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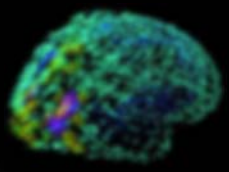

Neuroanatomical and neurofunctional brain basis of cognitive deficits in adolescent subjects who were born preterm. Structural and functional magnetic resonance study

Thesis presented by
Mónica Giménez Navarro,
to obtain the grade of Doctor by the University of Barcelona

Supervisor:
Dr. Carme Junqué i Plaja, University of Barcelona

Neurosciences Doctorate Program

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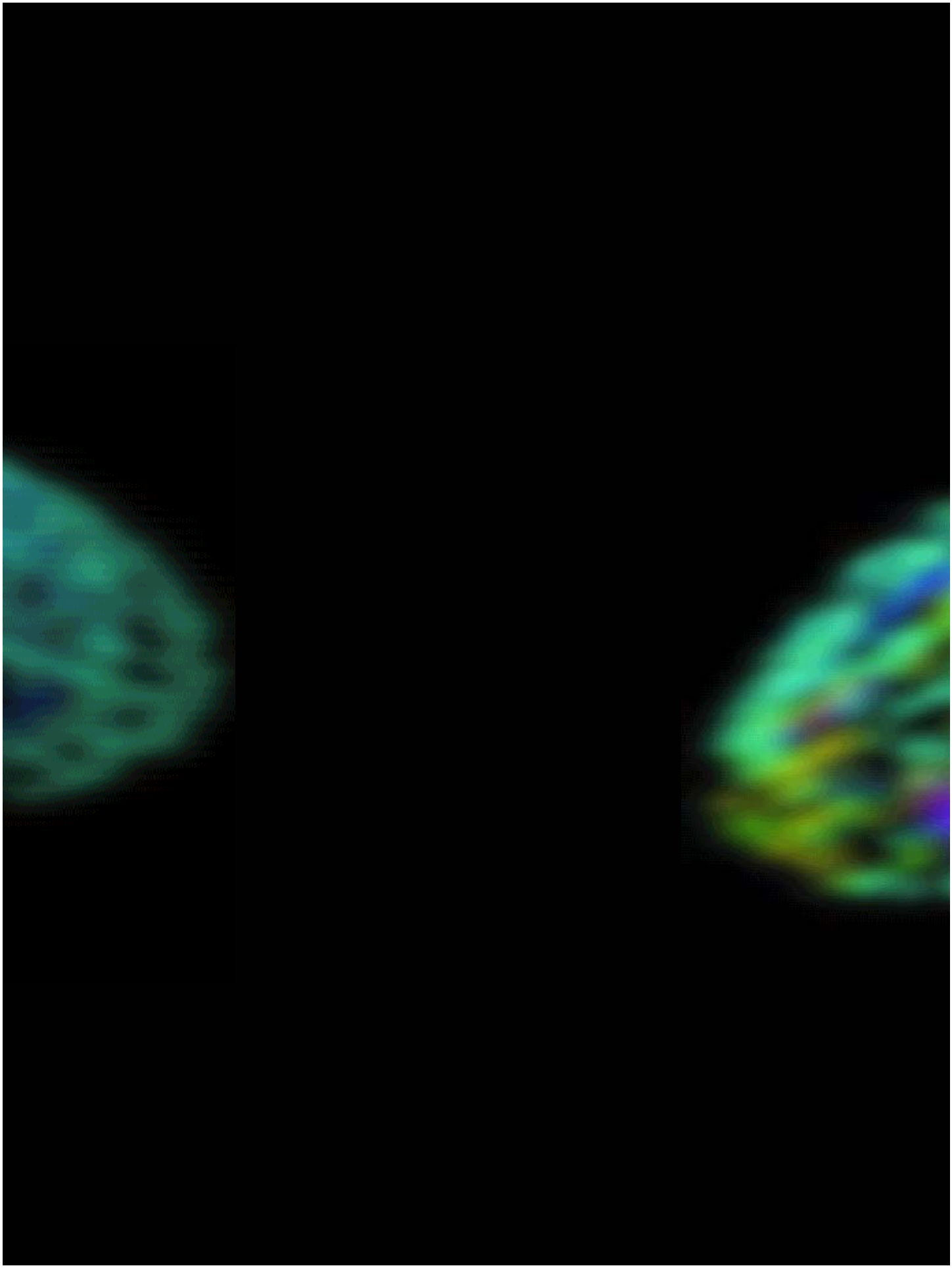

