The Effect of Early Human Diet on Caudate Volumes and IQ

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ABSTRACT: Early nutrition in animals affects both behavior and
brain structure. In humans, randomized trials show that early nutri-
tion affects later cognition, notably in males. We hypothesized that
early nutrition also influences brain structure, measurable using
magnetic resonance imaging. Prior research suggested that the cau-
date nucleus may be especially vulnerable to early environment and
that its size relates to IQ. To test the hypothesis that the caudate
nucleus could be a neural substrate for cognitive effects of early
nutrition, we compared two groups of adolescents, assigned a Stan-
dard- or High-nutrient diet in the postnatal weeks after preterm birth.
Groups had similar birth status and neonatal course. Scans and IQ
data were obtained from 76 adolescents and volumes of several
subcortical structures were calculated. The High-nutrient group had
significantly larger caudate volumes and higher Verbal IQ (VIQ).
Caudate volumes correlated significantly with VIQ in the Standard-
nutrient group only. Caudate volume was influenced by early nutri-
tion and related selectively to VIQ in males, but not in females. Our
findings may partly explain the effects of early diet on cognition and
the predominant effects in males. They are among the first to show
that human brain structure can be influenced by early nutrition.
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Numerous studies in animals demonstrate that suboptimal
nutrition in early life, particularly during rapid brain
growth, can permanently affect behavior (1,2). Many studies
linking early undernutrition in children to long-term reduction
in cognitive performance suggested that sensitivity to early
nutrition also exists in humans (3,4). Most were conducted in
the developing world where the potentially confounding as-

sociation in humans between malnutrition, poor social circum-
stances and lack of stimulation made causation difficult to
establish. Recently, however, randomized intervention trials
carried out in the developing and developed world have con-
firmed the sensitivity of the developing human brain to
nutrition, as demonstrated by long-term effects on cognition
(5–7). This sensitivity appears to be part of a more general
process of "programming," "the concept that a stimulus or
insult, when applied at a critical or sensitive period, may have
a long-term or life-time effect on the structure or function of
the organism" (8). Nutrition emerges as an important pro-
gramming trigger, affecting a range of outcomes relevant to
long-term health, in addition to long-term brain development.

In humans, the "brain growth spurt" begins around 3 mo
before term, lasting approximately 2 y (9). We have explored
the sensitivity of the human brain to nutritional intervention
during this potentially critical period, by randomly assigning
infants to different diets. The first such study was in infants
born preterm. The period between preterm birth and term
marks the beginning of the brain growth spurt. Since the
preterm infant is ex-utero during this period, we might expect
that environmental influences, including nutrition, would be
particularly relevant to their neural development.

In the original study, infants were randomly assigned to a
Standard-nutrient diet (term formula or banked donor breast
milk) *versus* a High-nutrient formula designed to meet the
increased needs of this population by fuelling more rapid
somatic and brain growth (10). Follow-up of two arms of this
cohort at 18 mo and 7.5–8 y (11) confirmed that early
nutrition had a long-term impact on cognitive performance. As
in animals, the major effect of early nutrition on cognition was
seen in males. There was also a selective effect on Verbal IQ
(VIQ) *versus* Performance IQ (PIQ). Thus, VIQ was 12 points
higher in males fed the High nutrient *versus* the Standard-
nutrient formula. Studies on the neural basis for such nutri-
tional effects need to explain both the gender effect and the
specificity of cognitive outcome.

The purpose of the present report was to use new imaging
techniques to explore a potential structural basis for the cog-

Abbreviations: ANCOVA, analysis of covariance; **PIQ,** Performance intel-
ligence quotient; **VIQ,** Verbal intelligence quotient

nitive effects of nutrition in humans. We hypothesized that the impact of nutrition on the brain might be both at a cortical and subcortical level. Our rationale for studying the latter aspect is recent evidence that the caudate nucleus may be particularly sensitive to environmental influences in the earliest part of the brain growth spurt, and may form an important part of the neural basis for cognitive performance. Thus, in a cohort of 7 y olds born preterm, Abernethy *et al*. (12) used magnetic resonance imaging (MRI) to measured volumes of the hippocampus and caudate nucleus, two structures susceptible to injury in preterm infants; the volume of the caudate nucleus, but not the hippocampus, was significantly related to IQ. They postulated that early postnatal nutritional insufficiency in preterm infants might impair the development of this structure, with important consequences for cognition, but lacked the data to test this hypothesis.

