Impact of intrauterine growth restriction and glucocorticoids on brain development: Insights using advanced magnetic resonance imaging

Stéphane V. Sizonenko a,∗, Cristina Borradori-Tolsa a, Delphine M. Vauthay a, Gregory Lodygensky b, c, François Lazeyras b, Petra S. Huppi a

a Department of Pediatrics, Geneva University Hospital, Switzerland
b Department of Radiology, Geneva University Hospital, Switzerland
c Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA

Abstract
There are now a number of evidences showing that the developing organism adapts to the environment it finds itself. Short- and long-term adjustments, referred as "programming", take place and will initially induce intrauterine growth retardation but will also have consequences that will appear later in life. The use of magnetic resonance imaging (MRI) techniques in IUGR babies has delineated changes in the central nervous system (CNS) development that correlate with altered neurodevelopment and could be implicated in the development of neuropsychiatric disorders in adult life. Similarly, the use of corticosteroid treatment in preterm infants has also been implicated in abnormal CNS development. In this review, we will focus on the modifications of CNS development that occur after exposition to adverse environment such as undernutrition or corticosteroid treatment that can now be studied in vivo with advanced MRI technology.

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1. Early life adverse events and developmental consequences
Striking evidence from a number of disciplines has focused attention on the interplay between the developing organism and the circumstances in which it finds itself (West-Eberhard, 1998). The organism can express specific adaptive responses to its environment which include short-term changes in physiology as well as long-term adjustments. The concept of "programming" refers to the consequences of adverse events to the foetus occurring during the intrauterine life that will primarily induce "intrauterine growth retardation" (IUGR), but will later on result in additional "programmed" adverse consequences, one well-known example being obesity (metabolic syndrome). The notion is that the metabolic insults during the foetal life period might disrupt several metabolic or endocrine set points with consequences appearing only later in life, with severe alterations of hormonally regulated functions such as growth, reproduction, and energy metabolism. Most of the supporting studies in this area have concentrated on grossly altered nutrition in utero leading to growth delays, and its striking influence on multiple aspects of adult health and disease risk (Barker, 1990). Epidemiological studies have shown that markers of malnutrition, such as low birth weight, small for gestational age, frank IUGR or clinically abnormal thinness at birth, strongly predict the subsequent occurrence in adult life of hypertension, hyperlipidemia, insulin resistance, type 2 diabetes, ischemic heart disease (Barker et al., 1993). Further, foetuses that are clinically malnourished during the first trimester of development are three times more likely to become obese as adults. In addition to malnutrition, adverse environmental exposures, such as exposure to nicotine or endocrine disruptors, present during in utero development, can have profound influences on foetal growth. The observed environmentally induced responses later in life could result from altered gene expression associated with altered cell production and cell differentiation involved in the establishment of cell lineages leading to the structural and functional characters of the tissues, organs, and systems that arise from these lineages. Early life events may therefore affect any organ including the brain.

Using advanced magnetic resonance imaging (MRI) techniques, altered central nervous system (CNS) development has been recently described in IUGR babies. These structural abnormalities correlate with altered locomotor and/or behavioural
developmental aspects and may represent an explanation for the link between IUGR and the development of neuropsychiatric disorders in adult life (Nilsson et al., 2005). Concomitantly, the use of corticosteroid treatment in preterm infants has been implicated in abnormal CNS development. A better understanding of altered CNS development after foetal adverse events requires translational research with the use of animal models mimicking these changes (Boksa, 2004).

In this review, we will focus on the modifications of CNS development that occur after exposure in utero to adverse environment such as malnutrition or corticosteroid treatment that can now be studied with advanced MRI technology both in patients and animal models.

