of the initial production of synapses that it was the “only neural event we have found that systematically fails to fit into the conserved developmental sequences” (Clancy et al., 2001, p. 8).

It makes evolutionary sense that synapse neurodevelopment is adaptively open. Neuron and axon development set up the brain structurally but they cannot anticipate the particular challenges posed by different environments. Their timetabled preparation of the brain, however, creates neural networks that can adapt to such environments through the flexibility of their synapse-based learning.

As shown above, such an adaptive capacity links to increased synapse numbers, and so is metabolically costly learning. But, the period in which brains need to most intensively learn about their particular environment is also one when they are encountering novel learning situations just after they have gained independence. Thus, an evolutionary dilemma exists in that the period in which they have the most need of the advantage of the cognitive learning offered by exuberant synapses is also the one in which they are least likely to have the necessary energy support—they are newly independent, and by virtue of the immaturity of their skills will be less than proficient in obtaining energy themselves.

This means that the costly nature of synapse neurodevelopment ties the evolution of exuberant synapse enhanced cognition to the events outside the brain that determine its energy support. Evolutionary changes to the energy supply of juveniles as a result can have a profound knock-on effect upon the evolution of cognitive capabilities.

5. PROLONGED EXPENSIVE NEURODEVELOPMENT AND HUMAN COGNITIONS

5.1. Evidence that humans have a prolonged expensive period of neurodevelopment

5.1.1 Energy costs are predominately increased in cerebral cortex

Childhood and adolescent brain energy consumption is above that found in adults, and these are highest in the cerebral cortex. Chugani and colleagues (1987, table 2) provide the figures below for percent energy increase in children of difference ages relative to those of adults:

<u>area</u>	<u>0-1 years</u>	<u>1-2 years</u>	<u>3-8 years</u>	<u>9-15 years</u>
cerebral cortex	0.72-0.93	0.99-1.25	1.85-2.24	1.52-1.78
brainstem	0.89	1.06	1.46	1.45
cerebellum	0.93	1.03	1.71	1.45
basal ganglia	0.75	0.93	1.55	1.41

5.1.2. Estimates for total brain energy consumption

If these figures (assuming white matter does not change in its metabolic needs with age) are combined with their adult metabolism figures (also given in (Chugani et al., 1987)), and those for the volumetric size of these areas in children and adults (Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; Filipek et al., 1994), they reveal that the total energy consumption of the child's brain between 3-8 years-of-age (and 8-15 years-of-age) is greater by something like 1.77% (and 1.49%). These figures provide rough estimates (they ignore gender differences, and metabolic differences between immature and mature white matter) but are consistent with those found using much older techniques 50 years ago (Kennedy & Sokoloff, 1957) that measured an 1.80% increase for cerebral flow and an 1.30% for cerebral oxygen utilization. It should be noted, that these changes do not link to smaller gray matter mass in the child than in the adult, as its volume starts to overlap with the adult range of volumes by 3-4 years-of-age. The gray matter of the average child brain increases by a few percent to reach a maximum volume around 6-9 years-of-age. However, since white matter increases with a different trajectory, it is several more years before the average child would reach their maximum total brain volume (Courchesne et al., 2000).

5.1.3. An alternative estimate of the child's raised brain energy consumption

An assessment of the wattage of a child's brain can be made by calculating the various BMRs of different organs, and the whole body, and estimate what remains to be accounted for by the brain. Hsu and colleagues provide the relevant data for body organs of an average child of 9 years-of-age weighing 30.5 kg, and provide a measure of their total BMR (Hsu et al., 2003). The total BMR was 59.2 W which is near that calculated using predictive equations for children of this age and weight (Henry, 2005). Of that 59.2 W, 27.6 W are accounted for by

the BMR of nonbrain components (liver, 6.6 W; heart 2.6 W; kidney 3.9 W; skeletal muscle 7.7 W; adipose 1.4 W; residual 5.3 W). At the age of 9, a child grows by 3.6 kg year^{-1} (growth chart spreadsheet data, Centers for Disease Control and Prevention) which requires 5.3 kJ g^{-1} (Webster, 1980), suggesting that the energy for body growth adds another 6.2 W. This implies that the child's brain consumes around 26 W. The child's brain BMR if it had a adult metabolic rate would be 17.5 W. The difference between the calculated child and adult brain metabolic rates here—1.49%—roughly matches that measured by Chugani directly for this age (though the wattage values are higher). (See Appendix 2 for more discussion on the problems and issues in determining the actual wattage of the pediatric and the adult brain.)

5.2. Changes concomitant with prolonged expensive neurodevelopment

An extended inverted “U” period is shown in fig. 4 in which human gray matter during childhood and adolescence has high energy consumption, together with that of the broad parallel of this change with raised numbers of synapses in fig. 5. The latter figure also shows the changes in synaptophysin levels (a marker of synapse numbers) in the prefrontal cortex (Glantz et al., 2007). (The pattern of cost reductions with myelination are likely to be smaller but are unknown).

The raised period of inverted “U” energy consumption of a child's brain correlates with cellular and blood flow changes.

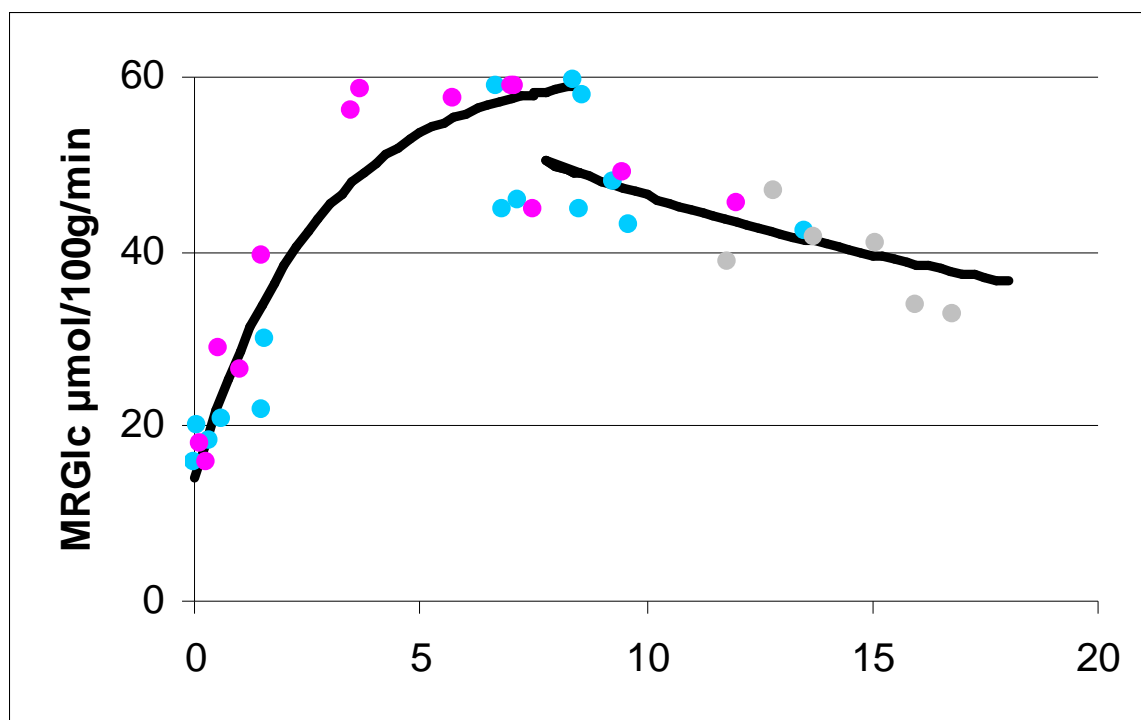
- There is increased blood volume flow into the brain (Kennedy & Sokoloff, 1957): 130% between 3 and 6 years-of-age and decline to near adult levels at 15 years-of-age.
- Parallel to this there is increased rate of blood flow per unit gram of the brain (Chiron et al., 1992).
- The ratio of N-acetyl aspartate (a molecular water pump in myelinated neurons) to choline (used to make cell membranes of dendrites) reaches a peak at 10 years-of-age (Horska et al., 2002).
- Intriguingly, but lacking sufficient childhood data points (autopsy individuals in some parts of this study were limited to a 2.5, and an 11 year old), research suggests that one oxidative metabolic enzyme, succinate dehydrogenase, undergoes a late, cortical layer and area related expression change (Farkas-Bargeton, Diebler, Rosenberg, & Wehrle, 1984).
- The capacity to synthesize serotonin changes in a pattern that is similar to that of changing metabolism (Chugani et al., 1999).

There are neurophysiological correlates.

- Slow-wave band EEG activity correlates with changes in gray matter density (Whitford et al., 2007), and metabolism (Feinberg, Thode, Chugani, & March, 1990), and synaptic density (Feinberg et al., 1990). This is also the case with the power of delta and theta bands of eye-open EEG and metabolism (Boord, Rennie, & Williams, 2007).
- The power of eye-open EEG components such as alpha, beta, delta and theta declines from infancy to adulthood by up to ten-fold (Boord et al., 2007, for example, in fig 1.; Dustman, Shearer, & Emmerson, 1999, fig. 5).
- Research finds that the delta EEG component of non-rapid eye movement (NREM) sleep declines by 50% between 10 and 20 years-of-age, with half that happening between 12 and 14 years-of-age (Feinberg, Higgins, Khaw, & Campbell, 2006). This delta during sleep has been suggested (Feinberg et al., 2006) to reverse in a homeostatic manner the effects of neuron metabolic activity during waking.

There are also neurocognitive correlates.

- A sensitive period exists after auditory deprivation in which cochlear implants can lead to normal neural responses to speech that ends between 3.5 and 7 years-of-age (Sharma, Dorman, & Spahr, 2002). For cataracts, there is an open period up to about 10 years-of-age for permanent deficit in letter acuity, a skill that in normal children continues to be perfected until 6 years-of-age (Lewis & Maurer, 2005). In both these cases, the period in which the primary sensory cortex remains plastic corresponds to the period in which it has exuberant synapses (which peaks and declines earlier than the prefrontal and other higher integrative cortex areas) (Huttenlocher, 2002; Huttenlocher & Dabholkar, 1997).
- Research on standardized cognitive tests finds that neurological changes associated with the prolonged expensive neurodevelopment also correlate with the most rapid period in cognitive development: cognitive ability increases more markedly between 5-8 years-of-age than between 9-12 years-of-age (Korkman, Kemp, & Kirk, 2001).
- Speed in tasks such as visual matching becomes increasingly fast during childhood but slows its rate of speed increase in adolescence at a rate similar to changes happening in brain size, and body mass, and it has been suggested “that all might have a common (unspecified) biological basis” (Kail & Ferrer, 2007, p.1769).



Adapted from Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. *Annals of Neurology* 22: 1987 487-497. copyright © 1987, Wiley-Liss, Inc. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Fig. 4 This graph shows the changing pattern of cortical metabolism of local cerebral metabolic rate for glucose in $\mu\text{mol min}^{-1} \text{g}^{-1}$ against age. Data regraphed from (Chugani et al., 1987) (blue ♂ and pink ♀ dots), and (Muzik et al., 1999) (gray dots, no gender given). The two graph lines are generated from the plateau and decline parameters in the 5-parameter developmental function calculated by Muzik and colleagues (1999). Plateau phase formula for metabolic rate of glucose = $(\alpha - C_{\text{birth}})(1 - \exp(-\beta \text{age})) + C_{\text{birth}}$, where $\alpha = 61.1$, $\beta = -0.365$, C_{birth} (glucose at birth) = 14.1; decline phase, metabolic rate of glucose = $(\alpha - C_{\text{adult}})(\exp(\gamma - (\text{age} - \Delta))) + C_{\text{adult}}$, where $\alpha = 50.3 - 24$, $\Delta = 7.8$, $\gamma = 0.072$, C_{adult} (glucose in adults) = 24.

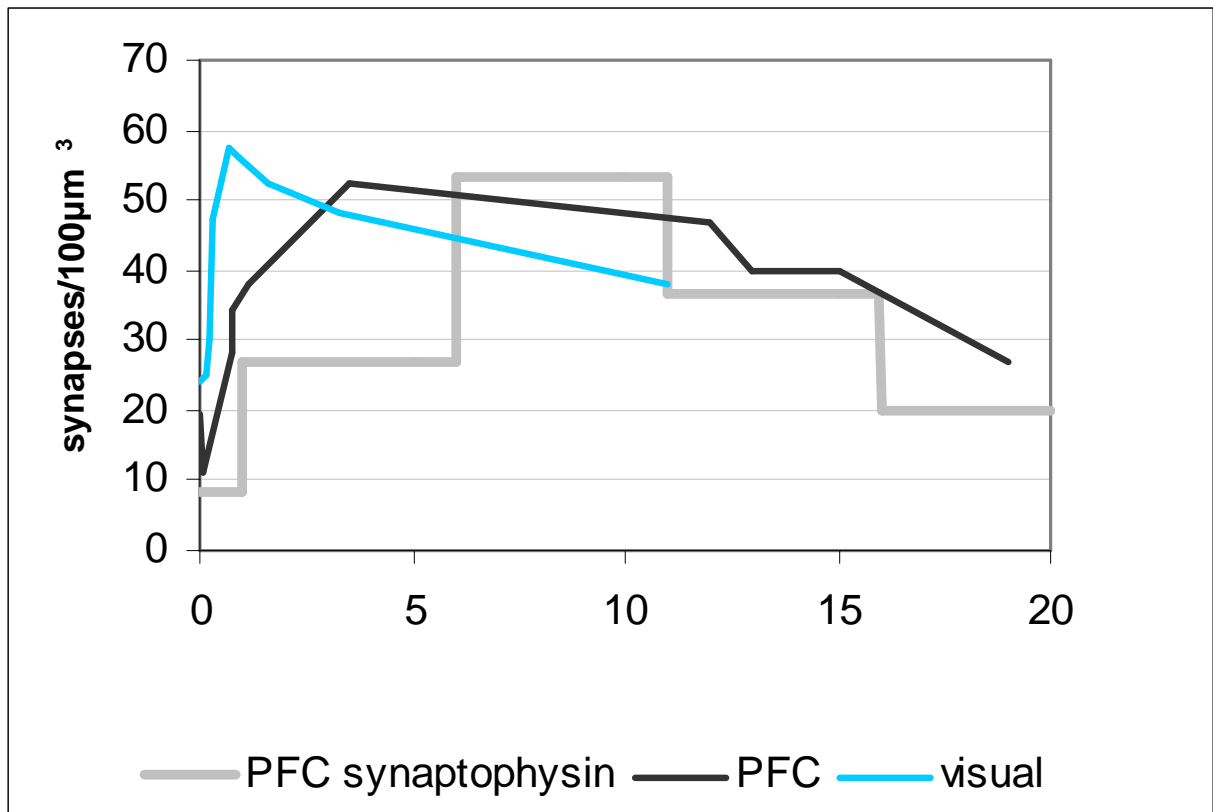


Fig. 5 The two graph lines show the increase of synapse numbers in the visual (blue) and prefrontal (black) cortices in terms of synaptic density data from table 3 (prefrontal) (Huttenlocher & Dabholkar, 1997), and table 2 (visual) (Huttenlocher & de Courten, 1987). Note, the synapse numbers in the visual cortex have been halved to make them comparable with those in the prefrontal cortex. The columns marked in gray outline show synaptophysin levels in the prefrontal cortex. The width of the synaptophysin columns reflect the ages across which data were summed, data taken from fig. 2 in (Glantz et al., 2007). Huttenlocher's data indicate that the prefrontal cortex has a later development than the visual cortex. The synaptophysin data imply that this underestimates somewhat the lateness of the proliferation of synapses.

5.3. Gray matter and white matter changes and information processing maturation

At present, the changes that occur in neural networks during the period of prolonged expensive neurodevelopment, and how this links to increased human cognitive capabilities, is not directly investigable at the level of the synapse and the dendritic arbor (but see the rare autopsy report of Jacobs, Schall and Scheibel (1993)). Volume changes, however, during this period to gray and white matter can be researched using volumetric MRI (Lenroot & Giedd, 2006; Shaw, 2007; Shaw et al., 2008; Sowell, Trauner, Gamst, & Jernigan, 2002).

For gray matter, this exists because its volume links to that occupied by glial cells and capillary vasculature that support the neuron's energy consumption (Sherwood et al., 2006; Sirevaag & Greenough, 1987). As noted (section 4.6), when the number of synapses increase, so does the energy support provided by capillary vasculature, mitochondria and glial cells.

The alternative explanation that the dendritic arbor itself expands is unlikely to be a major factor for gray matter increase, though certain elements of it might increase in some neurons during childhood, see the data reported for layer IIIC pyramidal neurons in (Petanjek, Judas, Kostovic, & Uylings, 2008). As the authors note, the data only suggest "slight dendritic growth might occur at that time [childhood and adolescence]" (Petanjek et al., 2008, p. 926). Further, though dendritic branches become more complex and long in enriched environments, "the increased dendritic branching tends to take place within the volume already occupied" (Greenough & Volkmar, 1973, p. 499).

Extensive change to dendritic dimensions is also unlikely since this might change the "cable" related electrical properties of dendrites that determine the spread of forward and back propagating currents that underlie their information processing (Segev & London, 2000): related to this, the morphological dimensions of dendrites are under tight homeostatic regulation (Samsonovich & Ascoli, 2006). Thus, it would appear that the increases in the volume of the gray matter is largely or mostly due to the enlarged space occupied by glial cells and capillary vasculature that exist to meet the increased energy needs of more synapses.