We, and others, have studied regional brain structure, and its cognitive correlates, using voxel-based morphometry and volumetrics to analyze MRI scans (13–16). Based on previous work, we formulated the generic hypothesis that the early nutritional impact on later IQ is related to selective growth restriction of specific brain structures, detectable at long-term follow-up. Our specific primary hypothesis here, rooted in the findings of Abernethy *et al*. (12), was that growth restriction of the caudate nucleus might, at least in part, provide a potential mechanism for the observed nutritional effects on IQ. Like Abernethy *et al*., we focused on the volumes of the caudate nucleus and hippocampus, but included measures of other subcortical gray matter structures to examine specificity. We planned to conduct explanatory analyses to explore gender differences, because of the earlier cognitive findings. Brain imaging was uncommon when our 7.5 to 8-y follow-ups took place, but we were able to collect scans and cognitive data at adolescence. We are not aware of any comparable experimental neuroimaging study that would permit the underlying hypothesis here to be tested.

SUBJECTS AND METHODS

Subjects. MRI scans and IQ data were obtained from 76 preterm children who were randomly assigned, in the original study, to one of two diet types. The Standard-nutrient group ($n = 38$) received either unsupplemented donated banked breast milk or a standard term formula, both suitable for healthy term infants and used widely for infants born preterm in the 1980s. The High-nutrient diet ($n = 38$) was formulated to meet the increased macronutrient and micronutrient needs of this population. The diets differed considerably in protein/energy content (Standard-nutrient: 1.45g protein, 68 kcal/dL milk; High-nutrient: 2.0 g protein, 80 kcal/dL milk). Full diet composition data and randomization details are reported elsewhere (11).

Mean age at assessment was 15 y 9 m (range, 13 y 3 m to 19 y 4 m) and 16 y 0 m (range, 13 y 6 m to 19 y 6 m) in the Standard- and High-nutrient groups, respectively; the male:female ratios were 18:20 and 20:18. All children had been judged neurologically normal based on history and examination at age 7.5–8 y. Neurologic reexamination was not carried out in the present study, but all children were attending mainstream school.

We also collected IQ data and MRI scans from 16 (8 M; 8 F) children born full-term (age range, 10–18 y). They do not represent a control group, but we present data for this small group where information about full-term subjects is relevant.

Ethics approval was obtained from: The Great Ormond Street NHS Trust/Institute of Child Health, Norwich District, South Sheffield Research, East Suffolk Local Research and Cambridge Local Research Ethics Committees. Written consent was obtained from all children and parents.
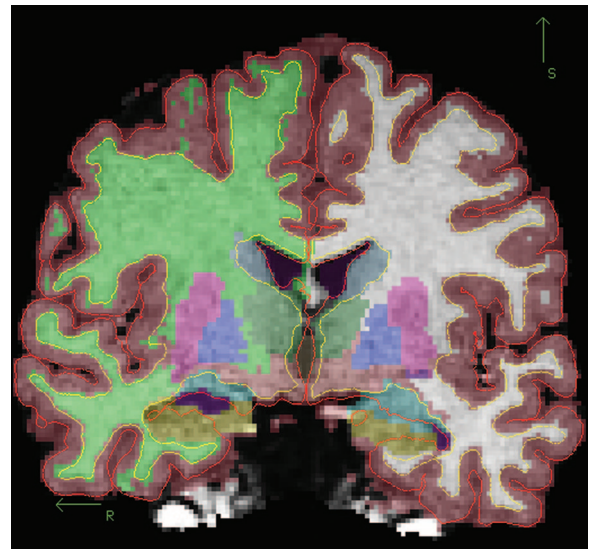

Figure 1. Typical segmentation and surface representation on one of the subjects.