2. Imaging techniques to study brain development

2.1. Human brain development

Recent advances in magnetic resonance (MR) techniques show great potential to expand our understanding of brain development and brain injury in the living organism. These MR techniques provide a unique ability to measure the impact of IUGR on subsequent brain development. Specifically, the development of three dimensional (3D) volumetric MRI and post-acquisition techniques allow quantification of the absolute volume of cerebral white matter (WM), both myelinated and unmyelinated WM components, as well as cortical gray matter (GM) and basal structures such as the striatum (Huppi et al., 1996, 1998a; Huppi and Barnes, 1997). While total brain tissue volume was found to increase in the period of 29 to 41 weeks, the principal determinant was found to be an increase in GM volume from 35 to 50%. This increase is thought to primarily relate to cortical differentiation rather than to an increase in the total number of neurons. This cortical GM volume increase was found to be associated with significant increases in surface area and gyral development (Huppi et al., 1998a). Furthermore, prior to 36 weeks of gestation, unmyelinated WM was the dominant type of brain tissue. However, starting at 35 weeks an almost 5-fold increase in absolute volume of myelinated WM was observed. This MR technique gives us the ability to measure quantitatively the impact both on myelination and cortical development of insults at the critical period of brain development. For example, in the premature infants with preceding WM injury, the volume of total gray matter, cortical gray matter and myelinated WM at term was significantly lower than in both the premature infants without prior WM injury and the infants born at term (Inde et al., 1999).

Advanced 3D MRI techniques and post-acquisition image processing with tissue segmentation algorithms, have been used to quantify total brain volume and absolute volumes of gray and white matter in premature infants (Huppi et al., 1998a; Borradori et al., 2001; Tolsa et al., 2004).

In addition to determination of brain volume, techniques such as diffusion-weighted MR imaging (DWI) and MR spectroscopy (\(^1\)H-MRS) now allow to study many previously undetected aspects of microstructural and metabolic changes in brain development. The DWI technique measures the diffusivity of brain water, quantitatively expressed as the “apparent diffusion coefficient” (ADC). Important changes in the quantitative measurements of water diffusion in the developing brain are present with a marked decline in the ADC values in the central WM indicative of a progressive decrease in water diffusion (Fig. 1) (Huppi et al., 1998b).

To provide insight into the nature of the microstructural developmental events associated with the decrease of the ADC described above, diffusion tensor analysis can be used to determine diffusion anisotropy, a measure of the directionality of water diffusion in cerebral WM. Developmental changes in diffusion anisotropy showed a striking increase in cerebral WM from 28 to 40 weeks (Huppi et al., 1998b). A similar increase in anisotropy precedes myelination in the developing rat and has been termed “premyelination anisotropy” (Wimberger et al., 1995). This phenomenon could relate to several possible developmental events, including axonal fiber development and orientation, as well as premyelination axonal ensheathment by developing oligodendrocytes (Back et al., 1996). Changes in anisotropy, therefore, may provide an in vivo tool to assess, at least in part, the microstructural brain development.

Proton magnetic resonance spectroscopy (\(^1\)H-MRS) yields normative data on regional cerebral metabolites in preterm and term newborns (Huppi et al., 1991, 1995). Recently, these data were completed with measurements of absolute metabolite concentrations during development which considerably extended the range of metabolites measured (acetate, alanine, aspartate, choline, creatine, gamma-aminobutyrate, glucose, glutamine, glutamate, glycine, lactate, myo-inositol, macromolecular contributions, N-acetylaspartate (NAA), phosphocholine, phosphoethanolamine, scyllo-inositol, taurine and threonine). Key findings include a significant increase with gestational age of N-acetylaspartate, glutamate and glutamine, creatines, taurine, as well as a significant decrease in lactate, myo-inositol and...
phosphethanolamine. Regional differences have also been established: subcortical areas such as thalamus showed early high levels of total creatine and NAA; by contrast periventricular white matter showed very little NAA, occasionally discernible lactate resonance, and increased resonance at 0.9 and 1.3 ppm (methylene, macromolecules) (Huppi et al., 1991, 1995; Kreis et al., 2002).

2.2. Animal brain development

Diffusion tensor imaging of cortical development in newborn rat pups was performed with a high field animal MRI system (4.7 T). Using diffusion-weighted imaging and diffusion tensor imaging we have evaluated normal early cortical development at 3 and 6 days of life (P3 and P6, respectively). Cortical ADC was reduced in the P6 group compared to P3, whereas a decrease in diffusion anisotropy could only be seen in the deep cortical layers between P3 and P6. A radial organisation of the outer cortical layers with the eigenvectors being perpendicular to the pial surface was observed, in the deep layers this radial pattern was not seen (Fig. 2). These data illustrate for the first time the radial organisation of the cortex at P3 and P6 in the rat with a reduction of water diffusion with age. The reduction in anisotropy that occurs during the period of cortical development is likely to be a representation of the significant decrease in radial glia fibres and increased dendritic sprouting that occurs during this developmental period (Sizonenko et al., 2004). Similar observations have been made in the developing brain of kittens (Baratti et al., 1999), mice (Mori et al., 2001), primate (Kroenke et al., 2005) and humans (McKinstry et al., 2002; Maas et al., 2004).

