Growth and Development of the Brain and Impact on Cognitive Outcomes

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Abstract
Understanding human brain development from the fetal life to adulthood is of great clinical importance as many neurological and neurobehavioral disorders have their origin in early structural and functional cerebral maturation. The developing brain is particularly prone to being affected by endogenous and exogenous events through the fetal and early postnatal life. The concept of ‘developmental plasticity or disruption of the developmental program’ summarizes these events. Increases in white matter, which speed up communication between brain cells, growing complexity of neuronal networks suggested by gray and white matter changes, and environmentally sensitive plasticity are all essential aspects in a child’s ability to mentalize and maintain the adaptive flexibility necessary for achieving high sociocognitive functioning. Advancement in neuroimaging has opened up new ways for examining the developing human brain in vivo, the study of the effects of early antenatal, perinatal and neonatal events on later structural and functional brain development resulting in developmental disabilities or developmental resilience. In this review, methods of quantitative assessment of human brain development, such as 3D-MRI with image segmentation, diffusion tensor imaging to assess connectivity and functional MRI to visualize brain function will be presented.

Understanding human brain development from the fetal life to adulthood is of great clinical importance as many neurological and neurobehavioral disorders have their origin in early structural and functional cerebral maturation. The developing brain is particularly prone to being affected by endogenous and exogenous events through the fetal and early postnatal life. The concept of ‘developmental plasticity or disruption of the developmental program’ summarizes these events [1, 2]. Plasticity of the brain therefore refers to the
brain’s ability to reorganize and recover from injury or alter its gestalt by adaptive mechanisms induced by environmental factors. Mechanisms known to provide plasticity include deletion of neurons through apoptosis, proliferation and pruning of synapses, activity-dependent modelling of synaptic connections and for certain areas persistence of neurogenesis and alteration of developing glia cells.

Increases in white matter (WM), growing complexity of neuronal networks suggested by gray matter and WM changes, and environmentally sensitive plasticity are all essential aspects in a child’s ability to think and maintain the adaptive flexibility necessary for achieving high sociocognitive functioning.

Despite marked improvements in perinatal practice, perinatal brain injury remains one of the most common complications causing life-long handicapping conditions [3]. Many of the cellular and vascular mechanisms of perinatal brain damage have been studied and show a correlation between the nature of the injury and the maturation of the brain.

During the past 15 years, the etiology of brain injury in human newborns has been considered by many to be multifactorial rather than only linked to cardiovascular instability and hypoxia-ischemia. Several prenatal, perinatal and postnatal factors (such as hypoxic-ischemic insults, excess release of glutamate, genetic factors of susceptibility, growth factor deficiency, oxidative stress, maternal infection yielding excess cytokines and other proinflammatory agents, exposure to toxins, maternal stress, malnutrition) have been implicated in the pathophysiology of brain lesions and developmental abnormalities associated with cerebral palsy and neurocognitive delay.

Advancement in neuroimaging has opened up new ways for examining the developing human brain in vivo and study of the effects of early antenatal, perinatal and neonatal events on later structural and functional brain development resulting in developmental disabilities and developmental resilience.

**Brain Development and Growth Visualized by Magnetic Resonance Imaging**

Distinct features of the developing brain can be visualized by both conventional magnetic resonance imaging (MRI) and diffusion imaging. The immature WM demonstrates a relatively homogenous low signal on T1-weighted images and a high signal on T2-weighted images compared to gray matter predominantly due to the higher water content of the immature WM. Discrete bands of altered signal intensity (high signal on T1-weighted images, low signal on T2-weighted images) have been described in the frontal WM and are thought to represent bands of migrating glial cells [4]. With increasing age, WM T1 signal intensity increases and T2 signal intensity decreases as an expression of the reduction in water content.
The rapid process of cortical folding between 24 and 40 weeks can be readily followed on MRI. Before 24 weeks of gestation, the brain is essentially lissencephalic with the exception of the Sylvian fissure, which is initially very wide and appears vertically orientated. From 24 to 28 weeks, the cortex shows the developing central Rolandic, pericallosal and intraparietal sulci; by 32–33 weeks, an increased number of gyri and shallow sulci appear; from 34 weeks, further thickening of the cerebral cortex is accompanied by the development of a nearly normal adult sulcal pattern by term [5](fig. 1).