IQ data. The full versions of the Wechsler Intelligence Scale for Children – Third edition (WISC-III) (17) or Wechsler Adult Intelligence Scale – Revised (WAIS-R) (18) were given (to 69 and 7 children, respectively). VIQ and PIQ scores were calculated (population mean = 100, SD = 15). All tests were administered by one individual, blind to group membership.

MRI acquisition. MRI studies were performed using a 1.5T Siemens Vision system. In addition to conventional multi-slice imaging, investigations included magnetization prepared rapid acquisition gradient echo (MPRAGE 3-D) (19) volume acquisition with repetition time 10 ms; echo time, 4 ms; inversion time, 200 ms; flip angle, 12 degrees; matrix size, 256×256; field of view, 250 mm; partition thickness, 1.25 mm; 128 sagittal partitions in the third dimension, and acquisition time, 8.3 min.

MRI analysis. We used a technique developed by Fischl *et al.* (20) to obtain volumes for total brain and a series of subcortical gray matter structures, including the caudate nuclei and hippocampus. This involves whole brain segmentation and automated labeling of the neuroanatomical structures, using T1-weighted images, and is based on probabilistic information estimated from a manually labeled training set. The data were labeled from an atlas created from 11 children, aged 9–11 y (Fig. 1).

Statistics. Group characteristics were compared using *t* tests. When diet was analyzed in relation to IQ, birth weight and gestational age were used as covariates. Age at scan was used as a covariate when analyzing scan-derived data. Total brain volumes were compared using analysis of covariance (ANCOVA), controlling for age at scan, birth weight, and gestational age. For all other neural volumes, total brain volume was used as an additional covariate. Exploratory analyses of gender effects used ANOVA. Results with significance levels of $p \leq 0.05$ (two-tailed tests) are reported; for information, results significant at a trend level, defined as $0.05 < p < 0.10$, are also reported.

RESULTS

Comparison of group characteristics. Comparisons of the two diet groups on a series of birth status and social characteristics (Table 1) showed significant differences only in birth weight ($p < 0.04$) and gestational age ($p < 0.05$) with the Standard-nutrient group lighter and slightly less mature at birth. To adjust for any possible confounding, we covaried these variables in data analyses, in addition to age at scan and total brain volume when appropriate. The groups did not differ on variables describing the neonatal course.

Conventional neurologic assessment of MRI scans obtained at adolescence is summarized in Table 2. The majority of scans were reported to be normal with comparable distributions of reported abnormalities in each group.

Table 1. *Means (standard deviations)/frequencies for perinatal and social variables in the Standard- and High-nutrient groups*

	Standard-nutrient group (n = 38)	High-nutrient group (n = 38)
Birthweight (g)*	1156 (234)	1276 (270)
Gestation (wk)*	28.4 (1.3)	28.9 (1.0)
Apgar–5 min	7.4 (2.1)	8.1 (1.8)
Days ventilation	5.8 (9.3)	3.6 (7.0)
Social class	3.2 (1.4)	3.1 (1.3)
Maternal education	2.6 (1.3)	2.8 (1.6)
Frequencies		
Infants born SGA (small-for-gestational age)	6/38	7/38
Neonatal Ultrasound findings—PVL†	0/20	0/13
Neonatal Ultrasound findings—IVH†	3/20	0/13
Numbers of neonatal infection‡	4/38	4/38
Required O_2 at 36 wk	0/38	0/38

* Difference significant at $p < 0.05$.
† Only partial data available because not in general use at time of study.
‡ Based on positive blood culture.
PVL, periventricular leukomalacia; IVH, intraventricular hemorrhage.