Department of Psychiatry and Clinical Psychobiology
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NEUROANATOMICAL AND NEUROFUNCTIONAL BRAIN BASIS OF COGNITIVE DEFICITS IN ADOLESCENT SUBJECTS WHO WERE BORN PRETERM. STRUCTURAL AND FUNCTIONAL MAGNETIC RESONANCE STUDY

Thesis presented by

Mónica Giménez Navarro,

to obtain the grade of Doctor by the University of Barcelona

Supervisor:

Dr. Carme Junqué i Plaja, University of Barcelona

Neurosciences Doctorate Program

Barcelona, july 2006

Dr. CARME JUNQUÉ I PLAJA, professor at University of Barcelona CERTIFIES that she has supervised and guided the PhD thesis entitled "*Neuroanatomical and neurofunctional brain basis of cognitive deficits in adolescent subjects who were born preterm. Structural and functional magnetic resonance study*", presented by Mónica Giménez Navarro. She hereby asserts that this thesis fulfils the requirements to be defended for the Degree of Doctor.

Signature,

Dr. Carme Junqué i Plaja
University of Barcelona
Barcelona, july 2006

This work has been carried out in the Neuropsychological Group of the Psychiatry and Clinical Psychobiology Department of the School of Medicine, University of Barcelona. The group belongs to the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). The presented work and the included studies have been financially supported by grants SAF2002-00836 (Ministerio de Ciencia y Tecnología), 2001SGR 00139 (Generalitat de Catalunya), and by a pre-doctoral grant from the Ministerio de Educación, Cultura y Deporte (AP2002-0737) to M. Giménez (Formación de Profesorado Universitario [FPU]).

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It has been a pleasure for me to have the opportunity of collaborating, during the preparation of the present thesis, with two important research groups: the Department of Neuropediatrics and Department of Women and Child Health, Neonatal Research Unit, Astrid Lindgren's Children's Hospital Karolinska Institutet and Department of Neonatology, Karolinska Institutet, Stockholm (Sweden); and The Pediatric Research, MR Department, of the Danish Research Center for Magnetic Resonance (DRCMR), Copenhagen University Hospital, Hvidovre (Dernmark). I would like to especially thank Dr. Hugo Lagercranz, professor of Pediatrics at Karolinska Institutet, Head of the Neonatal Programme, and Dr. Olaf Paulson and Dr. Terry Jernigan, professors at the DRCMR for their kindness and the given opportunity to stay at their centers. In regard to Dr. Olaf Paulson and Dr. Terry Jernigan I also would like to say thank you for your trust in my work there.

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Agradecimientos (agraïments)

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Y unas palabras para tí, Pi, la Dra. Pilar Salgado. Mucho ha llovido desde que te tenía sentada a mi lado izquierdo, en tu ordenador 'Sacha', y acabo el trayecto con la sensación de haber madurado, aprendido de tu relación conmigo. Agradezco empezar de una forma y acabar de otra. De cualquier otro modo, hubiera sido aburrido. Creo que Barcelona y Marsella nunca han estado tan cerca.

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Del Clínic vull destacar al Dr. Carles Falcón, la bondad feta persona, i a la Dra. Núria Bargalló. Gràcies per la vostra senzillesa i per l'ajuda desinteresada dins i fora del laboratori.

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També de l'Autònoma haig de recordar als amics de la Biblioteca d'Humanitats amb qui he mantingut el contacte malgrat la distància. I d'entre tots ells, l'Enric, ànima freudiana. Sempre que he necessitat de la teva companyia allà estaves.

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Oriol, t'he deixat pel final. Però quant més a prop un està del final, sembla que més coses ha de dir. No t'agrairé res; seré més egoísta. Et demano que et quedis on estàs, com fins ara. Considerant el futur que ens espera, és agradable somiar desperta.

A mi familia, a mi padrino.
A Oriol.

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ANNEX

Foreword

This thesis, presented to obtain the degree of Doctor by the University of Barcelona, is the result of different works carried out during a 4-year period at the Department of Psychiatry and Clinical Psychobiology, School of Medicine, University of Barcelona. During this period, I have obtained the *Diploma d'Estudis Avançats* (DEA) through the Neurosciences Program of the School of Medicine at the University of Barcelona.

The following papers have been published and/or accepted in international journals, as a result of the performed work, with a global impact factor (IF) of **24.738** (ISI of Knowledge, Journal Citation Reports 2004 and inferred from 2005):

Gimenez M, Junque C, Narberhaus A, Bargallo N, Botet F, Mercader JM. White matter volume and concentration reductions in adolescents with antecedents of very preterm birth: a voxel-based morphometry study. Neuroimage 2006;32:1485-1498.

Gimenez M, Junque C, Narberhaus A, Botet F, Bargallo N, Mercader JM. Correlations of thalamic reductions with verbal fluency impairment in those born prematurely. Neuroreport 2006;17:463-466.