5.4. Prolonged expensive neurodevelopment, volumetric changes, and human specific cognitions

Volumetric MRI research shows that volume changes to gray matter have (i) a trajectory of initial increase followed by decrease, (ii) that these trajectory changes differ according to particular cerebral cortex area, and (iii) that these different trajectories in their thickening and thinning link with human specific cognitive capacities (Lenroot & Giedd, 2006; Shaw, 2007; Sowell et al., 2002). Moreover, (iv) those areas that show the most elaborate volume changes are also those polysensory and high-order association areas that are most recent in cortical evolution (Shaw et al., 2008). Since cortex thickening and thinning links to increases in capillary and glial cell support for the energy needs of increased numbers of synapses, such

changes provides a window into the pattern of synapse exuberance neurodevelopment as it shifts across the cerebral cortex as children mature and acquire their adult cognitions.

Four areas of research exist—IQ related cognitions, expertise, literacy, and early blindness—that provide information about such volumetrically linked prolonged expensive neurodevelopment changes, and their relationship to human specific cognitive capacities.

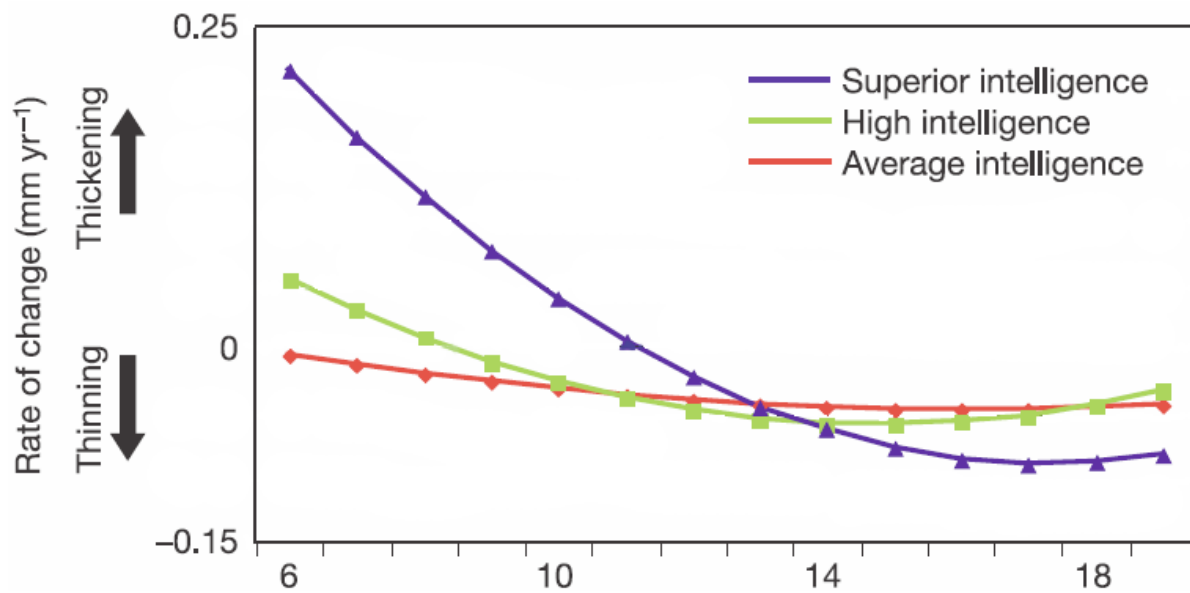
5.4.1. IQ related cognitions

Initially, gray matter thickens in childhood only then to thin again during later childhood and adolescence in a manner that links to IQ. The trajectory of this inverted U trajectory of change in cortical gray matter and its link to age and IQ is shown in figs. 7A and 7B on page 33. This trajectory suggests that the maturational and spatial pattern of recruitment of additional synapses across the developing brain reflected in these volumetric changes has a critical role in the process by which cortical neural networks get refined to enable human specific information processing.

Some evidence suggests that these changes can extend beyond adolescence: Sowell and colleagues (2003), for instance, found that the gray matter density in the left posterior temporal area continued up to 30 years, and linked this to the protracted maturation of language (i.e. human specific) functions.

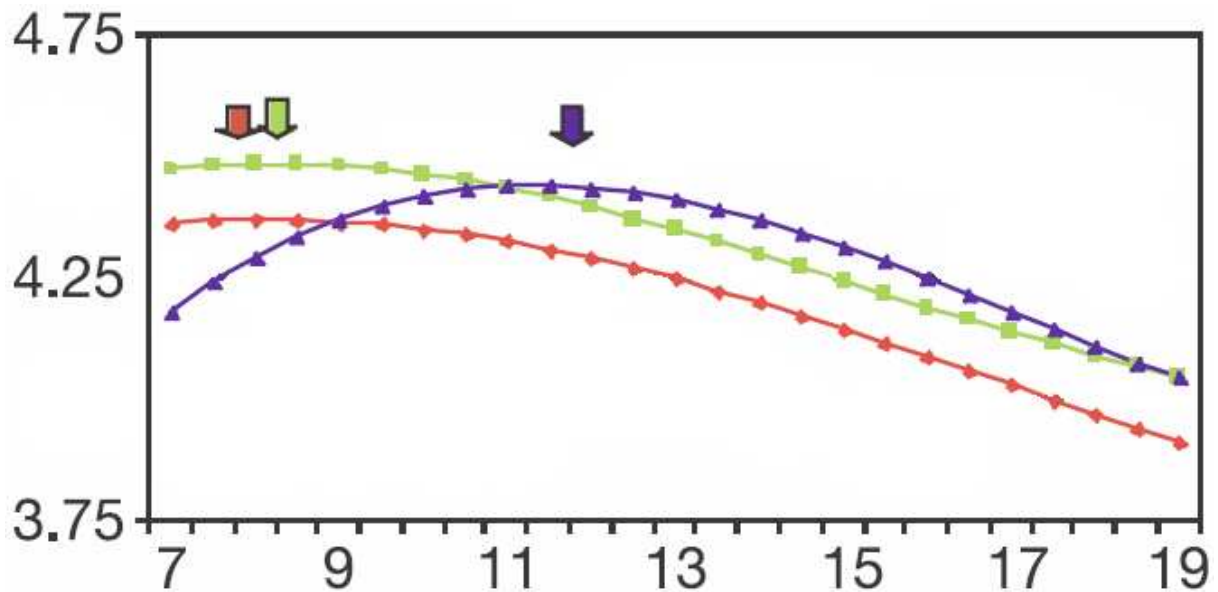
Gray matter changes also link to the degree to which an area is involved in integrating the information processing done in other areas. This is shown in the later development that happens in the higher associative cortical areas (such as the prefrontal cortex) in those with higher IQ over that done earlier in their sensory ones (Shaw, 2007; Shaw et al., 2006). This argues that cognitive abilities depend upon a complex pattern of energy demanding overproduction of synapses that occurs in a developmental sequence across the cerebral mantle. Moreover, the IQ association suggests that success in the acquisition of complex cognitive capabilities depends upon the trajectory of this pattern. These findings raise the question of how far this developmental trajectory is subject to complex inherited and environmental factors. IQ is inherited and effected by the environment (Bouchard, 1998; Dickens & Flynn, 2001), thus these volumetric changes, it would reasonably be supposed are also similarly affected.

Though changes to gray matter are at present better researched, changes also occur to the maturation of white matter connections, for example, those between the left frontal and parietal cortices correlate to increased working memory capacity, and white matter changes in the temporal lobe to reading capacity (Nagy, Westerberg, & Klingberg, 2004). There are also MRI detected properties of white matter that have an area relationship with IQ (Schmithorst et al., 2005), and ones in hippocampal white matter relate to the ability to navigate and orientate (Iaria et al., 2008).



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Fig 6 A. Superior intelligence = IQ range 121-149, high intelligence = 109-120; average intelligence = 74-108. The graph show the thickness increase and decrease in gray matter in the right superior and medial frontal gyrus. This prolonged expensive neurodevelopment is greatest in the cortical change in those with superior intelligence and minimal in those of average intelligence. Figure from (Shaw et al., 2006).



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Fig 6 B. Lines represent the same bands of intelligence as in fig. 7A. Cortical thickness is in mm. This shows how the cognitions associated with IQ link with changes happening in the left superior/medial prefrontal cortex. These are notably delayed in those with the highest IQ. Moreover, the more dramatic the developmental lateness and peak of thickening, the higher the IQ of the brain.

5.4.2. *Expertise*

Expert skills such as chess and instrument playing are acquired through prolonged (ten year) daily (several hours) deliberative practice (Ericsson & Lehmann, 1996). Such expertise correlates with area linked volumetric changes in the cerebral cortex gray and white matter. Crucially, such volumetric changes also link to how early—whether childhood or later—such deliberative practice starts (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Schlaug, Jancke, Huang, Staiger, & Steinmetz, 1995).

5.4.3. *Literacy*

Reading and writing are childhood acquired cognitive abilities. While normally identified with reading and writing skills, these skills also concomitantly change the brain's neural processing, a situation reflected in them effecting a wide range of other cognitive functions such as a better ability to detect speech phone units (Morais, Cary, Alegria, & Bertelson, 1979) and speech errors (Morais, 1987), a bias to process the rhyming of spoken words in terms of their orthographic spelling (Seidenberg & Tanenhaus, 1979), and an integration of orthography into the early prelexical processes in spoken word recognition (Perre & Ziegler, 2008). There has also been suggested to be an altered capacity in those with literacy to "abstract" or decontextualize ideas (Luria, 1979; Olson, 1996). Literacy cannot be entirely separated from the effects of "schooling", the learning environment in which reading and writing is normally acquired by contemporary children. Brain imaging upon groups that differ only in regard to literacy and schooling (daughters that for social-cultural reasons did and did not receive primary education) shows that it links to volumetric changes in the white matter connections between the cerebral hemispheres (Castro-Caldas et al., 1999; Petersson, Silva, Castro-Caldas, Ingvar, & Reis, 2007), and the inferior parietal/ parietotemporal regions (Petersson et al., 2007). These physical changes associate with functional connectivity differences in the cerebral hemispheres (Petersson, Reis, Askelof, Castro-Caldas, & Ingvar, 2000). Consistent with these findings is that the extent of a person's education (whether less than high school, high school, or university) links (the direction of causation is not known) to dendrite differences (more extensive higher-order branching in those with higher levels of education) (Jacobs et al., 1993).

5.4.4. *Early blindness*

The natural experiment of early blindness shows that neural circuits can radically change their functionality and underlie the processing of cognitive capacities for which they could not have been evolutionarily prepared: "ectopic cognition" (Skoyles submitted). The visual cortex in the early blind can acquire—in spite of its neural networks having been subject to nearly 180 million years of selection in mammals in regard to processing sight—human specific cognitive abilities such as semantics and syntax (Amedi et al., 2003; Burton et al., 2002; Roder et al., 2002) (for a review of such "ectopic cognitions" see Skoyles submitted). These

novel human specific cognitive capacities in the “visual” cortex closely link to white and gray matter changes (Lui et al., 2007; Noppeney et al., 2005; Ptito et al., 2008). This suggests that human specific abilities might be due not so much to innate neural network competences but the protracted period of synapse refinement and myelination during childhood that prune and changes their information processing capabilities.

6. SYNAPSE NEURODEVELOPMENT INNOVATIONS

How might a prolongation in the period of expensive neurodevelopment lead to enhanced cognitions?

6.1. Integration and differentiation of neural circuits

Here we must consider the nature of the information processing carried out by the brain. Central to this is the complexity of its integration and differentiation of function across different areas (Bassett, Meyer-Lindenberg, Achard, Duke, & Bullmore, 2006; Fair et al., 2008; Fair et al., 2007; Honey, Kotter, Breakspear, & Sporns, 2007; Tononi, Sporns, & Edelman, 1994). Neural complexity is high when the “components show simultaneous evidence of independence in small subsets and increasing dependence in subsets of increasing size (Torun, 2005, p. 5034). A related concept is the clustering coefficient and path length connectiveness of small world networks (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Watts & Strogatz, 1998). In parallel to these approaches, theories of intelligence link cognitive aptitude to the development of hierarchical mutualism between cognitive processes (van der Maas et al., 2006).

The human brain shows a strong capacity to create such adaptive functional connectivity by synchronized clustering and coupling between synapses on multiple frequency time scales (Bassett et al., 2006). Such connectivity in adults is regulated by top-down controllers in prefrontal and cingulate “hub” brain areas (Dosenbach et al., 2008; Fair et al., 2008; Fair et al., 2007).

The opportunity and the need for such complex integration and differentiation exists in part due to large brains in humans since size increases the number of cortical areas that have to be coordinated together: cortex area numbers expand at roughly the square root of the number of cerebral cortex neurons and so brain size (Changizi & Shimojo, 2005). How does this integration happen? One adaptation, it is reasonable to suppose is adding extra years for developmental synaptic refinement, since would provide greater opportunities for these processes to sculpt effective patterns of “small world network” neural interactions across its different areas.

Consistent with this, neural interactions in the brains of 7-9 years-of-age children are not so functionally segregated and integrated as in adults (Fair et al., 2008; Fair et al., 2007). Further,

integrative hub regions such as the prefrontal and cingulate areas as might be expected develop later than the ones that they coordinate (Gogtay et al., 2004; Huttenlocher & Dabholkar, 1997; Lenroot & Giedd, 2006; Shaw, 2007; Shaw et al., 2006; Shaw et al., 2008).

6.2. Developmental heterogeneity in timing

Since neural integration and differentiation are optimized by top-down controllers, neurodevelopment needs to happen in a stage-like manner to allow for later maturation by controlling hub areas. Restrictions upon this happening could limit the development of nonhuman brains. The rhesus macaque monkey brain, for example, like the human brain, has a period of exuberant synaptogenesis that associates with metabolic expensive neurodevelopment. But this lasts only to 3 years-of-age, and it occurs in a homogeneous manner across the cerebral cortex with, for example, synaptogenesis and pruning happening at the same time in the visual and prefrontal cortices (Bourgeois, Goldman-Rakic, & Rakic, 1994; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986)⁶.

While humans share with rhesus macaques a similar pattern of synapse proliferation and increased metabolically expensive brains, it occurs over a considerably greater number of years (≈ 15 , childhood+adolescence). This allows for the existence of marked heterogeneity in the developmental timing of different areas (primary cortex areas before prefrontal and temporal ones) (Huttenlocher & Dabholkar, 1997).

This is reflected in the greater mean peak branching complexity of dendritic arbors of adult human prefrontal cortex neurons than those in macaques (Elston et al., 2001):

	macaque	human
branching complexity	32.4	43.5
spine density per μm	24.0	32.5

Moreover, these differences have increased between humans and nonhumans primates with respect to primary cortical areas (Elston et al., 2001):

	marmoset	macaque	humans
branching complexity			
visual cortex	27.1	21.5	23.5
prefrontal cortex:	25.5	32.4	43.5

Also, in humans, prefrontal cortex gray matter shows a more complex trajectory of volumetric change in its cortex thickness compared to that in less integrative areas (Shaw et al., 2008).

6. Unfortunately, present empirical research on neurodevelopment and such factors as dendritic arbor complexity and synapse numbers is limited to the comparison between modern humans and rhesus macaques, a Cercopithecidae monkey: there is no data with which to compare humans with other hominoids such as chimpanzees, though these comparisons, if they could be obtained, would be theoretically more informative.

Thus, more complex and denser connected neurons have been selected that mature later. As a result, their dendrites have more complex capacities for information processing. This lets them engage in “hub” control over the small world networks they form with earlier maturing neural networks.

Consistent with this developmental pattern, there appears to be a multifaceted sequence of developmental integration and differentiation stages in overall brain maturation, for example, as indicated in the EEG changes identified by Thatcher and colleagues (1987), the earlier development of the auditory cortex to the language cortical areas (Devous et al., 2006), and the progressive expansion and thinning of cerebral cortex areas (Gogtay et al., 2004; Shaw, 2007; Shaw et al., 2006; Shaw et al., 2008).

6.3. Internal stimulation

Stanley Rapoport, has noted, that in addition to the bottom-up richness of the environment, there is also a top-down stimulation upon the brain from ideation and attention that can “stimulate widespread brain association areas . . . [and so] synaptic stabilization secondary to adaptive thought processes . . . New primate species may create new cognitive, social or cultural stresses which in turn can accelerate brain evolution” (Rapoport, 1999, p.160). Such internal nonenvironmental stimulation might be particularly important if it aided the integration and differentiation of the human brain’s large number of cortical areas.