Table 2. *Neuroradiological assessment of MRI scans (some scans showed more than one abnormality)*

	Standard-nutrient group (n = 38)	High-nutrient group (n = 38)
Normal	23	21
Thinning of corpus callosum	9	10
Body only	1	5
Entire structure	8	5
Enlarged ventricles (mild)	2	5
Small hippocampus	1	1
Immature myelin	1	3
PVL pattern—peritrigonal	3	3

Relationship between diet and IQ. At adolescence, the High-nutrient group had significantly higher VIQ than the Standard-nutrient group with no significant difference in PIQ (Table 3).

Relationships between diet and neural volumes. Volumes for total brain, total cortical gray matter, and subcortical structures are presented in Table 4; diet was significantly related to caudate volume only (ANOVA), the High-nutrient diet resulting in significantly larger caudate nuclei bilaterally. Although there were no significant differences between the groups for other structures, in every case the mean for the High-nutrient group was higher. For the remaining analyses, we present data only for the caudate nucleus and hippocampus.

Correlations between neural volumes and IQ. Table 5 shows the correlation coefficients between neural volumes and IQ scores, with relevant variables partialled out. For the whole group, neither IQ measure was significantly related to total brain volume or to either hippocampus. Both caudate nuclei, however, showed strong relationships with VIQ but no significant relationship with PIQ. Figure 2A shows the scatterplot of VIQ scores in relation to left caudate volume (right caudate shows a similar pattern).

Table 5 also shows the results for each of the diet groups separately. VIQ, but not PIQ, correlated significantly with bilateral caudate volumes in the Standard-nutrient group. Although the correlation with VIQ was higher than that for PIQ in the High-nutrient group, neither value reached significance. Neither total brain nor hippocampal volume was related to IQ scores in either the Standard- or High-nutrient groups. Scatterplots for the two diet groups separately are shown in Fig. 2B, C.

Full-term subjects. Mean caudate volumes for the full-term group were: Left, 4001 mm^3 and Right, 4175 mm^3. Correlations between VIQ, PIQ, and caudate volumes were not significant, though sample size (n = 16) was small.

Exploratory analyses—the impact of gender. Since gender had previously proved an important factor in cognitive outcome in this cohort, we carried out exploratory analyses examining its effect.

Relationship between diet and IQ. Although diet affected VIQ selectively for the group as a whole, the VIQ difference between the two diet groups was not significant for either boys or girls, except at trend level (boys: <0.09; girls: <0.06; see Table 3). This was probably because of decreased group size since the absolute values were similar to those in the whole group analysis. Although not significant, in both cases, the High-nutrient diet was associated with higher VIQ. There was no relationship between diet and PIQ in either gender.

Relationships between diet and neural volumes. There were no differences between diet groups in total brain volume or left and right hippocampal volumes for boys or girls. In boys, early diet was associated with large differences in the volume of the caudate nuclei at adolescence; the High-nutrient group mean volume was significantly higher for both left (p < 0.002) and right (p < 0.001) caudate nuclei, co-varying total brain volume (Table 6). There were no differences in caudate volumes between diet groups in girls. To corroborate this, we carried out ANCOVA for left and right caudate nuclei, with gender and diet group as main effects. In both cases, there was a significant interaction between gender and group (left caudate: F = 3.0; p < 0.05; right caudate: F = 5.7; p < 0.02).

Table 3. *Means (standard deviations) for adolescent IQ scores in the two diet groups and for boys and girls separately. p-values and 95% confidence intervals for the group differences result from univariate analyses of variance, covarying birth weight and gestational age*

	Whole group			Boys only			Girls only		
	Standard-nutrient (n = 38)	High-nutrient (n = 38)	p-values (95% CI)	Standard-nutrient (n = 18)	High-nutrient (n = 20)	p-values (95% CI)	Standard-nutrient (n = 20)	High-nutrient (n = 18)	p-values (95% CI)
VIQ at adolescence	94 (11)	102 (14)	<0.01 (−14 to 12)	94 (12)	101 (13)	<0.09 (−16 to 1)	94 (11)	103 (17)	<0.06 (−19 to 0)
PIQ at adolescence	96 (14)	98 (16)	NS (−9 to 5)	97 (16)	95 (14)	NS (−8 to 13)	97 (12)	103 (16)	NS (−17 to 3)