Gimenez M, Junque C, Narberhaus A, et al. Hippocampal gray matter reduction associates with memory deficits in adolescents with history of prematurity. Neuroimage 2004a;23:869-877.

Gimenez M, Junque C, Narberhaus A, et al. Medial temporal MR spectroscopy is related to memory performance in normal adolescent subjects. Neuroreport 2004b;15:703-707.

Gimenez M, Junque C, Vendrell P, et al. Hippocampal functional magnetic resonance imaging during a face-name learning task in adolescents with antecedents of prematurity. Neuroimage 2005;25:561-569.

Gimenez M, Junque C, Vendrell P, et al. Prematurity affects orbitofrontal sulcus depth (*accepted*).

Another article is currently under revision in an international journal:

Gimenez M, Junque C, Narberhaus A, et al. Proton magnetic resonance spectroscopy reveals medial temporal metabolic abnormalities in adolescents with antecedents of preterm birth.

Following Table shows the concrete studies that form this thesis with the corresponding Impact Factor.

Table. Papers forming the present thesis.

Objective	Paper	Journal	Impact Factor (year)
Neuroanatomical brain basis			
To compare the relationship between hippocampal and thalamic gray matter loss (by Voxel Based Morphometry technique) and memory impairment in a sample of adolescents with antecedents of prematurity and a matched control sample.	*Gimenez M, Junque C, Narberhaus A, et al. Hippocampal gray matter reduction associates with memory deficits in adolescents with history of prematurity. Neuroimage 2004a;23:869-877.*	Neuroimage	**4.869** (2004)
To investigate the relationship between thalamic grey matter reductions, and thalamic-related frontal areas, and verbal fluency in a group of preterm subjects compared to controls (extending data from the study 1).	*Gimenez M, Junque C, Narberhaus A, Botet F, Bargallo N, Mercader JM. Correlations of thalamic reductions with verbal fluency impairment in those born prematurely. Neuroreport 2006;17:463-466.*	Neuroreport	**1.995** (inferred 2005)
To investigate regional white matter abnormalities in subjects with antecedents of very preterm birth and without evidence of white matter injury on conventional MRI visual inspection.	*Gimenez M, Junque C, Narberhaus A, Bargallo N, Botet F, Mercader JM. White matter volume and concentration reductions in adolescents with antecedents of very preterm birth: a voxel-based morphometry study. Neuroimage 2006;32:1485-1498.*	Neuroimage	**5.288** (inferred 2005)
To study possible abnormalities in gyrification and their relationship with gestational age at birth.	*Gimenez M, Junque C, Vendrell P, Narberhaus A, Bargallo N, Botet F, Mercader JM. Prematurity affects orbitofrontal sulcus depth (accepted).*	Neurology	**4.947** (inferred 2005)
Neurofunctional brain basis			
To test the possible specific relationship between NAA/Cho ratio in the medial temporal lobe and memory performance in normal adolescents.	*Gimenez M, Junque C, Narberhaus A, et al. Medial temporal MR spectroscopy is related to memory performance in normal adolescent subjects. Neuroreport 2004b;15:703-707.*	Neuroreport	**2.351** (2004)
To establish and compare medial temporal lobe metabolite value patterns in the medial temporal lobe between a premature sample and a control sample (extending data from the study 5) and to analize their relationship with hippocampal atrophy .	*Gimenez M, Junque C, Narberhaus A, et al. Proton magnetic resonance spectroscopy reveals medial temporal metabolic abnormalities in adolescents with antecedents of preterm birth.*	*Submitted*	
To map hippocampal activation by functional magnetic resonance imaging during a declarative memory task in a sample of adolescents with antecedents of prematurity and to compare the hippocampal activation patterns in preterms to a control group.	*Gimenez M, Junque C, Vendrell P, et al. Hippocampal functional magnetic resonance imaging during a face-name learning task in adolescents with antecedents of prematurity. Neuroimage 2005;25:561-569.*	Neuroimage	**5.288** (2005)
TOTAL: 24.738			

Glossary of abbreviations

ADC	*Apparent Diffusion Coefficient*
BW	*Birth Weight*
CC	*Corpus Callosum*
Cho	*Choline*
Cr	*Creatine*
DTI	*Diffusion Tensor Imaging*
FA	*Fractional Anisotropy*
fMRI	*Functional Magnetic Resonance Imaging*
GA	*Gestational age*
GM	*Gray Matter*
HI	*Hypoxic-Ischemic Insult*
IQ	*Intelligent Quotient*
IVH	*Intraventricular Haemorrhage*
MR & MRI	*Magnetic Resonance & MR Imaging*
MRS	*Magnetic Resonance Spectroscopy*
NAA	*N-Acetylaspartate*
PB	*Preterm Birth*
PVL	*Periventricular Leukomalacia*
RDS	*Respiratory Distress Syndrome*
VLBW	*Very Low Birth Weight*
WM	*White Matter*