Conventional MRI features of chronic WM injury in the immature brain are characterized either by cysts and more importantly by a persistent high signal intensity of the WM in T2-weighted images representing diffuse WM injury [6]. This imaging characteristic is later associated with the thinning of the corpus callosum and loss of WM volume as a result. In several recent studies on preterm infants, brain diffuse excessive high signal intensity in the cerebral WM on T2-weighted imaging was reported to be present in up to 40–75% of low birthweight preterm infants imaged at term [7]. MRI is further ideally equipped to assess delayed myelination. The absence of myelination in the posterior limb of the internal capsule (missing T1 high signal intensity, T2 low signal intensity) at term age is a good indicator of later neuromotor impairment [8].

Cortical differentiation can be qualitatively appreciated by conventional MRI and preterm infants with diffuse WM abnormalities often show poor cortical gyrification at term with simple appearing gyri and sulci compared to complex tertiary sulci seen in the full term infant. Quantification of these changes can be assessed by 3D-MRI.

To quantify changes in brain development and assess long-term consequences of perinatal brain injury, 3D-MRI methods combined with image postprocessing techniques have been developed, which permit the volumet-
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Fig. 2. 3-D MRI in brain development. Examples of MRI segmentation classifying the brain into different tissue classes such as cortex, unmyelinated and myelinated white matter, basal ganglia but also specific brain structures such as the hippocampi and the cerebellum, which then allows absolute quantification of these brain structures.

RIC assessment of brain development and an absolute quantitation of myelination, an important step in brain development that allows normal motor development [9]. These techniques further allow exact definition of brain volume and can therefore accurately monitor brain growth, measure cerebrospinal fluid volume and volume changes in cortical gray matter. 3D-MRI morphometric techniques (fig. 2) were used to evaluate the effect on subsequent brain development of early WM injury in premature infants. In the premature infants with preceding WM injury, the volume of myelinated WM at term was significantly lower than in both the premature infants without prior WM injury and the infants born at term measuring and confirming the degree of delay of myelination. These studies further showed a marked decrease in cortical gray matter volume in the preterm infants with prior periventricular WM injury indicating impaired cerebral cortical development after early WM injury and may explain the intellectual deficits associated with periventricular leukomalacia in preterm infants [10, 11]. Effects of perinatal drug treatment can also be assessed by these Imaging techniques. Postnatal dexamethasone treatment for chronic lung disease has been shown to affect brain development with a striking reduction in cortical gray matter in preterm infants without other cerebral pathologies compared to preterm infants not receiving steroids [12]. These studies combined with functional outcome studies, have had a major impact on changes in the use of corticosteroids in the treatment of newborn ICU patients [13, 14]. Some of these volumetric structural abnormalities have been found to persist into later childhood and are associated with cognitive performance [15].

Conventional MRI has been able to delineate macroscopically early developmental events such as gyral development and myelination, but does not
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provide information on distinct microstructural changes during brain development, such as cortical lamination and establishment of WM connectivity. Diffusion tensor imaging (DTI) is a well-studied MR modality that allows in vivo assessment of biological tissues at a microstructural level.

**Microstructural Brain Development by DTI**

DTI, a recent MR modality which assesses water diffusion in biological tissues at a microstructural level, has revealed a powerful technique to explore the structural basis of normal brain development. In fact, the tissue organization can be probed noninvasively, and the age-related changes of diffusion parameters (mean diffusivity, anisotropy) reveal crucial maturational processes, such as WM myelination. The two primary pieces of information available from DTI studies – mean diffusivity (Dav) or water apparent diffusion coefficient (ADC) and diffusion anisotropy measures – change dramatically during development, reflecting underlying changes in tissue water content and cytoarchitecture, ADC being a quantitative measure (velocity) of overall water diffusion in tissue and anisotropy being a measure of directionality of preferred water diffusion in a given tissue.

Mean Dav values differ between pediatric and adult human brain. Dav values are higher for pediatric brain than adult [16, 17].

The precise cause of the decrease in Dav with increasing age is not known, though it has been shown to be influenced by both a decreasing water content, and increasing complexity of WM structures with increasing myelination [17].

The increase in WM anisotropy values during development appears to take place in two steps. The first increase takes place before the histologic appearance of myelin [16, 17]. This increase has been attributed to changes in WM structure which accompany the ‘premyelinating state’. Interestingly, the commissural fibers in the splenium and the genu of corpus callosum express the highest fractional anisotropy (FA) values in the immature human brain [18]. These fibers are largely unmyelinated in the newborn period and their high anisotropy is in part due to a high degree of parallel organization. The second, more sustained, increase in anisotropy is associated with the histologic appearance of myelin and its maturation. The earliest signs of this second stage change in anisotropy are observed in the projection fibers of the posterior limb of the internal capsule in the newborn period.