One internally stimulating cognition that would do this is language. Though language is usually discussed in terms of enhancing interpersonal communication, language also has been found to provide internal cognitive scaffolding (Luria, 1979; Vygotsky, 1986). This internal organization is variously called “private speech” or “internal speech”, and it coordinates thought processes (Sokolov, 1972). Reflecting this, language dominates human cognition. Words that describe objects in relative compared to absolute coordinate spatial frameworks organize the nature of spatial perception (Majid, Bowerman, Kita, Haun, & Levinson, 2004), and the availability of tense description words structure the temporal perception of events (Boroditsky, Ham, & Ramscar, 2002). If children are not exposed to intentional state words—such as want, know, or believe—this impairs and delays their ability to interpret other people’s behavior in terms of them having “minds” (Peterson & Siegal, 1995)⁷. Functional imaging shows that language even shapes low-level perceptual decision processes in the visual cortex (Tan et al., 2008). As noted in the case of special case of written language above (section 5.4.3), the internal experience of words created by literacy can profoundly shape the brain, and its cognition. Parallel to this, the meaning of action and perceptual words is

7. This situation happens in children born deaf to nondeaf speaking parents. In such a situation, a deaf child receives language from its parents that is based largely upon pointing. This situation does not apply to deaf children of deaf parents since they are proficient in sign language and so can communicate linguistically about intents, wishes and beliefs and so mental states. Few hearing parents have such skills in the early years of having a deaf child.

grounded upon cortical areas that process motor control and object perception (Hauk, Davis, Kherif, & Pulvermuller, 2008), and the linguistic processing of spatial relationships with that of spatial aspects of images (Wallentin, Weed, Ostergaard, Mouridsen, & Roepstorff, 2008). Thus, language by providing organization to cognition is not only closely involved in the internal stimulation that aids its neural integration and differentiation, but through this extends deep into the neural processing of human cognitions irrespective of their involvement or not in communication.

(For further possible ways synapse neurodevelopment might have led to enhanced cognition in regard to stimulation due to changes in axon connections, cerebello-cerebral reorganization, neuron types, dendritic arbor maturation, dendritic arbor geometry, developmental search space, and neurological neoteny, see Appendix 3. Higher-order association measurement of neural integration and differentiation is discussed in Appendix 4, while Appendix 5, discusses synapse neurodevelopment and its link with stages in cognitive and symbolic capacity development.

7. EVOLUTION AND NEURODEVELOPMENT

7.1. Prolonged expensive neurodevelopment and encephalization

The existence of prolonged expensive neurodevelopment in modern children raises the possibility, that it was not only extra encephalization but also an extension in the length of synapse neurodevelopment that was central to human evolution, or that it was at least of comparable or complementary importance.

Brain size within modern human range was achieved several hundred thousand years ago. Neanderthals, for example, have similar or greater cranial volume than anatomically modern humans (Holloway, 1981), even though the two species of humans separated with a common ancestor 311,000 to 435,000 BP (Weaver, Roseman, & Stringer, 2008). This lack of further brain size in anatomically modern humans increase is unexplained. One theory is that it could link to the difficulties of passing heads of larger size through the birth canal, in the context of obstetric problems, and limits upon further pelvis expansion due to the biomechanics of efficient bipedality (Rosenberg, 1992). Another factor could be that white matter increases as a proportion of the brain to the power of $4/3$ (Zhang & Sejnowski, 2000). As a result, any increase in brain size produces a larger proportional increase in white matter than gray matter, a situation which could act to create diminishing returns on the cognitive advantages of brain expansion to gain more gray matter neural circuits.

Research on the coefficient of additive genetic variance in human body organs supports the existence of an evolutionary ceiling restricting increase in human brain size. The human brain has a particularly low coefficient of additive genetic variance compared to other human organs such as the heart and the eye (Miller & Penke, 2007). This suggests that modern

human brain size is presently under strong stabilizing (average-is-better) selection (Miller & Penke, 2007). Indeed, the authors “caution that brain size may not be the most appropriate . . . endophenotype for understanding the evolutionary genetics of intelligence” (Miller & Penke, 2007, p. 108). Total brain size, moreover, only moderately correlates with IQ. Further, clinical reports exist in which brains due to microcephaly or surgical hemisphere removal (hemispherectomy) that possess IQs in the normal range but have brain volumes equal or even lower than that of *H. erectus* ($\approx 930 \text{ cm}^3$) (reviewed, Skoyles, 1999).

Larger brain size and high encephalization, however, are important. Larger brain size notably allows for more neural networks between mini-and macrocolumns (Casanova & Tillquist, 2008), and so more complex neural circuits, since the number of cerebral cortex areas as well as neuron number increases with the size of the brain (Changizi & Shimojo, 2005). But given that human brains had already arisen several hundred thousand years ago in the modern human brain size range, it seems that increase further in size was not necessarily of much advantage. Thus, additional evolutionary increases in cognitive ability could have come about through a nonsize change to the brain, such as the possibility reviewed here of an extension of the period of superabundant synapses during childhood.

7.2. Implications for understanding humans

Two things have been shown so far in this review.

The energy opportunity for the evolution of new cognitions radically changed with primates and, in particular, with humans.

In nonprimate vertebrates, the percentage of energy allocated to the adult brain exists within a narrow band (2.7-7.7%) (Mink et al., 1981), and this relates to the initial restricted energy support of the brain during its development (Martin, 1981; Martin, 1989, 1996). This argues that the allocation of energy to the brain has resulted (with the exception of a few animal groups such as primates) in brain development that receives only limited energy support. As a result, this has restricted the brain's evolution in regard to its potential neurodevelopment, and so its potential cognitive capabilities.

It has also been shown above that certain animal groups most notably primates have a greatly increased allocation of energy to the adult brain (primates >10%; humans 20%), and that in parallel to this, that they also receive substantial energy investment as juveniles. Therefore, a central event in the evolution of primates and humans has been that their neurodevelopment has not been constrained in its potential to acquire complex cognition by energy limits. This, for example, has allowed for increased encephalization in primates, and more sophisticated foraging techniques in hominoids.

If it can be supported, prolonged synapse neurodevelopment offers adaptive opportunities to enhance the complexity of cognitive functions.

It has been shown in section 6 that synapse neurodevelopment in its length of duration has a close relationship with the complexity of cognitive capabilities that are acquired by allowing for their greater integration and differentiation. Further, that synapse neurodevelopment is highly expensive due to exuberance in synapses and the high cost of synapse activation. Thus, if energy supplies available for development are increased, the evolutionary option arises for a prolongation in the period during which synapses are exuberant in numbers, and through this, the capacity of juveniles to learn more complex cognitions. From an evolutionary perspective, therefore, an intimate relationship exists between the energy provision to immature brains, synaptic neurodevelopment, the integration and differentiation of brain function, and the evolution of adult brains that have biologically sophisticated information processing faculties.

Thus, since (i) human juveniles have been shown to receive a radically enhanced energy supply compared to those of other animals (high-energy foods, food pooling behavior), and that also (ii) human juveniles and adults show novel cognitive capacities linked to integration and differentiation, this suggests that (iii) increases in energy provision might have played a central role in human evolution through enabling (iv) a particularly extended period of synapse neurodevelopment.

Prolonged and high energy consumption during human neurodevelopment does not happen, however, in isolation to metabolic events occurring in the rest of the developing body. One question that this raises is whether prolonged expensive neurodevelopment might have had an important but presently unappreciated impact upon the physiology of the human body, in particular, during the ages between 4 and 9 years-of-age. The next section addresses this possibility in the context of what is known about human “childhood”.

8. CHILDHOOD AND PROLONGED EXPENSIVE NEURODEVELOPMENT

8.1. Childhood as human unique

8.1.1. Metabolic slow growth

Barry Bogin has argued that childhood is an unique stage characterized by nonlactational dependence that has been inserted into *Homo* development between infancy (dependent upon lactation) and juvenility (capable of independent feeding prior to the onset of reproductive maturity) (Bogin 1997; Bogin, 1999b). Human childhood is metabolically notable as a period during which body growth is extraordinary slow—half that of juvenile chimpanzees (Walker, Hill et al., 2006). Indeed, the body growth of human children is on the mean allometric growth rate line not of mammals nor other primates but of reptiles (see fig 1, Walker, Hill et al., 2006, "With respect to growth rate alone, humans are more like a reticulated python than a

typical mammal" p. 578)⁸. This can be seen in fig. 9 on page 54 that illustrates the different pattern of growth velocity between chimpanzees and humans (Ache hunter-gather foragers). Final human adult size and stature occurs not because of childhood growth, but a rapid height spurt that peaks at 14-15 (males) and 12-13 (females) (Bogin, 1999a; Walker, Hill et al., 2006), see fig. 7. As it has been noted what has happened is that "we displace an otherwise 'standard' but condensed primate subadult growth spurt to a fairly late age" (Leigh, 2001, p. 231)⁹. Why did this period of very slow growth in human juveniles—childhood—evolve?

8.1.2. Slow growth concomitant with prolonged expensive neurodevelopment

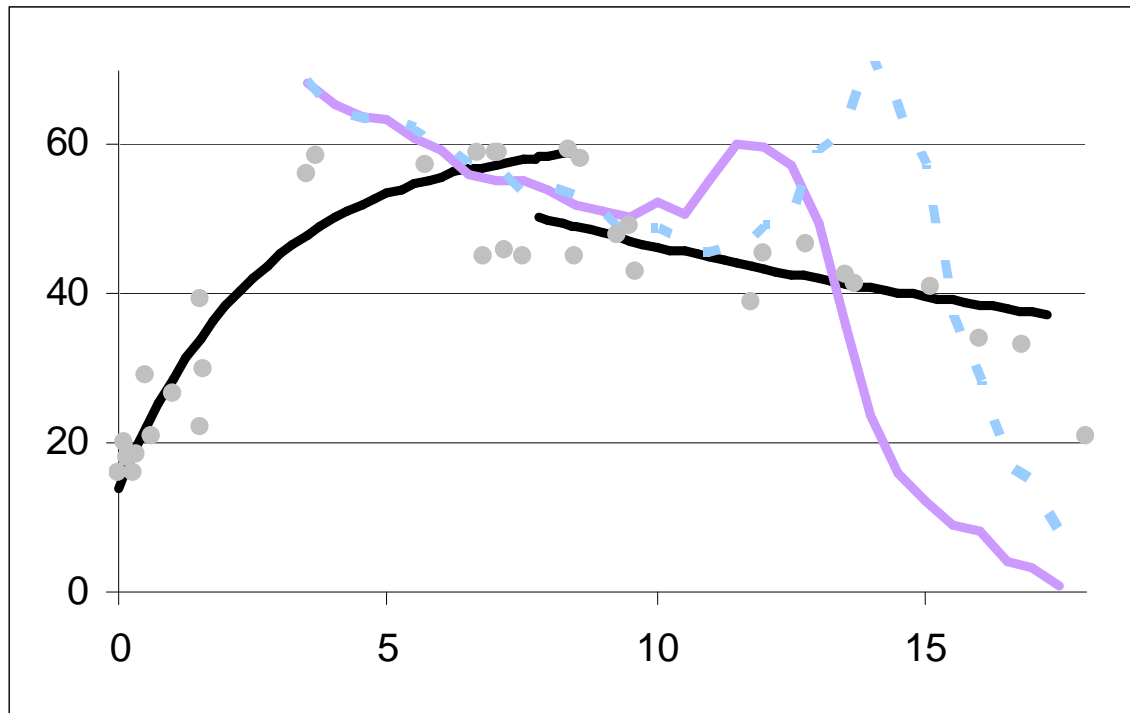
Bogin, while identifying childhood as an extremely retarded growth period specific to human development does not identify a definite adaptive reason why it should exist. (His suggestions are reviewed below in appendix 8). However, linking the slow growth of childhood to a prolonged period of expensive neurodevelopment could provide a parsimonious explanation since it integrates together diverse peculiarities of childhood brain and body physiology.

Human brain development is linked physiologically to body growth due to the competitive allocation of energy between the brain and the body. The childhood brain, indeed, due to its size and high energy consumption dominates the energy budget of the entire body (see figs. 2 and 3). The brain and body are in particular competition for energy when skeletal muscle requires energy during prolonged strenuous activity. This energy cannot be drawn from muscle reserves. This puts the child's brain and its skeletal muscle into conflict in regard to hepatic (liver) generated glucose. Importantly, the extent and intensity of this competition will relate to the quantity of the skeletal muscle that exists in juveniles and so their body size.

Moreover, strenuous exercise can have other types of metabolic disruptive impacts upon the brain (hypoxia, hyperthermia, dehydration and hyperammonemia) that impair it to the degree that skeletal muscle mass is large. Unlike glucose depletion, they are not, however, so well studied. Together with the above noted glucose competition, they might have acted to advantage the evolutionary selection of slow growth and the smaller body size that characterizes modern children. The plausibility of this idea is now reviewed.

8. Since infant growth is 70% adipose tissue (Kuzawa, 1998), the earlier postnatal musculoskeletal growth of infants can be considered, like that of children, also to be retarded.

9. Bogin takes childhood to last from the end of weaning until about 8 years-of-age which broadly covers the above discussed period of prolonged expensive neurodevelopment. A stage of juvenility, according to Bogin, occurs after this until the start of the growth spurt. This division is not followed here since the start of puberty is a more appropriate marker (due to its link to hormonal and metabolic changes, see appendix 6), and this is identified by Tanner stage II, and the on-start of adolescent growth that usually occurs in the years between 8 and 9 (girls) and 10 and 11 (boys) years-of-age.



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Fig. 7. Brain metabolic changes appear inversely linked to height velocity changes in this composite graph. The dots represent the glucose utilization of the brain in $\mu\text{mols per min per 100 gram}$ as in fig. 4. The added lines represents height velocity (rate of change in height, the solid light pink line for females, and the dashed light blue, for males). Skeletal muscle, it should be noted, scales by the square with height (Heymsfield, Gallagher, Mayer, Beetsch, & Pietrobelli, 2007). The growth velocity curves show that a shift occurs towards faster growth, “take-off”, at around 10-11 years-of-age (males) and 8-9 years-of-age (females), just after the start of the decline in the peak metabolism in the brain. This precedes the peak of adolescent growth that occurs later at 14-15 years-of-age (males) and 12-13 years-of-age (females) (Bogin, 1999a; Walker, Hill et al., 2006). Analysis of variance of chronological and skeletal level of maturity suggests that adolescent growth take-off links to changes signaled by the brain, while peak adolescent growth velocity links to the stage of skeletal maturity (Hauspie, Bielicki, & Koniarek, 1991). The brain data represent mixed genders; however, Muzik and colleagues (1999) note in their mathematical analysis of it that males had a later transmission (8.41 years) between the plateau and decline curves than females (7.54 years) paralleling the difference in the onset age of adolescent growth take-off. This difference in brain metabolism, however, did not reach statistical significance. The height growth velocity data come from the 2000 CDC Growth Charts spreadsheets compiled by the National Health and Nutrition Examination Survey of the Centers for Disease Control and Prevention.

8.1.3. Plausibility of developmental metabolic brain body link

The $\approx 50\%$ increased energy demands of the pediatric brain requires that the brain receives the vast majority of hepatically generated plasma glucose (Haymond & Sunehag, 1999).

Moreover, this supply needs to be particularly dependable and stable since the pediatric brain is neurologically impaired at a much higher plasma glucose level (4.2 mmol L^{-1}) than the adult one (3.0 mmol L^{-1}) (Jones et al., 1995).

Metabolically, as earlier noted, adult skeletal muscle can consume 40-fold more energy— 24 W kg^{-1} —than at rest— 0.6 W kg^{-1} , and so considerably exceed the activity of the brain (a five year-old child has 5.6 kg of skeletal muscle, a male adult, 29 kg , and female adult, 17.5 kg) (International Commission on Radiological Protection, 2002). While initially, this energy demand is supported by local muscle glycogen stores, and uses alternatives to plasma glucose such a free fatty acids, plasma glucose production still needs to increase considerably. In adults, hepatic glucose generation as a result goes up 5-fold—plasma glucose levels as a result can rise considerably (Rose & Richter, 2005). However, when exercise turns prolonged and strenuous in adults, it can overwhelm this plasma glucose increase and cause plasma glucose levels to fall below normal (Richter et al., 1988) to even those in which it can impair the brain and the body ($<3 \text{ mmol L}^{-1}$) (Coyle et al., 1986; Felig, Cherif, Minagawa, & Wahren, 1982).

The metabolic needs of muscles can also effect blood oxygen levels. Again compensating physiological actions occur, in this case, increased cardiac output and pulmonary activity and again in prolonged strenuous exercise these are also overwhelmed resulting in this case in restricted oxygen supply to the brain (Dempsey et al., 1984; Subudhi et al., 2008). The waste products of heat (Nybo et al., 2002; Nybo & Nielsen, 2001) and ammonia (Nybo et al., 2005) from intense prolonged physical activity can also negatively impact upon the brain. A further negative effect is dehydration. This results from sweat based thermoregulatory clearance of exercise generated heat, and is particularly detrimental to the brain in hot environments (Baker et al., 2007; Cian et al., 2001; Maughan, Shirreffs, & Watson, 2007).

If minimizing metabolic disruption upon the brain was the selective reason for children being small, evolution could also have been expected to have selected other adaptations that reduce this disruption in addition to that of limiting body size. This, indeed, is the case (reviewed below, in section 8.4). This provides independent support that it has been the advantage of minimizing metabolic disruption upon the brain, rather than some other factor, that has resulted in slow body growth.

In what follows, focus is given particularly to the better investigated effect of exercise upon plasma glucose, due to the limited availability of research findings upon other metabolic disturbances.

8.2. Glucose supply, strenuous exercise and the pediatric brain

Developmental exercise physiologists have noted that plasma glucose levels are compromised in children by strong exercise.

“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).

Evidence supporting this idea will now be detailed.