1. INTRODUCTION

1.1. Approach

The *American Academy of Pediatrics* and the *American College of Obstetrics and Gynecology* define preterm birth as delivery before the completion of 37 weeks of gestation (American Academy of Pediatrics – American College Obstetrics and Gynecology, 2002). The incidence of premature birth varies widely among different populations and is generally correlated with differences in living conditions between the developing and the developed countries. Viability for a baby to survive outside of the mother usually occurs after 25-26 weeks of pregnancy, being miscarriage delivered prior to 20 weeks. Nowadays, prematurity increasing rate is over 8% in Spain (*Instituto Nacional de Estadística de España:* www.ine.es), existing an increment of the 13% of the preterm babies or babies with low weight in the last four years (*Sociedad Española de Neonatología:* www.se-neonatal.es) (Figure 1). The etiology of premature birth is multifactorial and may be related to disease in the fetus or in the mother, despite in about half the cases the etiological factors are unknown. Fortunately, the numbers of prematurely born infants surviving into later childhood, adolescence and adulthood are really high.

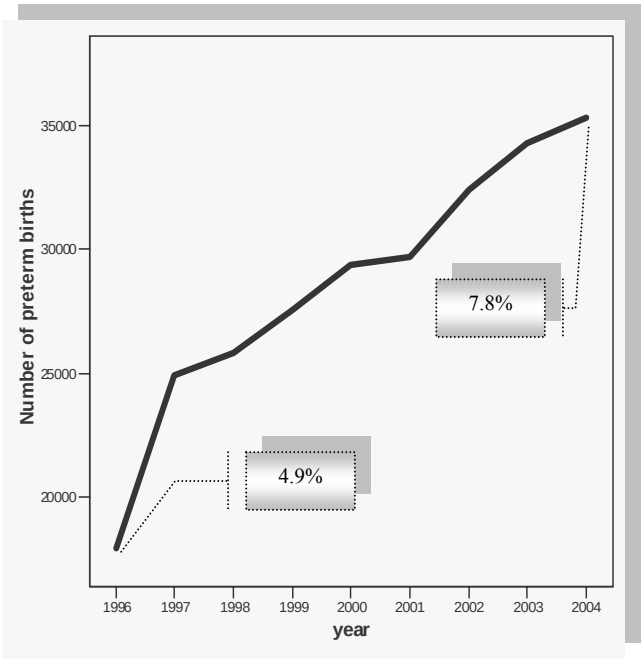

Figure 1. Estadistics of the Natural Movement of the Spanish Population 1996-2004. In 1996, the percent of preterm birth in Spain was of 5% regarding the total of births. In last years, the percent has increase over a 3%, reaching the 8-9% with respect to the total of births. *Source*: Instituto Nacional de Estadística de España.

In general, prematurity is a major challenge in perinatal health care and has become in an important risk factor for neurological impairment, including cerebral palsy (O'Shea et al., 1998; Wheater et al., 2000; Takahashi et al., 2005). Recent advances in neuroimaging techniques allowed to investigate the origin of the neuropsychological disfunctions described from the earlys '70 in preterm samples. A number of quantitative magnetic resonance techniques have been used in an attempt to identify relatively subtle pathology that might not be obvious on visual inspection. Until the publication of the works forming this thesis, few studies related quantitative volumetric brain data and neuropsychological performance in adolescents with premature birth (Peterson et al., 2000; Isaacs et al., 2000; Allin et al., 2001; Isaacs et al., 2001; Isaacs et al., 2003a; Isaacs et al., 2003b; Abernethy et al., 2002).

The present thesis provides new neuroanatomical and neurofunctional data by different quantitative approaches not used until now in the study of brain and cognitive abnormalities in preterm samples at adolescence. This can contribute to the knowledge about possible brain plasticity at long term derived from an early brain damage and it is the first step for future therapeutical approaches.

1.2. General objectives of the thesis

The general aim of this thesis is to study the cerebral basis of cognitive disturbances in adolescents with history of premature birth. For this purpose, we used structural, functional and magnetic resonance spectroscopy approaches as well as neuropsychological testing.

From a *structural point of view*,

- Firstly, few studies have correlated quantitative magnetic resonance imaging data with neuropsychological performance. In this sense, our first goal was to carry out a structural study by a voxel-based morphometry approach to analyze the possible structural correlates (focused on hippocampus and thalamus) of memory deficits in a young sample of subjects with history of prematurity (Section 4.1.1.).