Table 4. *Mean (standard deviation) volumes for total brain and sub-cortical gray matter structures by diet group.* p-*values and 95% confidence intervals for the group differences result from ANCOVA analyses, covarying birth weight, gestational age, total brain volume (except for total brain volume analysis), and age at scan. Total brain volume and total cortical gray matter are expressed in cm^3 and all others in mm^3

	Standard-nutrient group	High-nutrient group	p-values	95% confidence intervals
Total brain volume	1300 (132)	1318 (158)	NS	−14 to 54
Total cortical gray matter	660 (72)	666 (76)	NS	−40 to 27
Left caudate nucleus	648 (455)	3989 (711)	<0.05	−416 to −12
Right caudate nucleus	3855 (504)	4221 (750)	<0.04	−471 to −18
Left hippocampus	3758 (367)	3766 (357)	NS	−115 to 157
Right hippocampus	3852 (400)	3889 (392)	NS	−138 to 134
Left thalamus	7784 (968)	7890 (1089)	NS	−33 to 309
Right thalamus	7753 (1020)	7951 (1253)	NS	−433 to 243
Left putamen	4889 (589)	5147 (739)	NS	−392 to 67
Right putamen	4862 (644)	5095 (684)	NS	−374 to 634
Left pallidum	1284 (177)	1314 (223)	NS	−94 to 65
Right pallidum	1188 (228)	1206 (258)	NS	−100 to 120
Left amygdala	1532 (236)	1650 (217)	NS	−176 to 14
Right amygdala	1691 (288)	1757 (255)	NS	−151 to 82

Table 5. *Partial correlation coefficients between the adolescent IQ measures and neural volumes for the whole group and the two diet groups separately. Birth weight, gestational age and age at scan are partialled out for total brain volume; total brain volume is added as a covariate to the other analyses*

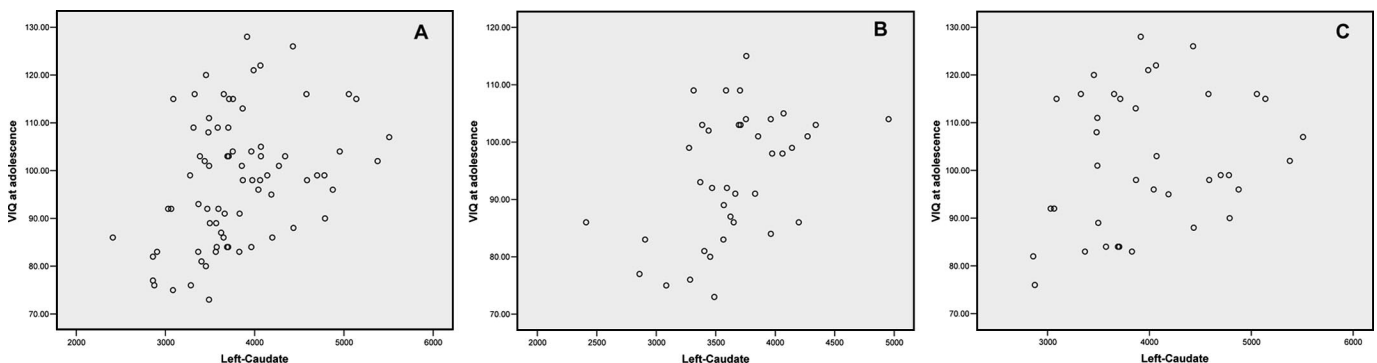|	Total brain volume	Left hippocampus	Right hippocampus	Left caudate	Right caudate
Whole group (n = 76)					
VIQ	0.147 (NS)	0.023 (NS)	0.125 (NS)	0.347 (<.004)	0.312 (<0.01)
PIQ	0.102 (NS)	0.070 (NS)	0.158 (NS)	0.035 (NS)	0.012 (NS)
Standard-nutrient group (n = 38)					
VIQ	0.131 (NS)	−0.018 (NS)	0.078 (NS)	0.429 (<0.01)	0.346 (<0.05)
PIQ	0.105 (NS)	0.227 (NS)	0.227 (NS)	0.184 (NS)	0.086 (NS)
High-nutrient group (n = 38)					
VIQ	0.112 (NS)	0.080 (NS)	0.175 (NS)	0.255 (NS)	0.223 (NS)
PIQ	0.001 (NS)	−0.091 (NS)	0.057 (NS)	0.001 (NS)	−0.001 (NS)