Developmental changes in brain metabolites have been measured using proton magnetic resonance spectroscopy (1H-MRS) in rat pups: 16 metabolites were quantified from three different brain regions (hippocampus, striatum, and cerebral cortex)
Bcl-x(L) (Almeida et al., 2000). Under normal conditions access molecule Bax relative to the antiapoptotic molecules Bcl-2 or al., 2006). In the hippocampus GR activation induces apopto-

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act predominantly via intracellular receptors, which function as ligand-activated transcription factors. There are two recep-
tor subtypes: the lower affinity glucocorticoid (GR) and higher affinity mineralocorticoid (MR) receptor.

Glucocorticoids are essential for many aspects of normal human brain development. They affect most regions of the develop-
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neural cell numbers and synaptic function in forebrain regions with a predilection for the male versus female brain (Kreider et al., 2006). In the hippocampus GR activation induces apopto-
sis of granule cells by increasing the ratio of the proapoptotic molecule Bax relative to the antiapoptotic molecules Bcl-2 or Bcl-x(L) (Almeida et al., 2000). Under normal conditions access of maternal endogenous glucocorticoids to the fetus is low, this is related to the expression of 11β-hydroxysteroiddehydrogenase type 2 in the placenta, which protects the foetus from high mater-
nal glucocorticoid concentrations.

Several clinical conditions potentially expose the fetus and the preterm newborn to glucocorticoids. Firstly maternal stress and placental insufficiency can lead to fetal exposure of higher cortisol levels; secondly, induction of lung maturation achieved by synthetic glucocorticoid administration antenatally; thirdly postnatal glucocorticoid treatment for chronic lung disease. Firstly maternal stress and placental insufficiency can lead to fetal exposure of higher cortisol levels; secondly, induction of lung maturation achieved by synthetic glucocorticoid administration antenatally; thirdly postnatal glucocorticoid treatment for chronic lung disease. Secondly, induction of lung maturation achieved by synthetic glucocorticoid administration antenatally; thirdly postnatal glucocorticoid treatment for chronic lung disease. In the mid-1980s, postnatal corticosteroids were increas-
ingly prescribed for the prevention or treatment of chronic lung disease, supported by evidence of benefit on some short-term outcomes, including earlier weaning from mechanical ventila-
tion and fewer episodes of hypoxic-ischemic encephalopathy in neonates. In 1990s, the use of corticosteroids for chronic lung disease was extended to preterm infants to improve lung function and reduce the risk of bronchopulmonary dysplasia. Several clinical conditions potentially expose the fetus and the preterm newborn to glucocorticoids. Firstly maternal stress and placental insufficiency can lead to fetal exposure of higher cortisol levels; secondly, induction of lung maturation achieved by synthetic glucocorticoid administration antenatally; thirdly postnatal glucocorticoid treatment for chronic lung disease. Secondly, induction of lung maturation achieved by synthetic glucocorticoid administration antenatally; thirdly postnatal glucocorticoid treatment for chronic lung disease. In the mid-1980s, postnatal corticosteroids were increas-
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Thus, it is now recommended that antenatal corticosteroids ther-

apty be limited to a single course in cases of imminent preterm delivery (Friedman and Shinwell, 2004; Walfisch et al., 2001; White et al. and Thoresen, 2000). Postnatal corticosteroid treatment for chronic lung disease resulted in a 30% reduction of cortical gray matter volume without any changes in white mat-
ter characteristics (Fig. 4) (Murphy et al., 2001). These data support the hypothesis that corticosteroid exposure to the develop-
ing brain during the critical period of cortical development will result in impairment of the very early phases of cortical development, detectable by volumetric MRI at term.