- Secondly, given that thalamic reductions observed in our first work were not directly related to the memory dysfunctions, and impairment of verbal fluency is frequent sequelae of thalamic lesions, we investigated whether thalamic atrophy can explain the

verbal fluency impairments observed in the preterm sample (Section 4.1.2.).

Recent neuroimaging studies support that, parallel to the presence of a periventricular white matter injury (characterized by a cell necrosis, axonal injury and/or microglia activation), a diffuse white matter myelination disturbance can be observed in other brain areas. The aim of the third study (Section 4.1.3.) was to examine and quantify by a voxel-based morphometry approach the long term disturbances in white matter in a large cohort of adolescents with history of very preterm birth with no evidences of white matter damage by magnetic resonance imaging visual inspection. A second objective was to characterize the influence of the gestational age and weight in the white matter integrity loss.

Finally, as it is well-known that the sequential development of the sulci in cerebral hemispheres depends on gestational age, we have designed a study to address if prematurity produces an abnormal development at long term of the sulci that mature later and relate sulcal characteristics with the nearby cortical volume (Section 4.1.4.).

From a *functional point of view*,

Considering the structural reduction of the hippocampus observed in preterm subjects, we hypothesize that the adolescents with history of prematurity will present subtle brain functional abnormalities. In this sense, we have designed two new studies.

Prematurity associates with structural changes and brain metabolites can expand on the structural information. Once having the metabolic state in a control sample by a spectroscopic study (Section 4.2.1.), we tested for a possible abnormal metabolic pattern in a sample of adolescents with history of prematurity compared to a control group (Section 4.2.2.). The work is performed in a sample of preterms without perinatal complications.

Finally, there were no studies focused on functional magnetic resonance imaging of memory function in adolescents with preterm birth prior to this work. So, in Section 4.2.3., we examine whether hippocampal damage alters the pattern of brain activation during a declarative memory task. Our study aims at finding out if the hippocampal damage is compensated by a hyperactivation or a contralateral compensatory mechanism.

1.3. Theoretical framework of prematurity

1.3.1. Initial clinical features following preterm birth

Preterm birth (PB) children present a variety of clinical features, most of which are described as perinatal complications (Section 1.3.2.). The accuracy of the early detection and treatment of them can have important consequences at long term.

Preterm infants are particularly vulnerable to heat loss immediately after birth (Knobel et al., 2005). In the immature infant the epidermal barrier appears poorly developed (Rutter, 2000). This fact can lead to poor thermal control capabilities. Among other factors, excessive evaporative heat loss and the relatively cool ambient temperature of the delivery room may be important contributors to an abnormal thermoregulation. Hypothermia may result in hypoglycemia, apnea, and metabolic acidosis (Table 1).

Fetal euglycemia is maintained during pregnancy by the mother (via the placenta). Hypoglycemia is also a common complication of PB (Zanardo et al., 1999). Preterm infants are usually under stress and have insufficient levels of glycogen stores. Normally, they have difficulty maintaining glucose levels within reference range after birth. In the preterm infant, hypoglycemia usually is diagnosed when whole blood glucose levels are lower than 40 mg/dL. Cornblath et al. (2000) recommended that a glucose concentration of less than 45 mg/dL should be used as a screening or treating level in preterm infants. Symptoms may be present but may not be as obvious as those in a more mature infant (seizures, lethargy, and apnea, among other things).

The management of fluid balance also has been considered an important clinical issue for the infant adaptation to the new low humidity environment (Modi, 2004). Compared to full-term newborns, preterm infants have proportionally more fluid in the extracellular fluid compartment than the intracellular compartment. Thus, the onset of extracellular fluid loss supposes a postnatal cardiopulmonary adaptation. Disturbances in this adaptation characteristic may result in or exacerbate morbidities, such as intraventricular haemorrhage (IVH), and chronic lung disease or bronchopulmonary dysplasia (Section 1.3.2.2.).

Another important compromised function in preterms is the renal functioning (Awad et al., 2002; Rodriguez-Soriano et al., 2005). The renal capacity is reduced in

the immature newborn (Modi, 2004), generating an abnormal sodium homeostasis. These facts can produce adverse effects of inappropriate sodium administration at early stages (Hartnoll et al., 2000). This is likely to be of particular relevance to babies with respiratory distress syndrome (RDS).