Central WM maturation is rapid in the first 3 months, with Dav decreasing in the peripheral WM more rapidly than in the deep WM, whereas anisotropy increase is more pronounced in the deep WM compared to the peripheral WM [19]. By the end of the 1st year, Dav values in all WM regions are approaching mean adult levels, which indicates that the microstructural changes in WM that are responsible for the restriction of overall water diffusion are mature after the 1st year of life. In contrast to this, the FA values in the peripheral
WM achieve only half of adult values, which indicates that WM organizational changes in microstructure that promote anisotropic diffusion continue after the 1st year of life [19, 20].

Another brain area in which anisotropy values differ between immature and mature brain is the cerebral cortex. Anisotropy values of cortical grey matter in children beyond term and adult brain are generally consistent with zero, meaning that water diffusion in grey matter is isotropic at the spatial resolutions currently available. As shown now in several human and animal studies, values for cortical grey matter in immature brain are transiently non-zero during development [21–24]. The tensor principal eigenvectors are then oriented radially to the cortical surface. The increase in anisotropy in this time period coincides with active neuronal migration along the radial glial scaffolding, whereas the decrease coincides with the phase of neocortical maturation with transformation of the radial glia into the more complex astrocytic neuropil.

Laminar organization of the immature cortex is further characterized by the presence of the subplate zone, a zone immediately underlying the cortical plate, which has a high content of extracellular matrix and sparse, large-size neurons. In DTI, this transitory zone present only between 18 and 32 weeks of gestational age is characterized by low FA values and intermediate $D_{av}$ values [22, 25].

Thus, developmental changes in anisotropy of the cerebral cortex reflect changes in its microstructure, such as the arborization of basal dendrites of cortical neurons, the innervation of the cortical plate by thalamocortical and corticocortical fibers and the transformation of radial glia into mature astrocytes, all processes which are an important basis of later functional connectivity.

ADC and anisotropy during brain development are therefore influenced by the degree of myelination, the volume of the extracellular compartment, the amount of extracellular water, changes in the composition of the extracellular matrix (e.g. subplate), density and geometrical organization of axons and dendrites, density of neurofilaments and other changes in the cytoskeleton.

**Developing WM Connectivity**

Fiber tracking based on DTI is another recent technique applied to the developing brain to study quantitative assessment of specific pathway maturation in WM. Berman et al. [26] were able to show significant differences in the maturational changes in FA and transverse diffusion between the motor and the somatosensory pathway in premature infants between 30 and 40 weeks’ gestational age.

In order to understand the underlying structural changes for the rapid development of motor and cognitive functions in the early months of postna-
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In early life, Dubois et al. [27] defined relative maturation phases of different WM fiber tracts. The corticospinal tracts appeared as the most mature bundle in the first 4 months of life and the anterior limb of the internal capsule and the cingulum as a limbic structure as the least mature bundles. Furthermore, this study allowed the differentiation of maturational stages within a functional system, for example with the fornix in the limbic system being in an advanced maturational phase compared to the cingulum, fornix being involved in associative learning, which is important in early functional development.

With tract-based spatial statistics analysis, a rater-independent method, important changes were shown in regions within the centrum semiovale, frontal WM and the genu of the corpus callosum that had a significantly lower FA in preterm infants imaged at term-equivalent age compared to term-born controls [28], thus assessing alterations of brain development in ex-preterm infants (fig. 3). Further changes in FA during brain development were mainly due to changes in axial diffusivity and were more pronounced between early adolescence and adulthood than between late childhood and adolescence [29]. Factors that might influence the changes in axial diffusivity at this age are increased neurotubules, neurofilaments and glial cells and increased fiber coherence. Using this technique, widespread age-related increases in FA were found through adolescence into young adulthood (13–21 years of age) with the most significant increase in the right body of the corpus callosum and the right superior region of the corona radiate and, in particular, in the frontal lobe association fibers [29, 30]. These data confirm earlier neuroanatomical description of slow maturation of the corpus callosum into adolescence and is in concordance with recent data showing a U-shaped development curve of the corpus callosum with peak values between 30 and 40 years and the prominent changes in volumetric and cortical density studies occurring in the

**Fig. 3.** Corticospinal tracts. Using DTI and fiber tracking, illustration of corticospinal tracts important for sensorimotor development can be achieved. Illustration of T2-weighted MRI with superposed corticospinal fiber tracts in a newborn brain.
frontal WM during adolescence [31]. These long-term changes fit with the assumption that learning and experience, which continue throughout adult life, are accompanied by structural changes. Experience-related changes in diffusion characteristics have been shown in practicing piano players [32] and confirm the experience-based structural plasticity in the brain.