8.2.1. *Glucose supply in children is fluctuation labile*

The hepatic production of glucose is closely linked to that of brain size in nonhuman animals such as the pig (Flecknell, Wootton, & John, 1980), as well as in humans (Haymond & Sunehag, 1999, see their fig. 4B). By 3-4 years-of-age, the human brain (and its high energy consuming cerebral cortex component) is near adult size, with the range of hepatic glucose production approaching that of adults (Bier et al., 1977).

This glucose regulation lability occurs in spite of the child's liver producing near adult levels of glucose in the context of a linear increase until around 8 and 10 years-of-age (Bier et al., 1977). Between the ages of 1 month to 6 years-of-age, the liver per 100 g produces three-fold more than that of the adult (between 6 and 14 years-of-age, over twice) (Bier et al., 1977). The liver, however, is substantially smaller (570 g) than in the adult (1800 g ♂, 1300 g ♀) (International Commission on Radiological Protection, 2002). The combination in children of a higher glucose consuming brain, and a small liver that is physiologically extended in its capacity to generate glucose could reasonably be expected to have a smaller margin than in adults in its capacity to counteract depletions by exercising muscles.

The glucose regulation in children indeed shows evidence of lacking the reserve margin found in adults to provide additional plasma glucose when there is heightened physiological demand.

- 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 (Haymond & Sunehag, 1999, table 1).
- Children during controlled insulin hypoglycemia react with a two-fold greater peak of the counter-regulatory hormone epinephrine to plasma glucose depletion than adults (Amiel, Simonson, Sherwin, Lauritano, & Tamborlane, 1987; Davis, Goldstein, Cherrington, & Price, 1994; Jones et al., 1995).

- The plasma level that triggers this epinephrine during its controlled insulin reduction is substantially higher in children (3.9 mmol L^{-1}) than adults (3.2 mmol L^{-1}) (Jones et al., 1991).
- Children aged 8.5-11 upon exercising show a drop in plasma glucose levels (Delamarche et al., 1994). After 18 minutes of 60% $\text{VO}_{2\text{max}}$ exertion on an ergometer, plasma glucose dropped in such children from $3.75\text{-}3.78 \text{ mmol l}^{-1}$ to $3.1\text{-}3.4 \text{ mmol l}^{-1}$ (Delamarche et al., 1994). This drop does not occur in adults. It is also followed by a rise in epinephrine that triggers gluconeogenesis (Delamarche et al., 1994; Delamarche et al., 1992).
- Following temporary starvation (fast), plasma glucose drops to hypoglycemia levels after 24-36 hours with corresponding up regulation of alternative energy sources (ketone bodies, see appendix 9) that are not seen in adults even after 2.5-3 days of fasting (Cahill, 2006; Haymond & Sunehag, 1999).
- The management of insulin-dependent diabetes mellitus is much more difficult in children than adults (Amiel et al., 1987).
- 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.

8.2.2. Intense strenuous exercise can potentially cause hypoglycemia

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 $0.5 \text{ mmol kg}^{-1} \text{ min}^{-1}$ (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)).

Moreover, physical exercise in one part of the body can metabolically limit another, for example, the glucose drawn by knees doing extensions drops by 20% when arm cranking is added (Richter et al., 1988). In adults, such exercise plasma depletion can also effect glucose availability to the brain: short intense exercise (35 min ergometer cycling) can reduce brain glucose uptake by 32% (Kemppainen et al., 2005) (for fuller details see appendix 9, page 82). (Heart muscle, it should be noted, while able to use glucose, normally uses free fatty acids (van der Vusse, Glatz, Stam, & Reneman, 1992), as does skeletal muscle at rest (Andres, Cader, & Zierler, 1956).)

8.2.3. *Children minimally engage in intense glucose depleting physical exertion.*

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 years-of-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). Consistent with this, children that engage in sports show reduced spontaneous activity that afterwards results in them having no greater total energy expenditure than children that do not engage in them (Falgairette, Gavarry, Bernard, & Hebbelinck, 1996).

This suggests that exercise in children is under tight metabolic regulatory control to minimize metabolic disruptions that in adults either do not occur, or can be tolerated. This could be because the brain monitors glucose availability in regard to energy/plasma glucose supply set points (Peters et al., 2004), and when this (and its small backup supplies of glycogen (Brown & Ransom, 2007)) due to excessively intense and prolonged exercise threatens to decline, the brain reacts with behavioral motor fatigue (Dalsgaard & Secher, 2007). A similar anticipation of exercise induced failure has been suggested for preventing catastrophic hyperthermia (Marino, 2004). Such regulation can also be based upon top-down expectations about energy deficits since neural adaptations and fatigue occur during the experience of intense physical activity even when muscles due to partial neuromuscular blockage prevents actual intense—and so glucose—depleting activity (Dalsgaard, Ide, Cai, Quistorff, & Secher, 2002).

8.2.4. The pediatric brain and glucose depletion

Such regulation and glucose minimizing adaptations could be important for prolonged expensive neurodevelopment. 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 the P300 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).

8.3. Glucose levels and neurocognitive development

8.3.1. Plasma glucose levels and the brain

The concentration of extracellular glucose in the brain after its transfer across the blood-brain barrier from plasma glucose was originally thought to be 2 mmol L^{-1} (Lund-Andersen, 1979), but more recent research upon rats suggests a lower figure that varies with brain region from 1.3 mmol L^{-1} in the hippocampus to $0.3\text{-}0.5 \text{ mmol L}^{-1}$ in the stratum (for review, see McNay, McCarty, & Gold, 2001). While only a small change occurs in the rat in the concentration of extracellular glucose with neural activation in the stratum, in the hippocampus it declines by around a third (McNay et al., 2001). In humans, while cognitive activations increase glucose consumption in cortical neural networks, it is usually thought that this is sufficiently well counterbalanced by parallel reductions elsewhere not to effect total brain consumption (Seitz & Roland, 1992). However, demanding cognitive tasks such as the Wisconsin card sorting test have been shown to increase global glucose consumption by 12% (Madsen et al., 1995). This investigation was by a method, the Kety-Schmidt technique, that directly measures actual arteriovenous differences in glucose (Madsen et al., 1995), and so unlike the PET method used by Seitz and Roland (1992) can estimate accurately actual brain glucose usage.

The possibility that insufficiency of extracellular glucose may become an important factor in neural function is suggested by increased 3-hydroxybutyrate (see appendix 9, page 82) up-take in the lower layers of the cerebral cortex (Hawkins & Biebuyck, 1979). This

insufficiency has been suggested to underlie the improvement effect of glucose ingestion upon cognition in rats, particularly memory (McNay et al., 2001). Only after 4-6 seconds following neural activation does blood flow increase to maximum which creates the possibility of a temporary energy shortage in neurons (Raichle & Mintun, 2006). Consistent with protecting against this, the hippocampus has larger stores of a very quickly activated backup reserve fuel, glycogen, (13 mmol L^{-1} compared to $5\text{-}6 \text{ mmol L}^{-1}$ in the cerebral cortex) (Dalsgaard, Madsen, Secher, Laursen, & Quistorff, 2007).

Supporting the above noted increase in total brain energy use with cognition, plasma glucose is reduced when people solve hard arithmetic problems by about 0.4 mmol (Scholey, Harper, & Kennedy, 2001). Likewise, constantly responding to whether color names printed in incongruent colors (the Stroop task) after 45 minutes (675 stimuli) causes plasma glucose to drop 0.7 mmol (Fairclough & Houston, 2004)¹⁰.

Brain energy consumption also increases due to the demands in the motor cognition needed to control the body during intense physical exercise (Secher et al., 2008).

8.3.2. Plasma glucose and child cognitive neurodevelopment

Plasma glucose availability might play a role in optimal cognitive development. For example, children at risk for malnourishment have improved cognition and learning at school if provided with a breakfast, and so a postprandial increase in plasma glucose levels (Cueto, 2001; Grantham-McGregor, 2005). Children in developed countries that skip breakfast have impaired cognitive performance that relates to a reduced plasma glucose (Benton & Parker, 1998; Cueto, 2001; Pollitt, Lewis, Garza, & Shulman, 1982).

Children's cognitive development, moreover, depends upon cognitions that are particularly sensitive to plasma glucose levels.

Memory. Recall and memorization are both important factors in cognitive development and both are sensitive to plasma glucose (McNay et al., 2001): "the glucose facilitation effect" (Allen, Gross, Aloia, & Billingsley, 1996; Meikle, Riby, & Stollery, 2005; Riby et al., 2008; Sunram-Lea, Foster, Durlach, & Perez, 2002). For example, the ingestion of 25 g of glucose at the time of learning a list of words improves their recall 24 hours later (Sunram-Lea et al., 2002). Consistent with this, not eating breakfast and so not having a postprandial glucose increase after the nighttime period of fast particularly impairs memory tasks (Benton & Parker, 1998). As noted above, the hippocampus, a part of the brain critical to memory has high stores of glycogen suggesting that due to its vulnerability to such energy disruptions, it has special evolved protection against temporary glucose deficits.

10. This plasma glucose reduction is unlikely to be due to the stress of these activities causing the body to lower its plasma glucose levels since epinephrine secretion stimulates them to rise sharply (Tse, Clutter, Shah, Miller, & Cryer, 1983).

Prefrontal cortex and executive cognitions. These skills as measured by the Raven's progressive matrices test are effected by plasma glucose depletion, both in those with type 1 diabetes (Sommerfield, Deary, McAulay, & Frier, 2003), and nondiabetics (Warren, Allen, Sommerfield, Deary, & Frier, 2004). Another group of prefrontal related skills that are sensitive to low plasma glucose levels concern sustained attention, frustration resistance (Benton, Brett, & Brain, 1987), and persistence on tasks and maintain "self-control" behavior (Gailliot et al., 2007, studies 3-8)¹¹. The more demanding a task, the more its performance links to hepatic plasma glucose levels (Scholey et al., 2001). Further, the longer a demanding executive task such as Stroop is carried out, and so requires sustained attention and "mental effort" (Gailliot et al., 2007), the greater drop that occurs in plasma glucose levels: 15 minutes, 0.2 mmol L⁻¹; 30 minutes, 0.4 mmol L⁻¹; and 45 minutes, 0.7 mmol L⁻¹ (Fairclough & Houston, 2004). This link is important since the ability to delay gratification (with which these tasks associate) is not only an important skill in its own right but also one that through its effects upon learning is strongly predictive of the academic success of children (4 and 5 years-of-age) when they are ten years older (Mischel, Shada, & Peake, 1988).

8.3.3. *Glucoregulation and cognition*

The relationship between plasma glucose and cognitive performance is an inverted "U" with low levels impairing cognition (as noted above), but also very high levels impairing it (Sommerfield, Deary, & Frier, 2004). Further, the evidence of shifts of brain area activation in adults to low glucose (Rosenthal et al., 2001) suggests that reductions that might lack apparent effects upon cognitive performance might still have subtle—and potentially disruptive—ones. As a result, the ability to regulate levels of plasma glucose against fluctuations even within the normal range could be important for optimal cognition (for more details about variation in plasma glucose levels see appendix 7).

Individuals that have good physiological abilities to regulate their plasma glucose after a glucose drink show better cognitive performance than those without them (Awad, Gagnon, Desrochers, Tsiakas, & Messier, 2002; Donohoe & Benton, 1999). Likewise, children that receive low glycemic load breakfasts that releases glucose more slowly in the blood with a lower postprandial glucose surge (a characteristic of better regulation) have improved attention, memory and less frustration compared to those that did not (Benton, Maconie, & Williams, 2007). Having such a breakfast also prevents a midmorning decline in cognitive performance in children (Ingwersen, Defeyer, Kennedy, Wesnes, & Scholey, 2007).

The above findings show that cognition is sensitive to the effectiveness of glucoregulation within a fairly small plasma glucose range—in this case in regard to the postprandial glucose level disruption that follows its intake. It might be reasonably supposed, that a similar

11. In the 1980s, there was concern that sugar intake led to hyperactivity in young children (Goldman, Lerman, Contois, & Udall, 1986), but this seems questionable (Wolraich et al., 1994).

cognitive sensitivity also exists for other factors—such as intense exercise muscle glucose depletion—that can disrupt glucoregulation through the steadiness or not of glucose removal and its hepatic replacement. Also, since these intake disruptions happen across a relatively small plasma glucose range, it raises the question of the cognitive impact of much larger depletion disruption caused by strenuous exercise by a large muscle mass. Moreover, when such disruption occurs, this happens in combination with other metabolic disruptions such as exercise induced hypoxia, hyperthermia, dehydration and hyperammonemia. Thus, it could be expected that the negative effects upon cognition and brain of plasma glucose depletion caused by strenuous exercise are considerably greater.

8.4. Child adaptations to minimize disruptive exercise glucose depletion

Children have a suite of adaptations 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 $\text{Vo}_{2\text{peak}}$ (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 height² (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 limited¹². 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).

12. This data deficit is surprising in view, not only of the ease of measuring appendicular skeletal muscle with MRI, but also that research groups have collected the information but for some reason have not published the raw information. One might also generally note the deficit of such information for nonhuman primates particularly hominoids, where the MRI data should be easily acquired (Theodore Grand's anatomical data mentioned in the text was collected 30 years ago) but for some unknown reason has not been gathered, in spite of its theoretical importance, and its availability without animal sacrifice. Likewise, the only hepatic production figures available for children are three decades old and do not provide age nor body composition information. There is a considerable need for data gathering and publication in regard to body composition interactions with metabolic physiology during development both in its maturational ontology and its evolutionary phylogeny. Considerably more is known about the physical parameters that determine stellar development and star composition than the development and composition of human bodies. This in part reflects the concern of astrophysicists to quantify the basic parameters of large cohorts of stars, a concern that is rare in those studying human developmental biology. The lack of such data is why on several occasions citation is made to the estimates given by the International Commission on Radiological Protection where such information as far as it exists has been gathered together for practical purposes. Such developmental/cross species data is particularly needed to complement the genomic discoveries being made about the metabolic genetic changes that characterize human and primate evolution—without the collecting of this information, much genomics will be difficult to interpret. Ironically, there are now many noninvasive new technologies for gathering the required physiological data. There is a scientific need for large cohort studies of the metabolic related factors changes that occur during human development to detect the macro level changes that are concomitant with genomic ones.

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).

<u>Age</u>	<u>body</u>	<u>fat</u>	<u>body - fat</u>	<u>muscle</u>	<u>Muscle % (body – fat)</u>
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.

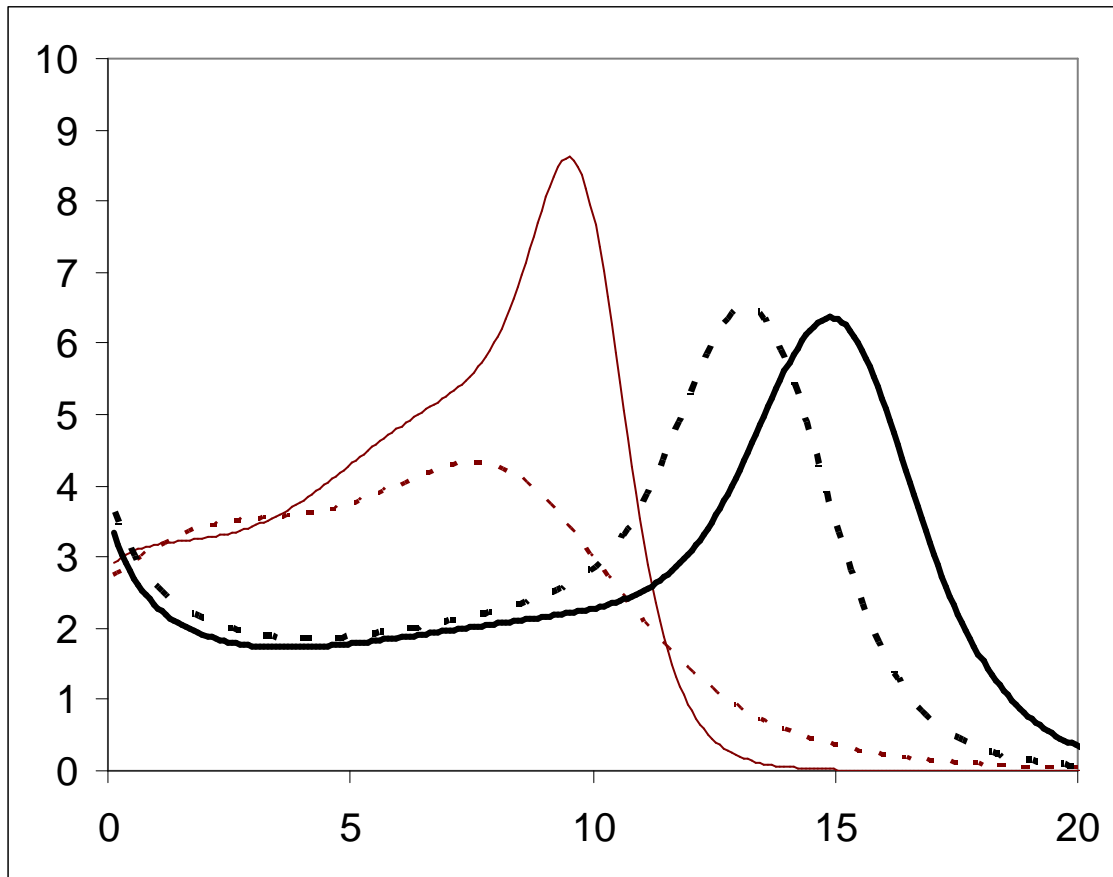


Fig 8. The brown thin line represents the velocity curve of male chimpanzees (dashed, female) and the black thick one, male humans (dashed, female) (Ache hunter-gather foragers). Both have similar adult weights. Velocity is in terms of kg year^{-1} . The two graphs show the marked difference in the pattern of growth in the two species with chimpanzees lacking the slow growth that occurs in the period of childhood in humans. The graphs are based upon the formula in table 1 in (Walker, Hill et al., 2006).