Nutritional elements are an important clinical feature of preterm samples. Thus, it is well-know that preterm infants are born with low body stores of vitamin A and are at high risk of vitamin A deficiency (Shah and Rajalakshmi, 1984). Vitamin A is essential for optimal growth and development, and adverse effects of a deficit in vitamin A in preterm infants involve different perinatal complications, such as respiratory disease (Inder et al., 1998), retinopathy of prematurity (Ambalavanan et al., 2003) or IVH (Zachman et al., 1996).

1.3.2. Risk factors and perinatal complications in the preterm newborn

The preterm infant is at risk of serious insults to the brain (from maternal infections), has a high vulnerability to inflammatory mechanisms (Dammann and Leviton, 1997; Dammann et al., 2002; du Plessis and Volpe, 2002), or oxidative processes (Haynes et al., 2005) along with perinatal complications (Volpe, 2001a). All these factors have been associated with brain damage, especially white matter (WM) injury, and cognitive limitations in preterm samples (Dammann et al., 2002). Some external factors such as younger maternal age, ethnicity, or smoking should be included in the list of the earlier variables than can act as risk factors for delayed brain and cognitive development in the preterm infant. In another way of things, we can not avoid the presence of other environmental factors (lower social class, less education, single marital status, and low income) that have deserved attention as risk factors for cognitive deficits observed in preterm samples.

1.3.2.1. Predictors of long term outcome

As PB is one that occurs before 37 weeks of gestation or in which the birth weight (BW) is below 2500 grams, longitudinal studies suggest that one of the most verified predictors of neonatal and long term outcome is *BW* (Taylor et al., 2004). The conventional division of infants attending BW would be the following:

- *Extremely Low Birth Weight (<750 gr)*
- *Very Low Birth Weight (750-1499 gr)*
- *Low Birth Weight (1500-2500gr)*

There are several studies based on schoolchildren and young subjects who were born with extremely and very low birth weight (VLBW) that reported a negative neuropsychological, cognitive and functional outcome in these samples (Hack et al., 2000; Saigal et al., 2000; Taylor et al., 2000; Bowen et al., 2002; Hack et al., 2002; Anderson et al., 2003; Hayakawa et al., 2003; Saigal et al., 2003; Taylor et al., 2004). Taylor et al. (1998) reported that the sum of major neonatal medical complications provided a predictive measure for early school age outcomes in VLBW children. Even avoiding social risks as predictors, the authors considered that neonatal complications predicted overall cognitive ability, just as the neuropsychological and behaviour outcomes. A study from Hack et al. (2002) stressed that the educational disadvantage associated with VLBW remains into early adulthood. In Section 1.3.6., some of these neuropsychological and cognitive abnormal outcomes are detailed.

Of note here, only around two thirds of low BW infants are preterm. In this sense, a related predictor to the BW is *gestational age* (GA) *per se* (despite the difficulty in determine the onset of pregnancy). Clearly, BW is related to GA, and the combination of both provides additional information; however, we can found a subgroup of preterm infants that are small for GA. These preterm infants are at risk for adverse neurodevelopment compared to samples with appropiatte weight for GA (Hutton et al., 1997; Kok et al., 1998). It has been reported that the combination of VLBW and small preterms for GA supposed the worse neuropsychological consequences (poor intelligent quotient (IQ) and NEPSY battery scores; the NEPSY consists of 37 tests that evaluate aspects such as attention, language, motor and sensory functions, visuospatial functions, or memory) compared to VLBW-with-approapiate-weight-for-GA subjects with signs of asphyxia and controls (Korkman et al., 1996).

Hovewer, there are few more recent investigations that go against this fact. The metabolic study from Roelants-van Rijn et al. (2004) demonstrated that there were no significant differences neither in cerebral metabolism, in brain development nor in neurodevelopmental outcome at the age of 2 years, in a group of small preterms for GA compared to an approapiate-weight-for-GA sample. Moreover, a study of the development of cerebral sulci and gyri in small-for-GA fetuses goes in the same way: no differences were found in cortical formation between this kind of sample and an approapiate-weight-for-GA sample (Abe et al., 2004). Possible advances in medical care in last years may have improved the outcome of these samples.

Regarding the GA, separately from weight, a study in very PB subjects found that the long term neurodevelopment (at 8 years) in infants < 28 weeks of gestation was more related to the *presence and type of brain lesions* than to the GA itself (Vollmer et al., 2003). Taking into account the *moment of the damage*, the results from Sie et al. (2000) reported similar conclusions. The authors demonstrated that the type of hypoxic insult, rather than the postconceptional age at occurrence, determines the pattern of brain injury.

The *course of neonatal treatment* also seems to influence later development. There has been an improvement of the neonatal intensive care in last years, facilitating treatments directed at specific conditions associated with PB. Thus, the management of immature lung development has used the surfactant therapy as an ordinary and institutionalized treatment from the 80's until now. The quotation of the neonatal cohort treatment in each case is an important point to take into account, because no in all cases the interventions are completely positive (Murphy et al., 2001).