4. IUGR and human brain development

IUGR preterm infants are at high risk for neurological mor-

bidities such as cerebral palsy, mental retardation, a wide spec-
trum of learning disabilities and pervasive developmental disor-
ders (Taylor et al., 2002; Huck et al., 2002; Burd et al., 1999) with an association to the development of neuropsychiatric dis-
orders in adult life (Ozanne et al., 2004). The foetus receives its nutrients from the maternal/fetal circulation via the placenta. Any disturbance in the placental/fetal circulation will there-
fore generate severe consequences on the supply of important nutrients such as glucose, aminoacids and oxygen. The pla-
centa itself is an active endocrine organ and therefore changes in nutrient availability will also affect placental as well as foetal endocrine function. One particular aspect is the dysregulation of the hypothalamo-pituitary-adrenal axis resulting in higher cortisol concentrations in IUGR infants (Economides et al., 1988; Seckl et al., 2000). Several important physiopathologic mechanisms occur during IUGR due to poor placental function. Hemodynamic changes lead to repetitive episodes of hypox-

emia (McMillen et al., 2001; Owens et al., 1987) and placental trophoblast cell dysfunction leads to loss of nutrients and alter-
ation of placental hormone homeostasis (Regnault et al., 1999;
Fig. 5. Early and near term cortical volumes measured with 3D-MRI in premature infants with IUGR compared to premature infant with appropriate intrauterine growth. Healthy preterm infants and preterm infants with IUGR due to placental insufficiency had MR imaging with 14 days after birth and at term equivalent for volumetric measurements of gray matter. (Left panel) Gray matter volume is significantly reduced near birth and at term equivalent in IUGR preterm infants compared to healthy preterms. (Right panel) Representative T1 and T2 MRI of the brain on coronal section from control and IUGR preterm scanned at term. A reduced cerebral volume is present and the brain appears less mature in the IUGR with less circonvolutions (Tolsa et al., 2004).

Gluckman and Harding, 1997a,b). Umbilical cord plasma levels of corticotrophin-releasing hormone (CRH) from the placenta are strikingly elevated in IUGR foetuses. Later on, these infants develop higher cortisol levels throughout life and are at risk for permanent hypertension, hyperglycemia, and type II diabetes (Seckl et al., 2000; Seckl, 2001, 1997). The mechanisms underlying foetal programming in this situation include determination of the ‘set point’ of the hypothalamic–pituitary–adrenal axis and of tissue glucocorticoid receptor expression. With the use of advanced magnetic resonance neuroimaging techniques, the effects of IUGR, on brain development are likely to be better characterised.

4.1. Volumetric MRI in preterm infants with IUGR

Quantitative assessment of neurostructural abnormalities in infants born with IUGR due to placental insufficiency revealed a significant reduction in cerebral cortical volume (Tolsa et al., 2004). Quantitative assessment of neurostructural abnormalities within the first 2 weeks of life in preterm infants born IUGR, documented a significant reduction in total brain volume and a reduction in cerebral cortical gray matter (CGM) volume. These reductions persisted in MRI performed at term (Fig. 5). Behavioural assessment showed a significant reduction in the attention-interaction capacity in IUGR infants. Further significant correlation of cortical gray matter volume at term and attentional capacity at term was found. These results suggest that placental insufficiency with IUGR result in specific structural and functional consequences on cerebral cortical brain development. Further preliminary results from the early assessment of the 12 months outcome data indicate that some of these functional deficits persist (Borrondi et al., 2003).

The hippocampus is known for its crucial role in cognitive function such as memory and learning. It is sensitive to hypoxia, to stress hormones and to undernutrition, all likely to occur in IUGR pregnancies. We therefore set out to study the hippocampal volume specifically by manual segmentation of the right and left hippocampus in a subset of our population and compared hippocampal volume in premature infants with IUGR compared to premature infants with appropriate intrauterine growth. The total volume of both hippocampal formations was found to be significantly smaller in the IUGR group than in the control group (Lodygensky et al., 2003). These results indicate that placental insufficiency resulting in foetal IUGR has long-term consequences on hippocampal development. This disturbance might explain the high rate of cognitive and memory dysfunction in this subpopulation of preterm infants.