Figure 2. Scatterplots showing the relationship between left caudate volume and VIQ for: (*A*) the total group; (*B*) the Standard-nutrient group; and (*C*) the High-nutrient group.

Correlations between neural volumes and IQ. As Table 7 shows, VIQ was significantly related to left ($p < 0.04$) and right ($p < 0.05$) caudate volumes in boys but PIQ was not. In girls, caudate volumes were not significantly related to either IQ measure. There were no significant relationships between total brain and hippocampal volumes and VIQ or PIQ in either gender.

DISCUSSION

It is important to emphasize that while our sample of children was drawn from the original cohort, the present investigation should be regarded essentially as an imaging study and not a follow-up. The sample was restricted to children with a gestational age of 30 wk or less who had

normal findings on neurologic examination at 7.5–8 y, the latter because of implications for MRI interpretation. We collected MRI data from 34% of the total number meeting the criteria in the Standard-nutrient group and 32% in the High-nutrient group. The numbers seen were limited by issues such as feasibility of travel to the hospital rather than by losses to follow-up in the usual sense. Generalizing to the whole cohort under these conditions would be inappropriate, but this was not the focus of the study. Our prime interest was in demonstrating that early nutrition could affect brain structure, so it was crucial to ensure that no major differences existed between the groups, other than diet, that could explain the imaging findings. Results presented above show that the two

Table 6. *Mean (standard deviation) caudate nucleus volumes reported by gender. p-values and 95% confidence intervals for the group differences result from univariate analyses of variants, co-variant total brain volume*

	Males				Females			
	Standard-nutrient ($n = 18$)	High-nutrient ($n = 20$)	*p*-value	95% confidence intervals	Standard-nutrient ($n = 20$)	High-nutrient ($n = 20$)	*p*-value	95% confidence intervals
Left caudate (mm^3)	3701 (475)	4305 (717)	<0.002	−805 to −187	3600 (442)	3630 (492)	NS	−338 to 174
Right caudate (mm^3)	3896 (569)	4575 (742)	<0.001	−880 to 235	3818 (450)	3816 (509)	NS	−312 to 204

Table 7. *Partial correlation coefficients between the adolescent IQ measures and neural volumes for males and females. Age at scan is partialled out for total brain volume analyses; total brain volume is added in all others*

	Total brain volume	Left hippocampus	Right hippocampus	Left caudate	Right caudate
Males					
VIQ	0.265 (NS)	0.005 (NS)	−0.028 (NS)	0.360 (p <0.04)	0.338 (p <0.05)
PIQ	0.252 (NS)	0.035 (NS)	0.063 (NS)	0.045 (NS)	−0.012 (NS)
Females					
VIQ	0.310 (p <0.07)	0.054 (NS)	0.117 (NS)	0.291 (NS)	0.265 (NS)
PIQ	0.271 (NS)	0.116 (NS)	0.211 (NS)	0.002 (NS)	0.019 (NS)

study groups did not differ on a series of critical variables. Only partial data are available in some cases since, in the early 1980s, ultrasound was not routine in the United Kingdom.