The impact of prenatal and early neonatal insults on brain development and structure is of particular clinical importance, as infants exposed to such adverse conditions are likely to show neurodevelopmental delays and disabilities later in life. The unique setup of in vivo imaging techniques allows the study of longitudinal changes in brain development subsequent to early environmental insults and evaluation of mechanisms of repair and plasticity.

**Imaging and Neurodevelopmental Disorders**

The subsequent neurological deficits after perinatal brain injury are grouped together under the term of cerebral palsy, and structural correlate of cerebral palsy has been assessed using DTI [33]. Tract-specific evaluation of children with cerebral palsy after periventricular leukomalacia identified most frequently alteration in WM fiber tract development in the retrolenticular part of the internal capsule, posterior thalamic radiation, superior corona radiate and in commissural fibers of the corpus callosum [34, 35].

The clinical relevance of injury and related modification of WM architecture detected in this fashion is not yet known, and long-term follow-up studies of prematurely born children are currently underway linking functional outcome to structural WM development assessed by DTI [28, 36–38].

Neurodevelopmental disorders in the pediatric population are frequent indications for MRI, and DTI contributes to understanding underlying brain structural abnormalities in many of these disorders. Attention deficit hyperactivity disorder is a childhood-onset neurodevelopmental disorder that affects up to 10% of children. It is characterized by behavioral symptoms with inattention, hyperactivity and impulsivity, and conventional MRI and volumetric assessments have identified abnormalities in the frontal lobe, in particular in the dorsolateral prefrontal cortex, but also in the areas of the cingulate cortex, with alterations suspected also in the corticostriatal connections. An earlier DTI study showed decreased anisotropy in the right premotor, right striatal, right cerebral peduncle, left middle cerebellar peduncle, left cerebellum, and left parieto-occipital WM regions of young ADHD patients [39]. More recent studies addressed the question of abnormalities in the specific neural networks leading to difficulties in attention control and executive functioning in adults with childhood ADHD [40, 41]. DTI has confirmed structural abnormalities linked to attentional and executive systems in adults, though to what extent these alterations are already present during early development needs to be further defined.
A condition associated with an increased risk of ADHD in which brain development can be affected long-term is intrauterine growth restriction [42] and postnatal growth restriction in preterm infants due to inadequate nutrition. Currently, the IUGR rate is the highest since over 20 years and is likely to rise further due to the increasing rate of infertility treatments, multiple pregnancies, older mothers and exposure to IUGR-inducing agents such as tobacco. All these conditions lead to poor nutritional status of the fetus and subsequent alteration of structural and functional brain development with reduction in cortical gray matter volume, reduction in striatal volume, and predominantly in boys, reduction in hippocampal volume [43, 44]. Gyrification of IUGR newborns is discordant with the normal developmental trajectory, showing a more pronounced reduction in surface in relation to the sulcation index compared to normal newborns [45]. Furthermore, these structural measurements of the brain at birth were predictors of infants’ outcome at term-equivalent age, for MRI-based cerebral volumes and neurobehavioral development evaluated with the Assessment of Preterm Infants’ Behavior (fig. 4).