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).

8.5. Oxygen exercise constraints paralleling glucose ones

An additional metabolic factor to glucose advantaging slow growth in children is exercise hypoxia. 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)¹³.

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

13. 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).

children compared to adults to support the combined oxygen needs of both the brain and activated high muscle mass.

8.6. Other strenuous exercise metabolic effects upon the brain

A third effect of strenuous exercise upon which there is research is dehydration. Humans use sweat thermoregulation for heat clearance particularly to remove the heat produced during exercise (to provide exposed surface area for this is why humans lack extensive hair cover) (Porter, 1993). A marathon runner, for example, can lose 5 L in a run, and people doing heavy exercise may lose two and half times as much fluid in sweat as urine. Dehydration could be expected to particularly impair children (D'Anci, Constant, & Rosenberg, 2006) since they have a higher surface area mass ratio than adults (5 year-old, 0.41; male adult, 0.26; female adult, 0.28: figures in $\text{m}^2 \text{kg}^{-1}$, data source: (International Commission on Radiological Protection, 2002)). Mild dehydration as a consequence of exercise and heat is reported to impair cognition, for example (Baker et al., 2007; Cian et al., 2001). These impairments start after body mass lost that is greater than 1% (Sharma, Sridharan, Pichan, & Panwar, 1986). However, voluntary 24 hour water deprivation in adults without exercise and heat stresses can produce 2.6% loss of body weight but little effect upon the performance of a wide variety of cognitive measurements including P300 event-related evoked auditory potentials (Szinnai, Schachinger, Arnaud, Linder, & Keller, 2005). In contrast, children of 10-12 years-of-age for whom drinking water was available that were dehydrated as measured by urine osmolality above 800 mosm kg^{-1} showed afternoon impairment (Bar-David, Urkin, & Kozminsky, 2005). Cognitive impairment, particularly due to heat and exercise is likely to be due to be loss of integrity to the blood brain barrier (Maughan et al., 2007).

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 $\mu\text{mol min}^{-1}$ detection level; following 3 hours exercise with glucose supplementation, 5.3 $\mu\text{mol min}^{-1}$, without glucose supplementation, 16.1 $\mu\text{mol min}^{-1}$) (Nybo et al., 2005). The effects of dehydration are greater and happen at a lower threshold in hot environments (Maughan et al., 2007).

The arguments made above in regard to glucose and skeletal muscle mass are also paralleled by these other exercise metabolic impacts upon the brain. As with the case of glucose depletion, reducing the quantity of skeletal muscle mass in the body will also act to protect the brain. Lack of more detailed review upon them is due not to the unimportance of these particular metabolic disruptions but the absence of research, especially in regard to children, and their impact, both in children and in adults upon cognition.

The above evidence of a mutually aggravating variety of negative effects of strenuous exercise upon the brain identifies a possible metabolic bottleneck in human evolution. Fast growth offers advantages to juvenile primates but this conflicts in juvenile humans with the need to protect their large brain and its extended period of expensive neurodevelopment from strenuous exercise induced metabolic disruptions. The conflict would seem to have been resolved by slowed growth and so reduced skeletal muscle mass during the period of maximum neurodevelopment vulnerability.

How likely is this idea? Above nonsize adaptations have been shown to exist that help protect the brain from metabolic disruption in children, at least in regard to plasma glucose. Their existence suggests that this metabolic conflict has played a role in shaping human childhood exercise physiology. This therefore suggests the possibility that the much bigger reducer of this conflict—limiting large mass muscle by slow growth and small body size—also evolved as a result of a similar selection to minimize metabolic disruption.

In summary, reduced body and concomitant skeletal muscle mass together with other adaptations would seem to provide a means by which children can (i) engage in the large amounts of moderate physical activity needed, for example, for cognitive and motor skill acquisition, while at the same time (ii) having a protracted period of experience neurodevelopment that is minimally disrupted by their active bodies¹⁴.

8.7. Neanderthals

Whether Neanderthals had a different growth pattern has been discussed for over 80 years. The excavators noted in 1928 of a Neanderthal juvenile: “It is possible that the growth of Neanderthal man was different from that of modern man” (Garrod, Buxton, Elliot-Smith, & Bate, 1928, p. 84), and Arthur Keith: “Apparently Neanderthal children assumed the

14. The metabolic impact of strenuous exercise and high muscle mass upon the pediatric brain raises the separate issue whether it might have also effected adult human body composition. Modern anatomical humans are more gracile than archaic *H. sapiens* species, such as Neanderthals (Holloway, 1981), while more recent *H. sapiens sapiens* are more gracile in body build than earlier ones (Ruff, Trinkaus, & Holliday, 1997). This has been explained in terms of climate adaptation and work load. The above discussion raises an alternative possibility: that lighter gracile bodies might have been advantaged during human evolution due to the benefit of reducing the impact of strenuous exertion upon the human brain. This might have increasingly become advantageous when the technologies of the upper Paleolithic put a premium upon cognition while reducing the importance to survival of muscular strength.

appearances of maturity at an earlier age than modern children” (1931, p. 346). Recent advances have made this question more definitely answerable with the development of the noninvasive imaging of growth patterns in teeth using x-ray synchrotron microtomography of tooth enamel (Tafforeau & Smith, 2008). Early reports on one Neanderthal juvenile (Smith, Toussaint et al., 2007) has confirmed earlier suggestions (Ramirez Rozzi & Bermudez De Castro, 2004) that Neanderthals had a quicker period of maturation. This is in marked contrast to evidence of a similar slow growth to modern *H. sapiens sapiens* in an early *H. sapiens sapiens* child of 160,000 BP (Smith, Tafforeau et al., 2007).

These findings are preliminary—some have argued for Neanderthals having a growth rate comparable with modern humans (Macchiarelli et al., 2006). However, if this recent x-ray synchrotron microtomography research is upheld by the examination of further juvenile Neanderthals, this would raise the possibility that extended costly neurodevelopment might be an autapomorphy of anatomical modern humans.

Such a possibility could find confirmatory support from the Neanderthal genome project (Green et al., 2006; Noonan et al., 2006). Modern humans show up regulated metabolic gene expression and metabolic gene changes (Caceres et al., 2003; Grossman et al., 2004; Haygood et al., 2007; Uddin et al., 2008; Uddin et al., 2004). Whether these changes are specific to humans rather than archaic *H. sapiens* such as Neanderthals is currently unknown. However, as the role of metabolic gene unregulated expression becomes better understood in modern humans, the genes/ gene networks responsible for controlling this will be identifiable as to their presence or not in the Neanderthal genome.

9. DISCUSSION

Human biology like all biology links closely to energy metabolism. This review identifies how innovations in this underlie five, possibly seven, evolved features that distinguish humans from other animals.

- (i) Humans engage in group food pooling behavior.
- (ii) Humans provision their young during a near two decade period of dependency.
- (iii) Humans have a biologically very prolonged period of costly synaptic neurodevelopment.
- (iv) Humans have a specific period of slow growth, “childhood”.
- (v) Human have the cognitive capabilities that underlie complex articulate thought, language and symbolic culture that support the acquisition of large quantities of high energy foods.

Further, (vi) humans during prolonged expensive neurodevelopment have adaptations that protect the brain from the metabolic disruptions caused by strenuous exercise, and (vii) that

genomic changes have occurred in the genes involved in human brain metabolism (Caceres et al., 2003; Grossman et al., 2004; Haygood et al., 2007; Uddin et al., 2008; Uddin et al., 2004).

The first five traits seem to be only found in humans in any marked form. This review both shows that they are closely linked (together with the other two), and that they offer many empirical opportunities for further integrative investigative research.

Moreover, this review identifies a new parameter linked to neurodevelopment that can be identified in the paleoanthropological record—slow childhood growth rate as a proxy for prolonged expensive neurodevelopment. This part of the review is important since this provides a direct means of evaluating the prolongedness of expensive neurodevelopment in earlier archaic human species such as Neanderthals. As noted, for 80 years it has been suspected that they had a faster growth during childhood, and that this has been confirmed by recent x-ray synchrotron microtomography of tooth enamel (Smith, Toussaint et al., 2007). This suggests that prolonged expensive neurodevelopment could be an unappreciated autapomorphy of anatomically modern humans.

9.1. Evolution of energy supported learning

It has been widely noted by others that developmental immaturity provides the opportunity, particularly when it is of long duration, for learning (Bjorklund, 1997; Bogin 1997; Bogin, 1999b; Joffe, 1997). How might the energy demands identified above with increased numbers of synapses link to the evolution of this prolonged neurodevelopment?

A key factor here is phenotypic plasticity (in which the effects of the environment upon the organism preliminarily adapt it) (West-Eberhard, 2003; West-Eberhard, 2005a, 2005b). The linkage between environmental richness, learning and synaptic numbers (Bennett et al., 1964; Volkmar & Greenough, 1972), noted above in section 4, indeed provides a good example of where the neurophenotype is environmentally plastic. In the context of evolution, a particularly interesting situation is where enriched environments accelerate the development of the visual system in mice (Cancedda et al., 2004). In this case, the environment not only alters the brain, but through behavioral change in the young, leads them to receive high levels of licking and so support from their mothers (Cancedda et al., 2004). This suggests that evolutionary feedback can potentially arise between increases in synapse numbers, greater learning and cognitive capabilities, and improved maternal support. As such, not only would neurodevelopment be modified by external stimulation, but this change would cause behavior that could lead to better energy support from adults to enable that neurodevelopment.

There is, of course, a limit here in that for such solicitation to be satisfied, adults must have the extra energy to give to their young. But an increased juvenile acquisition of cognitions could also create adults able to be better foragers and so obtain such extra energy. Thus, a loop can arise in which an increase in the abilities of adults to acquire food results in better

provisioned juveniles that in turn allows for the high energy supported neurodevelopment required for the cognitive capabilities that can acquire that food. This could cause profound phenotypic modification that can later produce genotypic change in an energy provision type of the Baldwin effect: “Animals may be kept alive let us say in a given environment by social cooperation only; these transmit this social type of variation to posterity; thus social adaptation sets the direction of physical phylogeny and physical heredity is determined in part by this factor” (Baldwin, 1896, p. 553). Moreover, as such phenotypic change is a feedback loop, it could self-amplify producing greater energy provision and greater cognitive capabilities. This could cause an evolutionary jump to a much higher cognition dependent food subsistence. This might have implications for modeling human evolution.

9.2. Wild vs captive chimpanzee—enhanced energy support and enhanced cognitions

One reason for raising the possibility of a phenotypic led evolution is the discrepancy between captive and wild chimpanzee cognition in the context of captive and wild chimpanzee nutrition. Trained chimpanzees not only show cognitive abilities such as proto forms of language (Savage-Rumbaugh & Lewin, 1994) not found in the wild, but also are provided with nutritionally high quality diets. Moreover, also from when young (and even before birth), they are constantly weighed, monitored and treated by veterinary experts, and so are physically in near optimal good condition. This high quality support physically changes them as they show more rapid physical growth and maturation (Zihlman, Bolter, & Boesch, 2004). For example, third molar eruption occurs in captive chimpanzees at 10.5 years-of-age, while in wild chimpanzees it happens at 10.8-14.2 years-of-age (Zihlman et al., 2004, table 1). Captive chimpanzees also have greater final body weights: compare the reports on age change in body weights in wild chimpanzees in (Pusey et al., 2005, fig. 9) to those of captive ones in (Hamada & Udono, 2002, fig. 1). Wild chimpanzee adult body weight from these graphs seems to be about 15 kg lighter than captive ones, (though this may reflect different subspecies status). Further, wild chimps show considerable body weight variance when young that only fully disappears when they reach adulthood (Pusey et al., 2005, fig. 19). This argues that wild juvenile hominoids often grow up with insufficient energy nutrition—otherwise their growth would not be stunted, delayed, and so developmentally varied. This energy insufficiency could impair their neurodevelopment, and stop them fully realizing their potential for complex cognition that might otherwise occur with good quality nutritional. It has, indeed, been claimed that they are cognitively delayed: “field observations on social and behavioral development suggest that wild chimpanzees take up to 3 years longer to mature compared with captive animals” (Zihlman et al., 2004, p. 10541). The unreliability of food supply for chimpanzees might therefore act to stop selection in them for enhanced cognitions that depend upon extended expensive neurodevelopment.

This raises the possibility that changes in food acquiring circumstances (the ability to exploit new foods, enhancement in food acquisition/food processing, increased cooperation/energy banking) might leverage novel forms of cognitive capacity through their impact upon

neurodevelopment. Importantly, such changes could enhance cognitive capacities without there needing initially to be a direct genetic change to the brain.

9.3. Origins of food pooling behavior

Food pooling behavior which is central to human hunter-gatherer energy support is an example of altruism in that an individual gives to others resources that they might otherwise consume, or not otherwise risk or spend their time and efforts in obtaining. There is considerable discussion of the origins of food pooling behavior (these issues are reviewed in Gurven, 2004; Kaplan & Hill, 1985). Modern theories of altruism (which underlies food pooling behavior) associate it to enhanced cognitive faculties, for example, Nowak and Sigmund (2005) link social cooperation to the perception of reputation, Mohtashemi and Mui (2003) to social information about trustworthiness, and Fehr and Rockenbach (2004) to judgments about the need for punishment. The basis of human food pooling behavior is likely to be complex involving several processes (including those noted above, and diverse cultural mediated ones that extend them such as morality, notions of normal and “correct” behavior, extended kinship and forms of nonbiological “kinship” such as name-sharing and age-sets). The reputation, trustworthiness and punishment processes involved are also dependent upon general cognitive abilities such as recalling of past events and anticipating future ones.

The capacity to acquire and use this information to modify behavior is limited in nonhuman animals (Stevens & Hauser, 2004). Moreover, these abilities are closely linked to prefrontal cortex skills such as enhanced memory, planning and behavioral regulation, that are only developed to a limited extent in nonhuman animals. Neuroeconomics, consistent with this, links the emotions such as perceptions of fairness that underlie food pooling behavior to prefrontal activations (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). It would seem therefore possible that the enhanced cognitive capabilities enabled by food pooling behavior might support its existence at a neurological level.

9.4. Encephalization

Increases in energy provision of humans supported the increased encephalization that has occurred in human evolution. Indeed, the evolution of greater brain size and its maturation has received much attention not only in paleoanthropology but also in life history theory (Parker, 1990), primatology (Vinicius, 2005), and by biologically orientated economists (Robson & Kaplan, 2003). The idea that energy provision played a key role in neurodevelopment has been suggested before but in terms of gross changes in brain size (Parker, 1990). While brain size is important, the energy input needed for its creation precedes childhood. The prolongation of synaptic neurodevelopment, in contrast, occurs postnatally, and so will be more directly effected by changes in energy provisioning of nonproductive juveniles.

A key question needing investigation is whether brain expansion but with a limited period of expensive neurodevelopment enhances cognition in certain ways (perhaps as occurred in Neanderthals), but while prolonging its expensive neurodevelopment enhances cognition in other respects—such as in aiding the acquisition of those cognitions associated with anatomically modern humans.

Adult anatomically modern humans are more gracile (i.e. less robustly built and muscular) than adult archaic humans such as Neanderthals (Holloway, 1981), and earlier adult anatomical modern humans (Ruff et al., 1997)¹⁵. There has been much debate whether this reduction in muscularity links to climate (Pearson, 2000), or to change in work load (Trinkaus, 1997). The negative effects identified above of large muscle mass during strenuous exercise that metabolically impair the brain raises the possibility that minimizing this disruption by reducing skeletal muscle mass might have been a factor in the development of modern human gracility.

A close study of the different impacts of strenuous metabolic disruptions and the sensitivity to them of the pediatric and adult brains, might also allow estimates of the degree to which size in modern humans has been selected in regard to reducing metabolic disruptions rather than other possible body composition factors such as reduced energy needs (see appendix 8).

Another question is raised by volumetric research upon IQ: how far is prolonged expensive neurodevelopment both in terms of global brain metabolism, and at the level of cortical change, due to inherited factors and to what degree is it the result of environmental ones?

9.5. Conclusion

The metabolic adaptations that are specific to modern humans have received little attention compared to human specific cognitive capabilities. However, these metabolic innovations put human neurodevelopment in a radically different situation to that which occurs in nonhuman animals. As shown in this review, this could have fundamentally changed the expensive phase of neurodevelopment linked to exuberant synapses by enabling it to be prolonged. Because the length of this period of neurodevelopment closely links to the opportunity of neural networks to be refined and so be differentiated/integrated, lengthening this period would have greatly expanded human information processing capabilities. This would have enabled the acquisition of novel forms of human cognition. Such cognitions, in turn, would enable novel means of acquiring high-energy foods, and so the increased energy provisioning of prolonged neurodevelopment. Thus, this metabolic situation could produce a feedback that might self-amplify itself, creating yet further metabolic, cognitive, and even species innovations.