For the group as a whole, differences in early diet were associated with significant differences in VIQ but not PIQ at adolescence. Our hypothesis that the caudate nucleus might be, at least in part, the neural substrate for such effects was based on the striking correlation between caudate volume and IQ reported by Abernethy *et al.* (12). Supporting this hypothesis, our experimental intervention was associated with larger left and right caudate volumes in those fed the High-nutrient diet, with no volume differences in other neural structures that we measured. Total cortical gray matter did not differ significantly between diet groups. Caudate volumes in our group correlated with VIQ, but not PIQ. Taken together, we suggest that the selective pattern of cognitive effects of early diet described here and previously (11) could, at least in part, be explained by differences in caudate volumes, programmed by early diet.

Abernethy *et al.* (12) did not find the selective relationship between caudate volume and VIQ reported here. In their study, caudate volumes showed significant correlations with VIQ, PIQ, and Full Scale IQ. When brain volume was corrected, only the PIQ effect remained. Variations in experimental procedure might explain this difference. For example, we measured IQ using full-form, rather than short-form IQ tests, so that our IQ estimates reflected a wider range of abilities; some abilities, not assessed by the short-form, might have influenced the correlations. Age at test was approximately 7 y *versus* approximately 15 y. Different methods for measuring neural volumes were used in the two studies and, in addition, total brain volume was estimated from head circumference by Abernethy *et al.* (12) but was measured in our study. It is worth noting that several studies report that VIQ seems to be particularly influenced by nutrition. In addition to the findings of Lucas *et al.* (11), other studies have shown that breastfeeding duration influences VIQ, but not PIQ (21), while term small-for-gestational age children have reduced VIQ scores compared with term appropriate-for-gestational age children

(22). The most important point, however, is that two separate studies have shown relationships between caudate volume and IQ in those born preterm.

The literature provides little information about the relationships between caudate volumes and IQ. Studies examining the neural bases of intelligence have identified a wide array of structures showing varying degrees of relationship to measured IQ (23,24) but the findings, usually based on magnetic resonance scans of normal adults, may not be pertinent to former preterms who frequently show altered brain development (25–27). One important difference involves the caudate nucleus itself, a vulnerable structure in preterm infants. The caudate nuclei are located close to the germinal matrix, a temporary structure involved in cell production during neural development, still extant at the time of preterm birth (28,29). The germinal matrix is a highly vascular structure, containing thin-walled blood vessels, and is prone to hemorrhage, increasing the risk of damage to the caudate in this population of infants who frequently show later neurodevelopmental problems. The germinal matrix disappears by full-term, making the caudate nucleus less vulnerable in infants born at term. It is possible, therefore, that the relationships between caudate volumes and IQ are specific to the stage of brain development represented in the preterm groups. Interestingly, in the small group of 16 full-term infants, there was no significant relationship between caudate volumes and IQ scores, though a larger sample would be required to confirm this. Importantly, the selectivity of our caudate findings suggests that caudate volume is not simply a general marker of preterm vulnerability to adverse influences on neurodevelopment.

Of course, the correlations between caudate volumes and overall level of intellectual ability do not preclude meaningful relationships with other neural structures not assessed here. Indeed, it would be surprising if such a diffuse ability was associated with one neural structure in particular. Neither are we suggesting that the structural effects we observe are the only changes in the brain associated with nutrition; plausible structural changes such as regional or general synaptogenesis may require different measurement techniques.

The initial correlations between neural volumes and IQ scores included all 76 members of the total group. As Figure 2 shows, it does not appear that the significant correlations were caused by the presence of extreme cases. Nevertheless, on examining the relationships within each of the diet groups separately, the correlation between VIQ and caudate volume was significant only in the Standard-nutrient group. An indication of why this might occur came from a comparison with the small group of full-term children. This revealed highly significant differences for left and right caudate volumes between the Standard-nutrient group and full-terms (both: $p < 0.01$) but no significant differences for the High-nutrient group. The High-nutrient diet seems to have "normalized" caudate volumes in this group of preterms and, like the full-terms, they no longer show a correlation between volume and IQ. It may be that the high-nutrient diet allows the caudate to grow to its full potential. Nutritional impairment, in the form of a lower-nutrient diet, on the other hand, does not facilitate this process and the final size attained continues to be related to cognition. This is speculative, needing systematic study.