1.3.2.2. Main complications in the preterm infant

There is increasing evidence that the main major disability after PB is caused by periventricular brain lesions (Krageloh-Mann et al., 1999), i.e., as a consequence of a periventricular leukomalacia (PVL) and/ or intracranial haemorrhage (de Vries, 1996; Volpe, 2001a).

Main complications of premature birth that have a significant impact on long term development and outcome are:

- *Respiratory distress syndrome*: a serious breathing problem that affects mainly babies born before 34 weeks of pregnancy.
- *Intraventricular haemorrhage*: this condition is most common in babies born before 34 weeks of pregnancy. It can cause brain pressure and damage.
- *Periventricular leukomalacia*: is defined as damage to WM that results in severe motor and cognitive deficits in preterm infants.

The RDS is the one of the most common problems in premature infants (Ward and Beachy, 2003). Babies who were born too soon have immature lungs that have not developed surfactant, a protective film that helps air sacs in the lungs to stay open. With RDS, breathing is rapid and the centre of the chest and rib cage pull inward with each breath. Extra oxygen can be supplied to the infant through tubes that fit into the nostrils of the nose or by placing the baby under an oxygen hood. In more serious cases, the baby may have to require an inserted breathing tube and receive air from a respirator or ventilator. A surfactant drug can be given in some cases. Extra oxygen may be needed for a few days or weeks. Bronchopulmonary dysplasia is the development of scar tissue in the lungs and it can occur in severe cases of RDS (Table 1).

Table 1. Neonatal complications following preterm birth

Apnea
Brain injury (intraventricular haemorrhage, periventricular leukomalacia)
Catheter complications
Chronic lung disease or bronchopulmonary dysplasia
Developmental delay
Growth reduction
Hearing impairment
Hypoglycaemia
Hypothermia
Infections (septicemia, nocosomial infections)
Meconium aspiration syndrome
Necrotising enterocolotis ± perforation
Neonatal abstinence
Patent ductus arteriosus
Perinatal and fetal distress
Polycythaemia or hyperviscosity
Respiratory distress
Retinopathy of prematurity
Seizures and cerebral palsy

Severity of respiratory distress, related to neonatal hypoxic-ischemic insult (HI) in preterm and immature infants can result in significant brain injury and cognition. In this sense, females seem to show more advantage in cognitive recovery from RDS than males (Lauterbach et al., 2001). Animal studies have provided a wide spectrum of studies evaluating the vulnerability of immature brains to hypoxia (Section 1.3.5).

The IVH is another significant complication of prematurity (Duncan and Ment, 1993; Vohr and Ment, 1996). It is a condition in which immature and fragile blood vessels within the brain burst and bleed into the hollow chambers (ventricles) normally reserved for cerebrospinal fluid and into the tissue surrounding

them. A haemorrhage in the brain that begins in the periventricular subependymal germinal matrix can progress into the ventricular system. Both incidence and severity of IVH are inversely related to the weight and the age of the infant (Kadri et al., 2006). Any event that results in disruption of cerebral oxygen and vascular autoregulation can cause IVH (Meek et al., 1999; Kissack et al., 2004), including pneumothorax, rapid fluid changes, hypoxia, or ischemia. In this sense, Kadri et al. (2006) demonstrated that the onset of bleeding was related to the occurrence of hypoxia and RDS requiring mechanical ventilation. The IVH is graded according to a scale of I through IV, based on the extend of haemorrhage as seen on ultrasound (Volpe, 2001a), with I being bleeding confined to the germinal matrix and IV being an extension of blood into the brain parenchyma. Grades I and II are not uncommon, and the baby's body usually reabsorbs the blood with no ill effects. In grade II, blood is present in the germinal matrix and a small amount of blood also appears in the ventricles. In grade III, the ventricles are >50% filled with blood. About the 15% of infants with grades I-III progress on to develop grade IV (Ward and Beachy, 2003). However, more severe IVH can result in hydrocephalus, a potentially fatal condition in which too much fluid collects in the ventricles, exerting increased pressure on the brain and causing the baby's head to expand abnormally. To drain fluid and relieve brain pressure, doctors either perform lumbar punctures, a procedure in which a needle is inserted into the spinal canal to drain fluid; install a reservoir, a tube that drains fluid from a ventricle and into an artificial chamber under or on top of the scalp; or install a ventricular shunt, a tube that drains fluid from the ventricles and into the abdomen, where it is reabsorbed by the body. Infants who are at high risk for IVH usually have an ultrasound taken of their brain in the first week after birth, followed by others if bleeding is detected. Intraventricular haemorrhage can not be prevented; however, close monitoring can ensure that procedures to reduce fluid in the brain are implemented quickly to minimize possible damage.