4.2. DWI with diffusion-tensor analysis in preterm infants with IUGR

In order to study the effects of IUGR on the microstructural development of the brain diffusion tensor images were analysed. Results show a higher ADC value in the internal capsule of IUGR infants at birth, which persists at term, indicating reduced maturation in this area, which represents a major white matter fibre tract system that is normally myelinating between 34 and 40 weeks. Further results indicate a reduced relative anisotropy, less well-developed fibre tract system at birth in the main interhemispheric connection system, the corpus callosum (Zimine et al., 2002). The new technique of voxel-based morphometry allowed to verify these findings by a group analysis, IUGR versus control, and revealed similar regions of microstructural changes in preterm infants with IUGR (Huppi et al., 2004).

4.3. Measuring local metabolism by 1H-MRS in preterm infants with IUGR

In order to study the effects of IUGR on the microstructural development of the brain diffusion tensor images were analysed. Results show a higher ADC value in the internal capsule of IUGR infants at birth, which persists at term, indicating reduced maturation in this area, which represents a major white matter fibre tract system that is normally myelinating between 34 and 40 weeks. Further results indicate a reduced relative anisotropy, less well-developed fibre tract system at birth in the main interhemispheric connection system, the corpus callosum (Zimine et al., 2002). The new technique of voxel-based morphometry allowed to verify these findings by a group analysis, IUGR versus control, and revealed similar regions of microstructural changes in preterm infants with IUGR (Huppi et al., 2004).
the striatum metabolites showed significant reduction in myo-inositol and lactate between the two visits, as well as an increase in total creatine and N-acetylaspartate. These changes were observed for both groups (IUGR and control). Myo-inositol was slightly higher at birth in IUGR infants, raising the possibility of an upregulation of this metabolite that acts as a major brain osmolyte. At term we found a significantly higher concentration of creatine in the IUGR infants (Borradori et al., 2003). Creatine as a main energy source seems to be preferably taken up or produced after foetal malnutrition and could be viewed as a mechanism of compensation. No changes in lactate concentrations between IUGR and control could be found in the striatum. The analysis of the metabolic pattern of white matter regions showed similar results to the striatum for creatine and myo-inositol comparing IUGR with control infants except that Myo-inositol concentration did not show the postnatal age-dependent decrease in IUGR infants. In the white matter region IUGR infants further showed significantly higher lactate levels both at the first examination and persisting at term. The significant findings from our human studies in foetal IUGR indicates that the energy supply mechanisms in the brain are altered with an increased lactate concentrations in the brain, which may be due to structural alterations with astrogliosis and normal lactate production or increased lactate production within normal astrocytes.