In animal studies, the effect of early nutrition on later learning and behavior is predominantly in males (1); in our previous follow-up of the current cohort at 7.5–8 y the cognitive effect was also predominantly in boys (11). The effect of diet on IQ was still selective to VIQ in our group, but this did not reach significance in either gender, perhaps because of decreased statistical power. Diet affected caudate volumes in males only and it was the boys who showed significant correlations between caudate volume and VIQ, suggesting that different relationships exist between brain structures and cognition in males and females. This is consistent with a large literature describing gender differences in brain development and structure (30–32) and in the relationship between brain structure and cognition (33–35). Our results suggest that the male and female brain at the earliest stage in the brain growth spurt may be differentially susceptible to environmental influences such as nutrition.

It may seem surprising that only 4 wk dietary exposure could lead to persistent brain changes. The participants in the present study, however, were born at the beginning of the chief growth spurt in the human brain, a "sensitive" period when it is particularly vulnerable to environmental influence. There have been many instances, in both animals and humans, of early experience altering life-long behavior (36,37). Although behavior has been the focus here, Knudsen (38) points out that sensitive periods are actually a property of neural activity. It is consistent, therefore, that the effects of diet on cognition should also be seen at a structural level, as we have demonstrated. The growth spurt lasts for approximately 2 y longer, and further research is needed to test whether dietary intervention later in this period would have similar effects.

The original demonstration that diet in the immediate postnatal period could affect subsequent cognition throughout childhood (11) had clear scientific and public health implications. We now see that effects persist into adolescence, suggesting that they may be permanent. However, our main focus here was to explore, in a study with carefully matched groups, the impact of diet on brain structures that could underlie the cognitive effects. The caudate nucleus emerges as one plausible candidate, at least in those born at the earliest stage of the critical brain growth spurt. The fact that early nutrition may program the development of specific brain structures is of fundamental biologic importance. Although studies are beginning to appear that link aspects of current diet to brain function (39,40), the data presented here are among the first to show that the structure of the brain can be influenced by early nutrition in humans.

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Erratum

Figures 1 and 3 appearing in the article, "Acidosis During Reoxygenation Has an Early Detrimental Effect on Neuronal Metabolic Activity," by Elisabeth Frøyland, *et al.*, appearing in *Pediatric Research* 2005; 57:488–493, were not typeset correctly. The correct figures appear below.
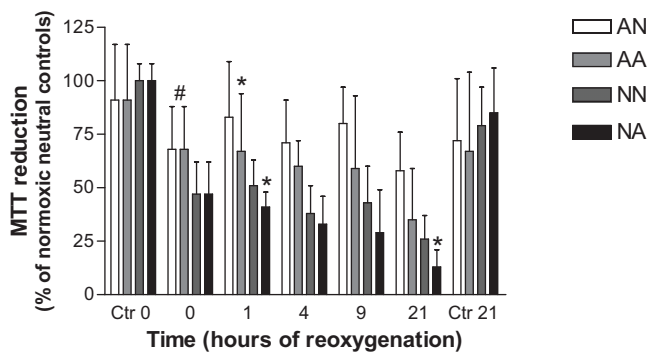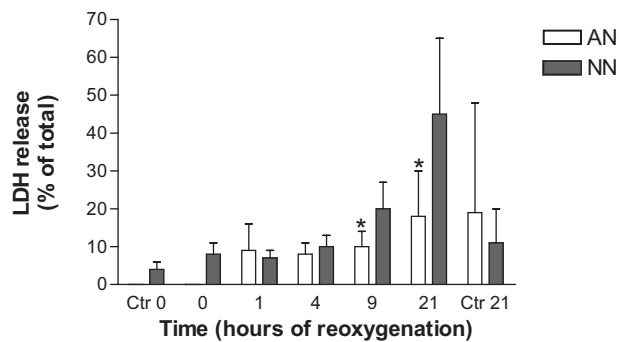

Fig. 1

Fig. 3