Children who had very low birthweight have multiple rather than isolated cognitive deficits including problems with attention, memory, reading and mathematics, as well as reasoning, and self-regulation [46, 47]. These cognitive deficits are likely to have an overriding central nervous impairment with underlying brain structural changes [48]. Recently, epidemiological studies assessing maternal nutrition have led to interesting observations by which maternal consumption of seafood during pregnancy leads to higher cognitive performance in their offspring, with again the most prominent effect on verbal IQ. [49]. Fatty acid metabolism is therefore an important component of both prenatal and postnatal brain development, and studies are underway investigating structural and functional changes in relation to nutritional interventions. Preterm and low birthweight infants are often growth-restricted at hospital discharge. Feeding infants after hospital discharge with calorie- and protein-enriched formula milk might therefore facilitate ‘catch-up’ growth. A recent study by Isaacs et al. [50] is one of the few studies that looked at specific brain structural effects of nutritional supplementation in two groups of ex-preterm infants born at a gestational age below 30 weeks at adolescent age who were treated with different perinatal nutritional protocols. They used an atlas-based segmentation technique to define total brain and cortical gray matter volume as well as volumes of the subcortical gray matter structures, caudate nucleus, thalamus, putamen, globus pallidum, hippocampus and amygdala and IQ testing with Wechsler Intelligence Scale for Children defining both VIQ and PIQ. The high nutrient group ex-preterm adolescents showed significantly better performance on VIQ measures. Structurally, the two groups showed significant differences in both left- and right-sided caudate volume, with the standard nutrition group showing lower caudate volumes, which further correlated with IQ scores with lower volume indicating lower VIQ. This was a gender-specific effect with mainly male preterm
Subcortical gray matter structures have been shown to be affected by premature birth with correlations to later cognitive outcome [10, 51, 52] as well as in neuropsychiatric disorders such as ADHD [53] and depression. In a prior study, deep nuclear gray matter volume reduction at term age has been shown to be correlated with gestational age at birth and severity of respiratory distress syndrome; thus, clearly immaturity at birth and comorbidities such as severe respiratory distress which are associated with oxidative stress lead to reduction in deep cortical gray matter volume at term. Immaturity and severity of RDS on the other hand are often associated with poor nutritional status in the preterm infant, and therefore the findings of the current study by Isaacs et al. [50] would suggest that some of these effects might be due to insufficient nutritional support and that some of these effects can be reversed by higher nutritional support.

**Fig. 4.** Effects of growth restriction on brain development. Growth restriction affects cortical development with a decrease in volume of cortex (C; **a**), white matter (W; **b**), brain surface (S; **c**) and cortical thickness (C/S; **d**). Data from Dubois et al. [45].
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Understanding the effects of early antenatal, perinatal and neonatal events on later structural and functional brain development, aberrant or regenerative, will no doubt be essential to develop interventions and treatments for preventing developmental disabilities that have their origin in early life. Several lines of evidence currently show that the developing organism adapts to the environment in which it finds itself. The use of MRI techniques in IUGR babies has delineated changes in the central nervous system development that correlate with altered neurodevelopment and could be implicated in the development of neuropsychiatric disorders in adult life.

Research aimed at defining which nutrients favor adequate development of brain structure and functions during gestation and early childhood, with the ultimate purpose of improving cognitive development and decreasing neuropsychiatric disorders, will be an important task in terms of public health of the future.

References

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Discussion

Dr. Qumruzaman: What are the common causes of the interruption of neuronal proliferation in the first trimester of pregnancy and how do you assess this?

Dr. Hüppi: You can't of course directly assess the number of neurons. We do that in the animal model where you can count neurons, but we think that the alteration of the cortical thickness, for example, clearly represents a reduction in probably the cortical neuronal load in these regions. In the hippocampus, for example, C1/A1 neurons in the situation of IUGR are clearly reduced in numbers.

Dr. Manzoor Hussain: You said that there is a negative effect of exposure to dexamethasone, although it has been advocated to stimulate surfactant production antenatally. Perhaps there should be a change in the timing of dexamethasone administration?

Dr. Hüppi: I didn't have time to show you all the data. What is known in regard to the effects of glucocorticosteroids in fetal and neonatal life is that indeed you can induce surfactant production, lung maturity, by dosing glucocorticoids in the third
trimester. This has been done by many centers and proved to be efficient. However, postnatal preterm lung disease treatment with long-term direct dexamethasone does negatively affect the brain. We have demonstrated it with the imaging that showed a reduction in cortical gray matter volume. There are also much more data showing that preterm infants exposed to glucocorticoids postnatally have reduced neurodevelopmental outcome. As for antenatal lung maturation, there are a couple of studies also showing that if you give multiple doses to the mother starting early, say 23, 24 weeks, it does affect surface measurements of the brain at birth, and it does negatively impact neurodevelopmental outcome. So now the recommendations are to not use postnatal steroids in the treatment of chronic lung disease except for studying purposes under direct control of protocols and to not repeat antenatal lung maturation above the one dose of lung maturation. Those are the current guidelines by the American Academy. And there are of course differences in certain steroids. You can go into discussions of dexamethasone vs. hydrocortisone and there seem to be slightly different effects.

**Dr. Islam:** As you said, dexamethasone and probably some other drugs can cause neural depletion. As pediatricians, we use steroids with the conception that their short-time use will not affect the brain. We use steroids quite often for the treatment of acute lung injury, in wheezy babies, for example. Can this short-term treatment have any adverse effect?