15. Though its generality to other nonhuman primates is unknown, the earlier noted two-fold greater strength per unit of mass of bonobo than human muscle (Scholz et al., 2006) raises the possibility of other changes to human muscle that might effect its ability to metabolically impact upon the brain.

APPENDIXES

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APPENDIX 1. Energy banking as key evolutionary innovator

The capacity to buffer energy is as much a critical adaptive factor in evolution as enhanced abilities in gaining increased amounts of energy. It has shaped not only the selection of individual species (such *H. sapiens sapiens*) but the adaptive innovations that specialize mammals compared to birds (Dall & Boyd, 2004). Mammals lactate. While this is energetically inefficient compared to direct provisioning (due to metabolic conversion), it allows juveniles to be supported on “bad luck foraging days” from maternal adipose tissue stores. Thus, a mother does not have to find food on a particular day to support her young. Due to the weight minimizing needs of flight as a specialization, birds cannot store substantial amounts of energy in this way, and so are required to directly provision their young. This allows mammals to exploit more patchy but higher energy resource environments (Dall & Boyd, 2004). Where birds exploit patch environments, it seems to require the efforts of two bonded parents to distribute foraging risk, whereas in mammals, young are raised in such patchy environments by a single unbonded (female) parent. It is notable that human food pooling also acts to buffer food resources but at the group bonded level (this benefits adults in this regard as much as dependent young and pregnant/lactating mothers), and so allows foraging humans to exploit more patchy but higher energy food sources.

APPENDIX 2. Uncertainties about actual brain wattage

The figures of Kennedy and Sokoloff (1957) are based upon the invasive sampling of blood from the superior bulb of the internal jugular vein. This fails to include all the blood draining from the brain (there is an alternative vertebral output that provides a near complete venous output when the internal jugular vein collapses when a person stands) (Doepf et al., 2004). Also the internal jugular vein receives output from nonbrain tissue such as the face and petrosal sinuses, as noted by the innovators of the blood sampling method they used (Kety & Schmidt, 1948, p. 478: "both [internal jugular veins] may be equally contaminated with blood which arises outside the brain"). This has been confirmed (Chierigato, Calzolari, Trasforini, Targa, & Latronico, 2003). These venous systems are variable (Doepf et al., 2004), and could like the arterial ones entering the brain undergo development change from childhood to adulthood (Schoning & Hartig, 1996). This early work, therefore, might have underestimated the brain's oxygen consumption, and so the energy demands of the pediatric brain.

Another problem is the low glucose metabolic rate noted by Chugani for the adult cerebral cortex brain: these range from 23.83 to 30.59 $\mu\text{mol min}^{-1} 100 \text{ g}^{-1}$ (Chugani et al., 1987). Chugani and colleagues used a PET machine with a 8.4 mm resolution. However, Wang and colleagues (Wang, Volkow, Wolf, Brodie, & Hitzemann, 1994) have shown that metabolic values for the whole brain in adults vary with the spatial resolution of the PET machine with medium range ones (8 mm) (such as used by Chugani and colleagues) reporting an average of 36.4 (range 21.6-53) $\mu\text{mol min}^{-1} 100 \text{ g}^{-1}$, that is lower than that from high resolution machines (2.6-6 mm) that report an average of 45.3 (range 34-68) $\mu\text{mol min}^{-1} 100 \text{ g}^{-1}$ (Wang et al., 1994, data from table 1.). As they note, studies reporting mean global values of less than 30 $\mu\text{mol min}^{-1} 100 \text{ g}^{-1}$ have been done with scanners having 8-17 mm resolution. Whereas studies reporting on values higher than 54 $\mu\text{mol min}^{-1} 100 \text{ g}^{-1}$ have used scanners having a 2.6-6 mm resolution (Wang et al., 1994, p. 1462). Given an average brain volume of 1380.1 cc (Filipek et al., 1994), 30 $\mu\text{mol min}^{-1} 100 \text{ g}^{-1}$ suggests a brain wattage of 19.3 W, while one of 54 $\mu\text{mol min}^{-1} 100 \text{ g}^{-1}$ suggests 34.7 W. One problem here is that higher resolution also more accurately delineates the gray and white matter compartments of the brain, and so might report a higher figure for a slightly smaller volume.

APPENDIX 3. Other synapse neurodevelopment possibilities

Several kinds of neuroanatomical changes and informational shifts could change synapse neurodevelopment by enhancing "Rapoportian" internal stimulation (Rapoport, 1999).

Changed axons connections

Humans in comparison with chimpanzees show profound changes in the connection of their brain particularly between the frontal cortex of the left hemisphere and areas in the temporal

lobe (Rilling et al., 2008). The arcuate fasciculus, for example, in humans but not chimpanzees has much stronger terminations in the middle and inferior temporal gyri that cannot be accounted for by general brain expansion (Rilling et al., 2008). The presence of these connection changes together with a much later development of connections involving the frontal and temporal parts of the human brain (Lebel et al., 2008; Zhang et al., 2007), might significantly change the ability of the prefrontal cortex to acquire cognitions, such as language, that could internally stimulate the brain. Moreover, the prefrontal cortex given its links and control over other brain areas (Blenner & Yingling, 1993; Knight, Scabini, & Woods, 1989; Zappoli et al., 1995), would be in a better position use such simulation to change the integration/ differentiation that happens across the rest of the brain.

Cerebello-cerebral reorganization

There is preliminary evidence that the volume of the cerebellum in modern humans (but not archaic *H. sapiens* such as Neanderthals) has expanded in the context of a matching volume reduction of the cerebral hemispheres (Weaver, 2005). The above discussion has focused upon the cerebral cortex but its functioning is closely linked with the cerebellum. The cerebellum is traditionally associated with motor control but recent research links the cerebellum also to internal modeling both of motor and nonmotor processes (Ito, 2006, 2008; Wolpert, Doya, & Kawato, 2003). Such internal models enable the monitoring of errors by comparing intended and achieved performance. They also allow for monitoring of expected and actual external and internal events. Internal models and this monitoring process thus could be expected to enhance internal brain simulation by enabling focused and sophisticated attentions and reflections upon events and happenings both in the world and those concerning the body and the individual's social presence (Ito, 2006, 2008; Wolpert et al., 2003). Remarkably, the age at which infants acquire bipedality correlates inversely with enhanced executive skills at the age of 33-35, and that half of the activated voxels in the cerebellum linked to such adult executive skills also link to those that retrospectively are associated with early bipedality (Ridler et al., 2006). This argues for a complex prefrontal cerebro-cerebellar processing in performance monitoring, attention and reflection that covers both motor and nonmotor neurodevelopment. This link between expanded cerebellum and internal simulation raises intriguing implications for *Homo* evolution (reviewed elsewhere, Skoyles, submitted). Such internal modeling like language would provide novel opportunities for internally simulating synapses, and so maintaining their exuberant numbers.

Late developing neuron types

Internal simulation might be enhanced by a change in the predominance of certain neuron types. For example, Von Economo neurons (also called spindle cells) found in the anterior cingulate cortex and fronto-insula seem unique to hominoids and certain Cetacea but are most common in humans. These neurons are later developing than other neurons increasing until 4 years-of-age (Allman, Watson, Tetreault, & Hakeem, 2005). Though few in numbers

compared to other neuron types, they have been suggested to have a crucial role in connecting cortical areas to each other (Allman et al., 2005). This would put such late developing and human predominate neurons in a position to shape the simulation and refinement of synapses, and so neural network development.

Late developing dendritic arbor changes

It has been found that the dendritic arbor of layer IIIC pyramidal human prefrontal neurons after an initial arbor formation in the first year has a second growth that starts at the end of the second year and continues into the third (Petanjek et al., 2008). Layer IIIC pyramidal neurons are important in connecting other cerebral areas to the prefrontal cortex through long ipsi- and contralateral cortico-cortical projections. Thus, the late development of this additional dendritic arbor could potentially have a widespread stimulating effects upon the internal functioning of the rest of the brain producing new forms of refinement upon the integration and differentiation of neural functions. Like with Von Economo neurons, such late developing dendritic arbor changes of neurons are *terra incognita* in regard to their influence upon neurodevelopment¹⁶.

The general problem here is illustrated by the fact there could be 100 neuron types per layer of the cerebral cortex (Stevens, 1998) about which virtually nothing at present is known in regard to their development, impact, or how specific or predominant they are to the brain of humans and the Hominidae (that is the great apes as well as humans, extinct and extant). Nothing, for example, is known about the arbor stages in the development of Von Economo neurons. There may be diverse trajectories of arbor development in these, and other neuron types, that, though involving only small numbers of neurons, have a profound effect across the brain through their knock-on effects upon its connectivity, and through this, novel forms of internal stimulation, and so changed synaptic neurodevelopment.

Dendritic arbor geometry

Another possibility is that of changes in dendritic arbor geometry. Synapse filling fraction has recently been proposed as critical to the structural plasticity of neurons (Stepanyants, Hof, & Chklovskii, 2002). Synapse filling fraction concerns the fraction of available sites upon dendrites for synapses that could be occupied compared to the actual number occupied. While above it was suggested that gray matter increases and decreases in volume in regard to glial cells and capillary vasculature (rather than changes in dendrite arbor size), a role for arbor

16. The above noted change in arcuate fasciculus connectivity could arise from such changes in view of the profound alteration that happen in white matter connections such as the occipito-fronto fasciculus, the superior longitudinal fasciculus, and the genu of the corpus callosum in those born blind (Ptito et al., 2008). It is not implausible that internal stimulation changes caused by Von Economo neurons might produce stimulations as radical in their effects upon the brain as those of having or not visual input. For example, they have been suggested to underlie mentalization and theory of mind (Allman et al., 2005), cognitions which are not only internal but are linked in humans to considerable “mental” stimulation.

expansion and shrinkage is still possible given present uncertainties, see the various data in (Petanjek et al., 2008). On the other hand, the dendritic arbor is homeostatic in regard to various parameters including its morphology (Samsonovich & Ascoli, 2006). This creates problems. First, if the absolute number of synapses increase without concomitant increase in the arbor upon which they are located then this will reduce the fill fraction and so lower its structural plasticity (Stepanyants et al., 2002). Changing the size of the dendritic arbor might keep it constant but this will change the electrical properties that govern the spread of forward and back propagating currents, and so determine its information processing (Segev & London, 2000).

A second issue is that adding extra synapses makes the dendritic membranes more “leaky” if their activation scales up with their increased numbers (Segev & London, 2000, p. 746). Indeed, as noted above in section 4.5.5., synapses in enriched environment not only increase in numbers but show signs of such greater activation. At present, there is no data to assess whether the arbor might homeostatically expand to maintain constancy in the filling fraction. Compensation alternatively might possibly happen through change in the electrical “cable” properties of the dendrites by adjusting the density patterns of voltage dependent channels and their composition (it has 17 types that can be varied (Poirazi et al., 2003, p. 998)).

Development as an exploration in connectivity and synaptic arbor search space

The information processing capacity of neural networks and their circuits depends upon forming the particular synaptic connections with the particular synaptic activation thresholds that produce functionally efficacious mapping of neuron input into neuron output. The mere capacity of a network if appropriately connected and otherwise setup in its thresholds to do this, however, does not by its mere possibility of hypothetical existence ensure that such a capacity will actually arise as a result of neurodevelopment. It may be—and usually will be the case—that this state exists in a vast multidimensional space defined by neurodevelopmental variable parameters (such as those determining arbor structure, individual synapse locations and thresholds etc). Cognitive function acquisition thus involves a search by which such exceedingly rare states can be realized though pruning and refinement, even though these desirable states are considerably “hidden” in the vastness of the brain’s possible neurodevelopment.

Cognitive development, therefore, will depend considerably upon factors that narrow that search. Very little is understood about how the prolongation of the stage of synapse exuberance aids this process. One factor could be time—simply, a prolonged development allows for a better chance to explore through such potential information processing states. Another is that heterogeneity together with longer maturation across the brain might allow for more complex forms of clustering coefficient and path length connectiveness in its small world networks, and that this allows for such possibilities to be more effectively explored. A more complex hub organization allowed for by longer maturation could, for example, aid this

process. For some developmental research that explores these issues from a different, though not necessary incompatible perspectives, in statistical mechanics, see (Barbato & Kinouchi, 2000), and neural network modeling, see (Felch & Granger, 2008).

This neurodevelopment search may also occur in regard to the dendritic arbor and its synapses. It has been suggested that dendrite arbors store memory information in terms of a distributed system of spatio-temporally correlated branch threshold encodings (Losonczy et al., 2008). This indicates that the dendrites' physical branching is paralleled by an informational one in which arbor coupling map inputs upon outputs. The informational capacity of the arbor in these terms as noted above has been modeled as being as high as $2.7 \cdot 10^4$ bits (Poirazi & Mel, 2001). Neurodevelopment therefore might be concerned not only with a trajectory through a multidimensional space defined by possible connections between axons and synapses, but also at a neuron one in the trajectories in a multidimensional space defined by combinational possibilities of dendritic/arbor defined states.

The possibly also exists that neurodevelopment might usually achieve a satisfactory but only a limited degree of information processes efficacy, and so never hit upon the best forms of information processing of which it is in theory potentially capable. It is notable that humans in the last few thousand years seem to have acquired novel forms of cognition that did not previously exist in earlier periods. This might be because earlier humans could not exploit their neural capacities as fully as more recent ones due to innovations in educational support, and what has been called "gifted environments" (Skoyles & Sagan, 2002, chapters 15, 17 and 18).

Retained immature synapse processing in integrative areas

Humans compared to rhesus macaques and marmosets have higher numbers of synapses per μm dendrite in their prefrontal cortex (Elston et al., 2006). One theoretical possibility could be that evolution might have selected a retention in human adults of increased numbers of synapses from their earlier childhood/adolescent neurodevelopmental period. This might be advantageous if the cognitive capacities of these immature neural circuits were in certain respects superior to the mature ones. This would happen, for example, if their greater flexibility in learning was adaptive in enabling adult behavior to be more adjustable to changing circumstances. In this case, increased synapse numbers in the adult human prefrontal cortex would be an example of neurological "neoteny" (Gould, 1977).

APPENDIX 5. Higher-order associations and measures of neural integration and differentiation

A core issue in neurodevelopment is measuring the degree of effectiveness of the neural integration/differentiation that arises during neurodevelopment in regard to clustering coefficient and path length connectiveness of its small world networks and the result of this

upon behavioral and cognitive adaptiveness. One approach is to look at such integration and differentiation in terms of higher-order spaces that describe the associations formed between neural processes in different brain areas.

In this section, first, the nature of first-order and higher order associations will be explained. After this, the application of such ideas to integration and differentiation will be discussed. The notions suggested here of higher-order associations and context extraction into multi-dimensional spaces come from the ideas and modeling of latent semantic analysis (LSA), an approach to the computation and cognition of word semantics created by Landauer and Dumais, (1997), but that can be applied much more widely, see also Skoyles (in preparation).

First- and higher-order associations

An example of a first-order association is that between words “big”, “vast”, respectively with “man” in the two word strings “the large man is running”, and “the big man is running”. An example of a second-order one is that between “large”, and “big” between these two sentences. The words “big” and “man”, and “vast” and “man” have first-order associations with each other since they occur in the same informational chunk or episode. “Large” and “big”, however, do not associate themselves directly together in this way. Instead they associate through other words—second-order links—with which they occur in the same sentence contexts—in this case “man” and also “running”.

Such higher-order associations in words underlie both context and meaning in that meaning is what word synonyms (such as “large” and “big”) share, and context is what is shared in common between them. A core demonstration of LSA is that word intersubstitutability does not have to be synonym exact. Few words are precisely synonymous but may share much weaker degrees of closeness (“vast”, “gigantic”, “moderate”, “small”, “heavy”). LSA shows that such semantic distance even of relatively weak kinds can be experimentally extracted from the higher-order associations that exist between words. Moreover, that such extracted higher-order “semantic” space plays a critical role in cognitive development since it enables the first-order information associated with known words to be used to identify the location in this higher-order “semantic” space of an unknown one that occurs amongst them. LSA has established that this process is central to word learning and so vocabulary acquisition (Landauer & Dumais, 1997).

Though latent semantic analysis focuses upon words and context meaning, the same computational theory (as its authors acknowledge) can apply also to other information domains. For instance, consider the case of enabling adaptive actions in which episodes are defined in regard to the constituents needed to successfully solve problems. In this, a chunk of associations consists of a set of means, events, and target states. A common adaptive action problem is to create another functionally similar set with a different member to replace one that is missing. Suppose, for example, if you cannot use your hands to open a door (say their

bones are broken and fixed in plaster), how do you move its handle? The normal set of { need to open door, closed door, moveable handle, hands} lacks an essential key member. An adaptive brain can take this incomplete set and create another with a substitute set member such as “knees”, “chin”, “elbow”, “friend”, or “knock”. This kind of problem is solved constantly from how to construct informative statements, understand the intent and plans of others, and organize daily interaction with unexpected events and challenges. As such, it underlies the behavioral adaptability that is expected of functionally “normal” adults. The ability to extract and use higher-order associations would thus seem crucial to understanding the adaptive nature of adult human cognition.