5. IUGR animal model: effects on brain development

Animal research has documented a deleterious effect of early malnutrition, alteration of glucocorticoid homeostasis and IUGR on brain development with a reduction in cell number and cell size with overall lower brain weight (Mallard et al., 2000; Rees and Inder, 2005; Rees et al., 1997, 1998; McEwen et al., 1999). Experimental studies in different animal models of IUGR have shown neuronal degeneration in the hippocampal pyramidal neurons, loss of dendritic branches and density of granular neurons in the dentate gyrus with an overall reduction of cellularity by 30% (Uno et al., 1990), which resulted in reduced overall hippocampal volume measured by MRI (Uno et al., 1994). These findings are particularly related to the neurotoxic effects of excessive corticosteroids on brain structures acting by altering glucocorticoid receptor gene expression and the corticotrophin-releasing hormone system (Welberg et al., 2001). Recently we have investigated the effects of gestational caloric restriction on brain development in the Sprague–Dawley rat, again combining in vivo quantitative MRI and histological assessment. Indeed, the development of animal models has been essential in the search for the mechanisms that govern programming. Maternal undernutrition has been used extensively to induce foetal programming in a variety of species including sheep, guinea pigs and rats (Lesage et al., 2001; Huizinga et al., 2000; Lingas et al., 1999). The impact of altered nutrient availability differs at different stages of gestation and both, the timing and the degree of reduced maternal nutrition may be important to determine the postnatal phenotype. In our experiment, we applied maternal undernutrition throughout gestation, generating a nutrient-deprived intrauterine environment. All animals were fed a standard laboratory chow, then after confirmation of mating, control females were fed ad libitum, and those intended for the malnutrition group were food-restricted to 30% of the daily control food intake from day 1 until the end of gestation. After birth, pups from undernourished (UN) mothers were cross fostered onto dams that received ad libitum feeding during gestation and litter size was adjusted to 8 pups per litter in order to provide adequate and standardized nutrition during lactation. Maternal food restriction did not affect length of gestation and litter size but resulted in foetal growth retardation reflected by a significantly decreased body weight at birth (30%) in the offspring from UN mothers. The impact of malnutrition on brain development was studied in the newborns.
with severe intrauterine growth retardation. At P7, body weight remained significantly lower (13.8 ± 0.7 g for ad libitum pups versus 7.5 ± 0.5 g for UN pups), and UN pups showed a 30% decrease in brain size. MRI assessment was performed at P7, 14, 21 and 28 to compare progressing brain growth and maturation. Volumetric assessment of the rat brain using 3D algorithm revealed a reduction of 39% of brain volume in our rat model of intrauterine growth restriction. Brain volumes remained smaller in IUGR rats at P14 (15.6%), P21 (13.9%) and P28 (8.6%) with intrauterine growth restriction. Brain volumes remained smaller in our rat model of intrauterine growth restriction. Brain volumes remained smaller in IUGR rats at P14 (15.6%), P21 (13.9%) and P28 (8.6%) with a small catch up growth of the IUGR group (Figs. 6 and 7). Histological assessment of myelin basic protein showed differences in myelination pattern at P7 and P21 between the IUGR and control pups. At P7 no myelin basic protein (MBP) immunostaining was present in the cortex, hypothalamus and hippocampus, but in the control group few patches of MBP could be seen in the corpus callosum and internal capsule. None was detectable in the IUGR animals. In the control animals at P21 myelination appeared complete with dense staining in the white matter tracts (corpus callosum and internal capsule) and in clusters of fibres within the striatum and thalamus. In contrast in the IUGR pups MBP staining did not appear as dense in these areas, suggesting delayed myelination or loss of axonal fibres.

6. Developmental plasticity in the brain

The developing brain is particularly prone to be affected by endogenous and exogenous events through the foetal and early postnatal life. The concept of “developmental plasticity” or disruption of the developmental program” summarizes these events. Plasticity for the brain therefore refers to the brain’s ability to reorganise and recover from injury or alter its gestalt by adaptive mechanisms induced by environmental factors (Johnston, 2004). 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 glial cells. Such glial plasticity may parallel neuronal remodelling (Dong and Greenough, 2004). Increases in white matter, which speeds up communication between brain cells, growing complexity of neuronal networks suggested by gray matter changes, and environmentally sensitive plasticity are all essential aspects in a child’s ability to mentalise and maintain the adaptive flexibility necessary for healthy transition into adulthood. Aberrant structural plasticity in neuronal and non-neuronal tissue is therefore increasingly recognized as a major determinant of developmental disabilities and disorders with life-long consequences (Casey, 2003). As advancement in neuroimaging has opened up new ways for examining the developing human brain in vivo, the study of structural developmental plasticity has become possible. Neuroimaging is providing new insights into the dynamics of the neural circuits involved in cognitive and behavioural development and molecular genetic research is producing an abundance of new target molecules responsible for the developmental plasticity (Altman, 2004; Diamond et al., 2004; Lipton, 2004). 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 for the modifications of obstetrical and neonatal care to develop interventions and treatments for preventing developmental disabilities that would have their origin in early life.

7. Future perspectives

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 set up of in vivo techniques will allow the study of longitudinal changes in brain development subsequent to early environmental insults and evaluate mechanisms of repair and plasticity. Identification of regional abnormalities in cerebral development (3D-MRI and DTI) and metabolism (DWI and 1H-MRS) and correlation of those abnormalities with histopathological, biological and genomic data will provide clues on the long-term disturbance of brain development after intrauterine exposure to different environmental conditions. Identification of the structural, metabolic and genomic brain defects or modifications following in utero insults, could lead to the design of early pharmacological interventions able to reverse or ameliorate the identified “programmed” effects and prevent their manifestations later in life.

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