**Dr. Hüppi:** It’s obvious that corticosteroids are used in pediatric treatments. I think it’s a timing issue, we are here talking about the brain that is in a developmental stage where apoptosis, for example, is a prominent modulator, which is much less the case when you consider a 5- or a 6-year-old. On the other hand, it’s known that if you give high-dose steroids, for example in the situation of oncology patients, you do arrest brain growth. There is clearly no growth of head circumference during the steroid treatment. What is seen in those cases is that once you stop administering steroid, the growth restarts. What we see in the preterm population is that the brain seems to be altered following corticosteroid treatment. We, for example, measured cortical volume 10 weeks after stopping the corticosteroid dexamethasone treatment, and we still observed a 30% reduction in cortical gray matter volume. So I think the effect of dexamethasone is probably most harmful in the third trimester of pregnancy and for the premature infant in the early postnatal life.

**Dr. Mobarak:** Nowadays, studies say that prednisolone is neuroprotective. What is your comment on this because we are using prednisolone instead of LCTH in cases of infantile spasm. In some neurological disorders of the babies, we also prefer to use methylprednisolone and prednisolone. My second question concerns dexamethasone. It’s a common practice in Bangladesh to use dexamethasone to stimulate surfactant production, that is to prevent RDS antenatally, but in India a single dose of betamethasone is used. Is there any difference between betamethasone and dexamethasone? Is betamethasone as bad as dexamethasone?

**Dr. Hüppi:** Betamethasone, dexamethasone, hydrocortisone, prednisolone, all these glucocorticoids have a different degree of affinity to either mineral corticoid or glucocorticoid receptors, and that does make a difference in the brain. What is especially bad for the brain is a high affinity to glucocorticoid receptors because those are the ones that induce, for example, the apoptotic cascade with Bax upregulation. So if you take, for example, hydrocortisone, which has a much higher mineral corticoid receptor affinity, this negative effect on the brain is to much lesser extent. Again, I think the answer to your first question is corticosteroids seem to be particularly harmful during third trimester gestation. With respect to this time period, current recommendations are to give one course of lung maturation, not repetitive courses of lung maturation, and if you then do that with dexamethasone or betamethasone, I think there is no clear evidence to prefer the one or the other.
Dr. Lucas: I wonder if I could ask you to speculate probably a bit beyond the data, but do we know anything about the thresholds for cortisol effects on the brain? You have been talking about the pharmacological range, but what about the physiological range? There are a number of stress states that preterm infants and indeed fetuses can go through that could produce quite large rises in endogenous corticosteroids. Do you image those having any impact on brain development?

Dr. Hüppi: It’s hard to speculate. Anand in his pain studies clearly demonstrates that high stress levels are detrimental to the brain. We don’t have much clear evidence for it. From our studies, I think what we see is clearly an effect of chronic exposure to a relatively high dose of steroids. I must also say that I did perform a study looking at the effects of hydrocortisone at 5 mg per kg as a treatment of chronic lung disease, and these babies do not express any changes in cortical gray matter volume either at term or at 8 years of age, so there seem to be differences. The interpretation for these data right now is the difference in affinity between the mineralocorticoid and glucocorticoid receptors. As for physiologic levels, we have unfortunately not performed any saliva measurements of cortisol in these babies. I wish we had designed the study differently when we did the IUGR study to see if the regulation of basal cortisol levels is different postnatally. We can only assume that the situation of placental insufficiency that was documented by abnormal Doppler in these studies actually confirmed the situation of higher fetal exposure that has been shown in situations of placental insufficiency.

Dr. Cooke: Dr. Hüppi, would you like to speculate about nutrition and the brain, given that brain mass in preterm and term infants is ~12–13% compared to 3–5% in the adult, and recent data which suggest that increasing energy and protein intake to 120% of the normal requirement improves neurodevelopmental outcome in infants with perinatal brain injury [1]?

Dr. Hüppi: I will speculate on my MR data because these are the ones that I know best. If you look at the changes in the metabolites that we measure in the brain in the human preterm, then the things that may change the most are, for example, creatine and phosphocreatine. There is a massive increase in creatine and phosphocreatine between say 28 and 40 weeks, and that is a clear proof that energy provides building blocks and energy to the brain. So in my view, that would be a measure of how well we provide energy to the brain, the accretion of creatine and phosphocreatine in the brain measured in vivo. Another one could probably be choline, but choline is a lipid precursor that is very important for all the lipid membranes in the brain. Interestingly, choline stays very stable during brain development, which suggests that direct growth probably doesn’t directly vary choline levels in the brain.

Reference