Higher-order associations and the integration/ differentiation of the brain

Higher-order association can also be used to describe relationships, and potential relationships that might exist between different processes carried out by the brain. These arise because in their small worlds of interactions they have patterns of connectivity, and so associations. Such associations of connectivity might be first-order, if they are activated together, but they also might exist as well at higher-order levels. For example, it may be that process A working with processes C and D (first-order associations) enables a function. But also that process F can also work with processes C and D enables also that same function, or one very similar (process F has second-order association with process A).

Like with the contextuality that underlies slight differences in word meaning, such connectivity might allow for second-order association substitutability. There are several examples in the brain where processes might be slightly different but also related in function in their activation such as (i) homologous left and right cortical areas following temporary brain inhibition or injury, (ii) prefrontal and cerebellar areas and posterior cortical and basal ganglia ones during and after learning, (iii) hippocampal and cortical ones during and following consolidation of memories, (iv) superior colliculus and the medial lateral intraparietal cortex, (v) the different cortical that get recruited during aging that preserve cognitive performance. Much of the flexible adaptivity of neural function will be in the appropriate recruitment of different brain areas where they offer subtly different contributions in their substitutability. For example, the homologous left and right areas specialize in slightly different aspects of processing, and so are broadly similar—the brain must in some manner ensure that they are appropriately recruited. Likewise, the prefrontal cortex can do many tasks in an attention demanding manner that can be done automatically either posteriorly or subcortically. A skilled brain will shift between them when it is most appropriate.

Different patterns of integration/differentiation activation will, in effect, therefore contain different amounts of higher-order association information. For example, the processes A, B, C, and D activated together might produce a particular cognitive function, but that in a particular circumstance, the activation of B, C, D, and F, would be more adaptive. A more

adaptive neurodevelopment would be one that would turn on the latter activation pattern as it contains more higher-order association information in its flexibility. Thus, integrative/differentiation neurodevelopment can be interpreted as happening within a high-dimensional space that characterizes its recruitment effectiveness.

It might be suggested that acquiring the integration/differentiation that embodies in this way increased amounts of higher-order association information might depend upon how long neurodevelopment is protracted.

APPENDIX 5. Innovations in synapse neurodevelopment and child development

Human child development complimentary to the prolonged existence of human synapse neurodevelopment and cortical area integration and differentiation (Bassett et al., 2006; Fair et al., 2008; Fair et al., 2007; Honey et al., 2007; Tononi et al., 1994) is develops through stages (allowed for by extended development) that build hierarchically upon earlier ones by differentiation and integration (Inhelder & Piaget, 1958; Piaget, 1952, 1971; Piaget & Inhelder, 1967). Piaget identified and found empirical support for the existence of four broad stages in child development that link with these changes.

- A sensorimotor period that occurs before two years-of-age. This consists of substages concerned with reflexes, habits, coordination, object permanence and the discovery of the use of goals. This cognitive development corresponds to the period before brain development reaches adult levels of synapse and metabolism.
- A preoperative stage that occurs roughly between 2 and 6 years-of-age. In this, a child gains the ability to use words and images about what is not immediately present to control the use of objects. There is also a poor sense of time. This stage corresponds to the early period in which the numbers of synapses and corresponding metabolism of the brain first rises and peaks in its sensory and motor cortices.
- A concrete operational stage that occurs roughly between 6 to 11 years-of-age. In this period, a child starts to think logically about concrete events, however, without grasping abstract or hypothetical concepts. This period corresponds to the shift of synapse exuberance and raised metabolism to the prefrontal and higher-integrative areas.
- A formal operational stage that occurs after ≈ 12 years-of-age. In this period of cognitive development arise the ability to think abstractly. It is the period in which synapse and metabolism starts to decline but in which continuing refinement is still continues to develop in white matter connections.

The existence of some of these stages has directly been linked to brain development. For instance, concrete operational stage skills such as “conservation” of fluid volumes across different sized containers associate with shifts towards greater prefrontal involvement in cognition (Zhang et al., 2008).

Neural networks, it has also been suggested to develop through stages by which earlier ones enable the development of later ones. For example, the networks underlying nonphonological reading abilities in children depend upon networks processing earlier acquired phonological word identification skills (Skoyles, 1988). Another example is that the acquisition of spoken vocabulary depends upon earlier developed abilities to vocally mirror overheard words so that they can be imitatively pronounced and so incorporated into spoken usage (Skoyles, 1998). A central facet of development would appear to be the “bootstrapping” of one developmental capacity upon that of another (Skoyles & Sagan, 2002, chapter 17). Indeed, it is widely accepted in child development that children show highly complex and progressive changes in their cognitive capacities, and that this is linked to on going changes in their neural networks (Mareschal et al., 2007). The artificial stimulation of network learning that underlies such cognition acquisition also identifies the ability of networks to reconfigure themselves dynamically and acquire additional processes as essential to their development, and as such, a possible factor that has caused human childhood to be so prolonged (Elman, 1993).

It has also been suggested that the human capacity for symbols and so symbolic culture relates to the changing of the inputs and outputs of neural processes that underlie novel nonevolved representations (Skoyles & Sagan, 2002). For example, the emotions that underlie attachment bonds have become linked to artifacts (such as wedding rings) that act as public and permanent stand-ins cues for what would otherwise have been transient and private emotional reinforcers (such as physical touch/intimacy). Similarly, iconic images (numeral symbolization) linked to number concepts allows for the complex processes of the right posterior parietal cortex (such as those that underlie the parietal number line) to be available to manipulate mathematical representations (Skoyles & Sagan, 2002, see particularly chapter 14). Such processes presume that development occurs in stages in which earlier forming ones can be in later stages symbolized by culturally shaped and dependent processes such as master/apprentice instruction, initiation rituals, and classroom education.

APPENDIX 6. Metabolic changes at puberty

The period of puberty growth coincides with the period in which the energy demands of the brain start to decline to adult levels and so reduce its vulnerability to metabolic disruptions by large bodies and high muscle mass (see figure 7, on page 43). That puberty and the adolescent growth spurt link to increased availability of energy is suggested by the fact that its on-start is closely associated with energy balance changes that decrease the ratio of BMR to lean body mass (a proxy for skeletal muscle mass) (Brown, Kelnar, & Wu, 1996). The BMR of children

is also unlike that of adults in that it is not effected by the adipose tissue secretion of adiponectin (Hosking et al., 2007). Their levels decrease at puberty though this apparently does not increase adiposity ((Hannon et al., 2006), the authors suggest that this lack of effect may be due to a small sample size). This secretion is inversely related to adiposity in adults but not in prepuberty children (Hosking et al., 2007). This suggests that a different relationship exists potentially between BMR and adipose tissue as regulated by adiponectin in children and adults.

Further, teenagers at 14 years-of-age with constitutional delay of growth (1.45 m and 34.8 kg, vs. 1.65 m 54.2 kg in age-matched controls) that show a delayed onset of puberty (92 ng dl⁻¹ vs 542 ng dl⁻¹ testosterone in controls) also have an abnormal energy balance (Han, Balagopal, Sweeten, Darmaun, & Mauras, 2006). They have a nearly double ratio of nonBMR energy expenditure to their BMR (2.52 vs 1.27): this energy output does not link to more exercise (they did not show a statistically significant increase in time spent in this) suggesting that it links to other unknown energy consuming factors—proposed possibilities include increased fidgeting, muscle tone, posture maintenance/ other low level physical activities, and increased thermogenesis in skeletal muscle or adipose tissue. The result is slow growth that results in an adult height in the lower part of their mid-parental height zone/short stature, and delayed puberty onset (Han et al., 2006). This parallels a similar delayed puberty with reduced stature that occurs following high energy expenditure in chronic illness such as cystic fibrosis (Byard, 1994), and low energy intake when individuals are undernourished (Satyanarayana et al., 1989).

APPENDIX 7. Variation in plasma glucose levels

Generally, normal levels of plasma glucose are between 4 and 6 mmol L⁻¹. However there is considerable variation over the day¹⁷. One study of 30 healthy volunteers (25-55 years-of-age) at Surrey University (Marks, 1987b) that were followed throughout a normal day found that while they had an average plasma glucose of 4.2 mmol L⁻¹, it had a peak at 14.00 after lunch (4.9 mmol L⁻¹) and was lowest in the afternoon at 17.00 (3.9 mmol L⁻¹). Significantly, 5% of plasma glucose measurements were below 3.0 mmol L⁻¹ (occurring in 10 of the volunteers) and 2.8% of them were below 2.8 mmol L⁻¹ (5 of the volunteers). At such times, they did not report any lack of well-being.

Plasma glucose variation occurs particularly after meals. For example, before a glucose drink a person's plasma level may be 4.9 mmol L⁻¹, but 45 minutes later this may be 8.7 mmol L⁻¹,

17. It should be borne in mind that the brain is not metabolically static. Not only are there activations related to information processing, but fluctuations due to cardiac output and pulmonary respiration. There are other even lower frequency <0.35 Hz spontaneous fluctuations that show a 1/f power spectrum in blood flow, blood volume, cytochrome aa₃, reaction time performance and neurotransmitter release whose origins are unknown (Fox & Raichle, 2007; Fox, Snyder, Vincent, & Raichle, 2007; Vern et al., 1997). One *terra incognita* of neuroscience concern fluctuations of plasma glucose levels, both whether they exist on similar timescales (they have not been looked for), and if so, whether they effect cognition (again unexamined).

from this it declines so that nearly four hours later it sinks to a nadir of near 3.5 mmol L^{-1} (Tse et al., 1983). This pattern reports data from nonobese young (average age 24 years) men and women. Where more mixed but general population type groups are studied, a percentage that varies from 23% and 48% of people have a plasma glucose drop that is “asymptotically” hypoglycemic 2.8 mmol L^{-1} (Cahill & Soeldner, 1974; Hofeldt, Adler, & Herman, 1975).

A glucose drink is an atypical food. However, similar but less dramatic findings have been for a high glycemic index (GI) “high-sucrose diet” meal but not a low GI “high-starch-diet” meal (Daly et al., 1998)¹⁸. For example, the “high-starch-diet” produced 1 to 2 mmol L^{-1} increases following meals, and similar declines afterwards, while the “high-sucrose diet” produces 2 to 3 mmol L^{-1} increases followed by slightly larger dips— 2.2 to 3.2 mmol L^{-1} (Daly et al., 1998, fig. 4).

APPENDIX 8. Candidate theories for slow growth during childhood in modern humans

The growth pattern of human juveniles is counterintuitive since one might expect in humans the pattern of sustained fast growth that happens in the young of other hominoids (Bogin, 1999a; Hamada & Udono, 2002; Pusey et al., 2005; Walker, Hill et al., 2006). If these have an adolescent growth spurt, it is minor and linked to a catch up growth following earlier poor nutritional stunting (Hamada & Udono, 2002). A larger juvenile body should be advantageous as it reduces the risk of predation, as it also does the risk of mortality and morbidity (for example, human infants are larger in societies where they face the highest rates of infectious diseases and parasites (Thomas et al., 2004))¹⁹. There is amongst human small scale hunter-gatherer populations a slight effect that also acts in this direction: where infant survival is low, there is a faster juvenile growth at least in females: a 10% decrease in survivorship is associated with an additional growth of 0.172 kg per year (in the context of a range of 1.1 —

18. High GI diets are an evolutionarily novel challenge to human glucoregulation since this has been adapted by 80 million years of primate evolution to low GI foods, while high GI foods are products of the agricultural revolution 10,000 BP, and mostly that of historically very recent innovations in industrial food processing. The postprandial hypoglycemia noted in the text is limited to meals of high GI foods. Harris (1924) raised the possibility of a hypoglycemia paralleling the hyperglycemia of diabetes. By the 1970s, “hypoglycemia” had become a common complaint. However, few individuals that experienced “hypoglycemic” episodes, in fact had during them low plasma glucose (Yager & Young, 1974). On the other hand, there is more recent evidence that such a syndrome does in fact exist (Brun, Fedou, Bouix, Raynaud, & Orsetti, 1995).

Postprandial periods of low plasma glucose are mostly due to a neural inhibition of the hepatic production of glucose that is concomitant with food entering the upper intestine. It does not appear to link to an “overshoot” of low insulin levels (Tse et al., 1983), as had been suggested by (Harris, 1924). It has, for example, been recently found that the quick emptying of the stomach into the upper intestine triggers a circuit from receptors there to the brainstem that stop hepatic glucose production (P. Y. Wang et al., 2008). Such an inhibition makes sense given blood following such entry will be saturated with energy (glucose, free fatty acids) absorbed from digested food. Normally, slow stomach emptying and food stuffs that are not immediately absorbed but requiring prolonged enzymatic digestion would ensure a gradual period of glucose/fatty acid release as the food lumen travels down the intestine. Much of this will happen long after a meal in the colon where commensal microbes create fatty acids, and this would have been the dominant pattern in primates before *Homo* given their larger guts and largely vegetarian diets.

19. Newborns are 50 gram heavier for those facing 12 rather than 9 infections. Note, having multiple infections reduces birth weight—the observation is that beyond having 9 of them, weight was found to increase.

2.9 kg weight gain (unadjusted for final body weight), and probability of survival to the age of 15 of 0.33 to 0.80) (Walker, Gurven et al., 2006). It should be noted the effect is smaller than the effect of final body size, and did not reach significance for males (Walker, Gurven et al., 2006, table 4).

The existence of a growth spurt in adolescence that is a consequence of early slow growth is also nonadaptive since it results in most adult bone mass being acquired in only a few years (Parfitt, 1994) (40% between 12 and 16 years-of-age in boys, and 40% between 10 and 14 years-of-age in girls (Zanchetta, Plotkin, & Alvarez Filgueira, 1995)). As a consequence, skeletal bone modeling occurs so fast that calcium depositing lags behind bone growth causing a temporary state of osteoporosis (Parfitt, 1994), and a resultant peak in adolescent fractures (Bailey, J.H., McCulloch, Martin, & Bernhardson, 1989). Thus, the adolescent growth spurt creates an injury risk that would not exist except for a postponed shift of growth from childhood into adolescence.

Several possible factors could explain why in spite of these disadvantages, children have a slow growth rate. Bogin (1997) provides a review.

Direct effect of the brain upon body growth

The higher metabolic rate of the brain in itself might advantage physical delayed maturation (Foley & Lee, 1991). Rats raised in enriched environments show signs of increased brain metabolism (Sirevaag & Greenough, 1987), and also reduced body size (Bennett et al., 1964), or at least initially reduced body size (Black, Sirevaag, Wallace, Savin, & Greenough, 1989). Also, William Leonard and Marcia Robertson (1992) have argued that the far greater energy demands of the pediatric brain would have advantaged the reduction of nonessential growth as a means of limiting competition to its energy need.

In this case, it would be a pediatric version of what has been called in human adults, “the expensive tissue hypothesis”. This theory argues that adult human gut size has been reduced to allocate energy to the high energy demands of the adult brain (Aiello & Wheeler, 1995).

The percentage figures for skeletal muscle in adults in the table given above further suggest the possibility that a reduction in this body component might have occurred also for this reason in humans. Though the metabolic cost of exercise has been discussed above, even resting skeletal muscle is a major energy consumer. This is because though the resting energy use per unit mass of skeletal muscle is low (0.63 W kg^{-1}) (Elia, 1992), it makes up a high percentage of body BMR due to its high contribution to total body mass (Zurlo, Larson, Bogardus, & Ravussin, 1990). The resting skeletal muscle is responsible, as noted in the figures above, for 13% of a child’s BMR—7.7 W of 59.2 W. It should be noted that only $\approx 20\%$ of its energy consumption is accounted for glucose (Andres et al., 1956) suggesting an adaptation to spare glucose for the brain. This could suggest an advantage (parallel to that for

the gut) for its general reduction. However, limiting comment upon this is that the body composition of human foragers in regard to skeletal muscle and maturation is unknown, and this might differ considerably from that in the populations that provide the present estimates for its percentage in modern humans.

Advantages of needing less food

It might be that smaller size and reduced need for food is adaptive when pooled food is reduced in quantity and quality due to temporary adverse circumstances (draughts, flooding, widespread illness). Small size has been suggested for this to have been selected in food limited circumstances such for small size on islands (Palkovacs, 2003) and for human pygmy populations (Shea & Bailey, 1996), though in the latter case this has recently been questioned (Migliano, Vinicius, & Lahr, 2007; Walker, Gurven et al., 2006).

Small size aids receiving food

Another factor might be that children are more likely to receive food if they are not perceived as potential competitors to adults or retain the infantile look (Bogin 1997). Reduced size would also help this, both because this, together with reduced strength, means that *de facto* they are not able to physically challenge adults, and that smallness marks them out visually as categorically different.

Slow growth spares food for parents to have more dependents

It has been suggested that small body size might enable parents to support more dependent offspring, also called “stacking” (Bogin 1997; Gurven & Walker, 2006; Robson et al., 2006). Gurven and Walker (2006) provide calculations to show that a human—rather than a chimpanzee-like-growth rate—would spare substantial energy for parents to allocate to other children. However, these calculations seem in need of further analysis before definite conclusions can be made. Notably, they do not appear to adjust for the complexity of the quicker maturation of chimpanzee-like growth of human children when modeled with the equations that describe actual chimpanzee growth (though they adjust for differences in weight between humans and chimpanzee, see the electronic appendix to that paper). Using the equations (Walker, Hill et al., 2006, table 1) for male chimpanzee and male Ache (which reach similar adults weights, 57.33 kg and 59.47 kg), male chimpanzees stop growth (in terms of not adding more than 10 g each month) at the age of 13.4 years while the Ache do so at 21.4 years. The chimpanzee data concern those in captivity, and wild ones might be one or more years later in development (Zihlman et al., 2004). Even so there is a profound difference in the duration of development that must be incorporated into any model of “chimp-like” human growth. If this is not done, the growth savings of such growth will include not only the effects of slower early growth but also differences in maturational age see fig. 9 below.

Calculating the contribution of these different factors to energy consumption (fig. 10) is complex

There is also an apparent anomaly in (Gurven & Walker, 2006) in that the graphs in (Gurven & Walker, 2006, fig. 2) show that humans with a hypothetical chimpanzee-like-growth would consume more energy before adolescence than during adolescence—predictive equations both for TEE (Torun, 2005) and BMR (Henry, 2005) show that there is always an ascending increase in energy needs with greater age until adulthood.

Further, humans during the Middle Paleolithic did not live in populations that were expanding (as they were do later in the Upper Paleolithic), and so would be under constant reproduction replacement rates. Unless there was usually high adult mortality, parents would be only raising the few number of children that would allow for their own replacement. This would not involve them having several dependents at any one time (as in contemporary humans), and so needing the energy sparing advantage of slow growing children. The fact that modern hunter-gather humans support multiple on-going dependents could relate to technology that derives from the later Upper Paleolithic and modern period (such as the bow and arrow and iron tools) that allows a far large acquisition of energy with which to support dependents. Energy availability is known from agrarian societies to increase the number of concurrent dependent children.

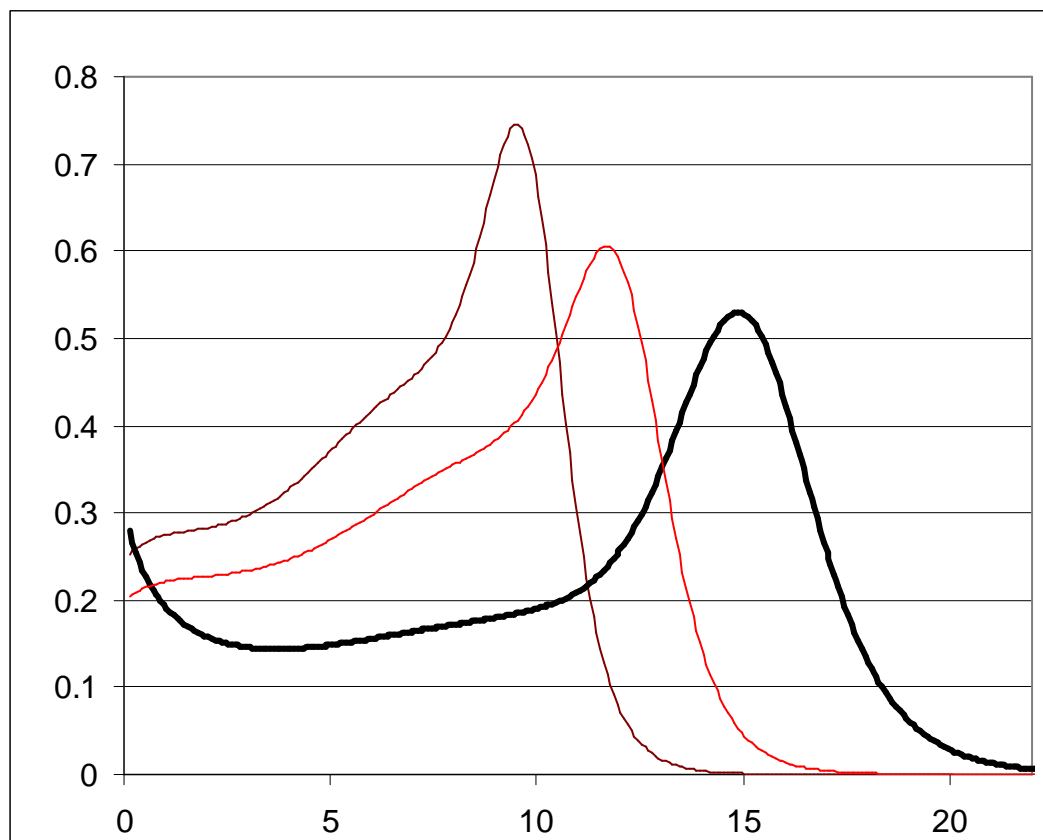


Fig 9. This like fig. 8 shows the change in the male chimpanzee growth velocity (brown thin) compared with the male Ache human line (black thick), and human with chimp-like adjustment (middle red thin). The chimpanzee growth line differs from that in fig. 8 in that the final body weight has been made exactly equal to the Ache human (59.47 kg). Gurven and Walker (2006) seems to model human growth as if it has a chimpanzee pattern of growth—that is equivalent to the chimpanzee growth line shown here. However, chimpanzee development not only has a different growth pattern to humans but also matures much earlier. This can be seen in the cessation of chimpanzee growth around 13 years-of-age. The thin red line has taken the predictive equations used to model chimpanzee growth and corrected for the shorter maturation so growth occurs over an additional four years. The energy associated consumption differences can be seen in fig. 10.

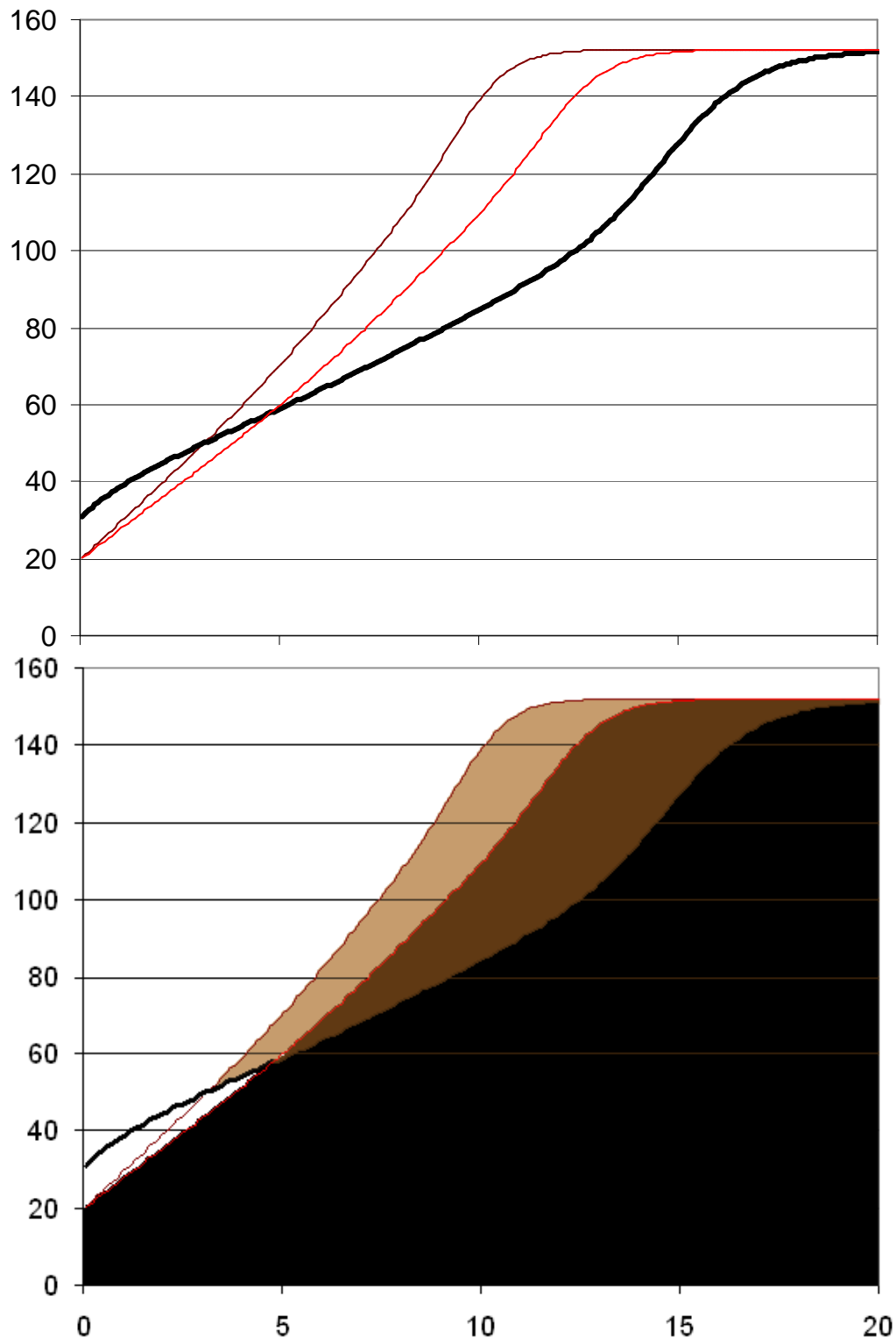


Fig 10. The top graph shows the change in the total energy expenditure in watts needed for the above growth trajectories using the predictive equations in (Torun, 2005). The filled graph lines shows the difference in energy between a chimpanzee-like growth that adjusts, and does not adjust, for the difference in the duration of growth. Gurven and Walker (2006) predict the human pattern of slow childhood growth would save the energy represented in the light and dark brown areas, and thus make it available for other dependents. While growth adjusted for the greater duration of human growth still indicates an energy saving—the dark brown area—this is much less. Given that a slower growth risks higher mortality due to small body size, it would appear that the human pattern of growth is unlikely to be adaptive by allowing parents to have more on-going dependents.

APPENDIX 9. Nonglucose fuels and the brain

Glucose has been treated traditionally as the obligate energy source of the brain under normal circumstances (Siesjö, 1978). But research shows that the energy needs of the brain can be met by four types of plasma carried energy moiety: ketone bodies (produced by the liver from triglycerides i.e. “fats”), lactate (the product of glycolysis), nonesterified fatty acids/glycerol, as well as glucose. The blood-brain boundary is relatively impenetrable to a fifth major body energy moiety, esterified free fatty acids (triglycerides), the predominant energy source, for example, of the heart (van der Vusse et al., 1992), and muscles at rest (Andres et al., 1956). The brain also has a small quantity of glycogen that can be drawn upon, and this seems, contrary to early views, to be functionally important for coping with very short bursts of energy shortage—hemodynamic response to neural activation is delayed by a few seconds and this could advantage a very quick release energy buffer such as provided by glycogen (Brown & Ransom, 2007; Raichle & Mintun, 2006; Swanson, Morton, Sagar, & Sharp, 1992). However, once glycogen has been used it needs to be regenerated using plasma energy moieties. Each plasma energy moiety has its particular situational dependent advantages for the brain.

Ketone bodies. Ketone bodies (β -hydroxybutyrate and acetoacetate) are the major energy supply to the brain during lactation being created from blood brain boundary impenetrable free fatty acids (Nehlig, 2004). During famine, the brain can subsist with 60% of its energy needs being supplied by their hepatic conversion via lipid mobilization from adipose tissue (Bougnères, Lemmel, Ferre, & Bier, 1986). It has recently been suggested that when the equivalent of two alcoholic drinks (0.5 g kg^{-1}) of alcohol depresses glucose measured brain metabolism by 23%, acetoacetate makes up the deficit (Volkow et al., 2006)²⁰. However, ketone bodies have pharmacokinetic properties that are distinct from those of glucose. This is most evident in the ketogenic diet treatment of epilepsy for which these differences provide its neurological effectiveness. The specific effects of the ketogenic diet and a high use of ketone bodies by the brain are not well understood but seem to link to alterations in the metabolism of the major excitatory neurotransmitter, glutamic acid (Yudkoff, Daikhin, Nissim, & Lazarow, 2001). Such alternations could have a potentially disruptive role in neurodevelopment since key glutamate receptors, such as AMPA and NMDA are closely involved with the regulation of the stability of synapses (Adesnik et al., 2008; De Paola, Arber, & Caroni, 2003).

There is evidence from hippocampal slices that ketone bodies cannot maintain neural activity comparably to that of glucose (Arakawa, Goto, & Okada, 1991). Consistent with this, weaning rats fed a ketogenic diet grew up to have impaired visual-spatial learning and memory defects and reduced brain size (Zhao, Stafstrom, Fu, Hu, & Holmes, 2004). In one

20. Interestingly, alcohol also induces hypoglycemia (Marks, 1987a) suggesting a shift in the carried energy composition of plasma.

study, the production of ketone bodies that are produced in hypoglycemia were inhibited by the drug acipimox: the absence, however, of hypoglycemia induced ketone bodies due to acipimox did not increase the cognitive and effects of hypoglycemia (Fanelli et al., 1993). This suggest that ketone bodies do not compensate the brain for the plasma glucose deficit in hypoglycemia (Fanelli et al., 1993). It has been suggested that ketone bodies “spare glucose for the emergence of various functions such as audition and vision as well as more integrated and adapted behaviors whose appearance during brain maturation seems to critically related upon active glucose supply and specific regional increased use” (Nehlig, 2004, p. 265). Thus, ketone bodies and glucose are not equivalent in their effects upon the brain, particularly during its development, and this might, if high in percentage contribution, make it a suboptimal replacement.

Lactate. Lactate has been suggested to play a local role in neuron-glia cell metabolism in which glucose is initially converted into lactate by glial cells and then shuttled for use by neurons (Pellerin & Magistretti, 1994). This is consistent with the above (section, 4.6.) noted expansion of glial cells and their context with neurons when synapse activation is increased by enriched environments. However, this glial cell-neuron theory has recently been questioned on the basis that the uptake kinetics of transporters would adequately support directly the glucose used by neurons (Simpson, Carruthers, & Vannucci, 2007). The direct use of lactate replacing 17% of glucose needs from plasma has been advocated (Smith et al., 2003). Consistent with this, research suggests it can replace 25% of glucose during hypoglycemia (Lubow et al., 2006). The lactate produced in intense exercise has also been estimated to provide 33% of the brain’s energy needs (Dalsgaard, 2006; Kemppainen et al., 2005), also see (Secher et al., 2008). In vitro research on hippocampal slices suggests the ability to use lactate might, however, take 20-30 minutes to replace that of glucose (Saitoh, Okada, & Nabetani, 1994), and might not be entirely comparable in the ability to support neural activity (Wada, Okada, Uzuo, & Nakamura, 1998). Thus, while lactate probably can substitute some glucose for the brain, this is limited, at most, to a third of its needs.

It might be argued in view of the finding that the adult brain can replace 33% of the brain’s energy needs with lactate during exercise (Dalsgaard, 2006; Kemppainen et al., 2005) that this also happens in children. However, lactate is produced from glycolytic (i.e. a glucose substrate metabolism), and children show less of this during exercise than adults (Boisseau & Delamarche, 2000) shifting to fatty acids instead. Consistent with this, children also show evidence of actually producing less lactate than adults during exercise (Delamarche et al., 1994; Delamarche et al., 1992; Timmons et al., 2003). Parallel to this, less lactate is present in their blood following recovery from exercise than in adults (Hebestreit et al., 1996), and this correlates with a greater ability in children to recover from high-intensity exercise than adults (Hebestreit, Mimura, & Bar-Or, 1993) (though total energy expenditure is lower even when adjusted for lower body mass/ fat free body mass (Delamarche et al., 1994)). It should be acknowledged that this could be partly due to child’s brain more effectively removing lactate (due to its greater energy consumption) than in adults. However, even if this is the case (and

the processes involved are complex), it would still only provide an incomplete buffering against the glucose depleting effects of intense exercise.

Further, concomitant with strenuous exercise there is a knock-on effect limiting oxygen supply to the brain (Dempsey et al., 1984; Subudhi et al., 2008). But the metabolism of lactate requires oxygen (unlike glucose that can generate ATP energy nonoxidatively in glycolysis). This suggests it will be an unsuitable brain fuel during such strenuous exercise (Nybo & Rasmussen, 2007, for argument details, p. 116).

Nonesterified fatty acids/glycerol. These can enter the brain and reduce neurohormonal reactions (autonomic symptoms such as faintness) to hypoglycemia but do not prevent impairment to cognition (Evans et al., 1998). They also play a role in providing the lipid needs of the brain (which need only be transported into the brain at a very low rate compared to that needed if used for energy) for its cellular formation and maintenance (Bourre, 2006).

In addition to the other comments in this review, it should be noted that blood glucose can be used by all tissues but only erythrocytes, lymphocytes and the inner medulla of the kidney seem to have an obligate requirement. Further, glucose tissues divide into those whose uptake is insulin sensitive (skeletal muscle, adipose tissue), and those that are not (the brain and blood cells). Nearly all basal glucose uptake (between two-thirds and 80%) occurs in noninsulin sensitive tissues with 10% into skeletal muscle and 10% into nonskeletal muscle tissue (adipose tissue, heart, gut) (Baron, Brechtel, Wallace, & Edelman, 1988). An important glucose generating tissue is the kidney renal cortex, but its glucose is normally consumed by the kidney renal inner medulla, an organ that in parts has a near obligate need for glucose (Gerich, Meyer, Woerle, & Stumvoll, 2001). The renal cortex production of glucose, however, could be an important factor in glucose regulation during fast, diabetes and following liver impairment (Gerich et al., 2001).

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