Joining the IVH, PVL and a diffuse cerebral WM damage also appear as common brain injury in preterm infants (Back and Rivkees, 2004; Blumenthal, 2004), with significant long term influences on children's development (Gardner, 2005). Periventricular leukomalacia occurs most often at the site of the occipital radiation at the trigone of the lateral ventricles and around the foramen of Monro. The origin of PVL is believed to be multifactorial (Haynes et al., 2005). The presence of PVL, particularly cystic PVL, is associated with an increased risk of cerebral palsy (Folkerth, 2005).

A summary of additional neonatal complications related to shortened gestation, not mutually exclusive, includes perinatal and fetal distress, apnea of prematurity (a condition in which the infant stops breathing for periods lasting up to 20 seconds, with or without bradycardia or cyanosis. The incidence is inversely correlated with GA and weight), or meconium aspiration syndrome, among other things (Table 1).

1.3.3. Cerebral maturation: developing brain features

Human brain development is a process that begins early in gestation (Achiron and Achiron, 1991) and follows an invariant sequence, partly modulated by genetic factors (Hayakawa et al., 2005; Molnar et al., 2006). The first half of gestation corresponds to the neurulation, brain vesicles differentiation and neurogenesis. The second half implies an important growth of the cerebral hemispheres and the establishment of gyral and sulci formation (Encha-Ravazi and Sonigo, 2003). The gyral formation continues during pregnancy until term.

From a **cellular point of view**, Kolb et al. (2000) summarize basic stages in the cellular neurodevelopment: the neurogenesis, the cellular migration, the dendritic growth and the synapse formation. Most of the brain's neurons are formed and migrate to their assigned position during embryonic and early postnatal life. However, exceptions include the olfactory region (Liu and Rao, 2003) and hippocampal neurons in animals, including primates, which continue to be formed in adult life (Gould et al., 1997). In addition, the synaptic pruning has been added as an important stage in puberty and adolescence for selection and modification of cellular architecture (Zehr et al., 2006). The PB can occur during or before the dendritic growth. These stages in the neurodevelopment are interrelated and changes in brain plasticity would depend on them (Section 1.3.4.2.).

Apart from the cellular development, there are studies focused on the **ontogenesis and folding development**. Magnetic resonance imaging (MRI) studies let us visualize and quantify changes in maturation in fetus and neonates at first days of life and prenatal ultrasound results seem to corroborate the normal pattern of sulcal development observed by MRI (Toi et al., 2004). The developmental pattern of cortical gyri and sulci has been accepted as a reflection of fetal brain maturation and follows a temporal-spatial schedule (Chi et al., 1977; Lan et al., 2000; Garel et al., 2001; Ruoss et al., 2001; Abe et al., 2003; Abe et al.,

2004). In this sense, GA appears to be interrelated with both cortical gyri and sulci measures (Monteagudo and Timor-Tritsch, 1997): as the fetus approaches term, there is an increase of the appearance of gyri and sulci. The early anatomopathological study from Chi et al. (1977) initiated the basis of the two trends in the sequence of fissural, sulcal, and gyral development. Firstly, the mediolateral trend, by which sulcal variability develops from the medial to the lateral part; secondly, the posterior-anterior trend, by which sulci develop from posterior to anterior regions. Figure 2 illustrates the temporal trends in the gyral and sulci development (Encha-Ravazi and Sonigo (2003) synthesize main features of this development). In 1996, van der Knaap et al. reported the latest areas to be developed by a visual MRI introspection in preterm and term neonates and they corroborated that brain gyration and sulcation development was latest in the frontobasal and frontopolar areas and the anterior part of the temporal lobe. Abnormalities in the predictable maturation in fetal brains can be indicating pathological situations (Slagle et al., 1989; Levine and Barnes, 1999).

1.3.3.1. Gray and white matter development during normal human brain maturation

Structural integrity and maturity of brain tissues result essential for the developmental descriptions of brain. Thus, some time ago post mortem studies provided information of WM integrity (Benes et al., 1994), and nowadays despite MRI techniques can dilute gray matter (GM)-WM brain tissue differentiation (depending on the quality of acquisition), their approach can let us *in vivo* assess GM and WM development with the possibility of combine it with simultaneous neuropsychological and behavioural data collection.

Maturation processes underlying the brain evolution have been widely accessible by different MRI techniques, such the *in vivo* diffusion tensor imaging (DTI) approach or the T1-weighted conventional MRI. With increase computational complexity, approaches

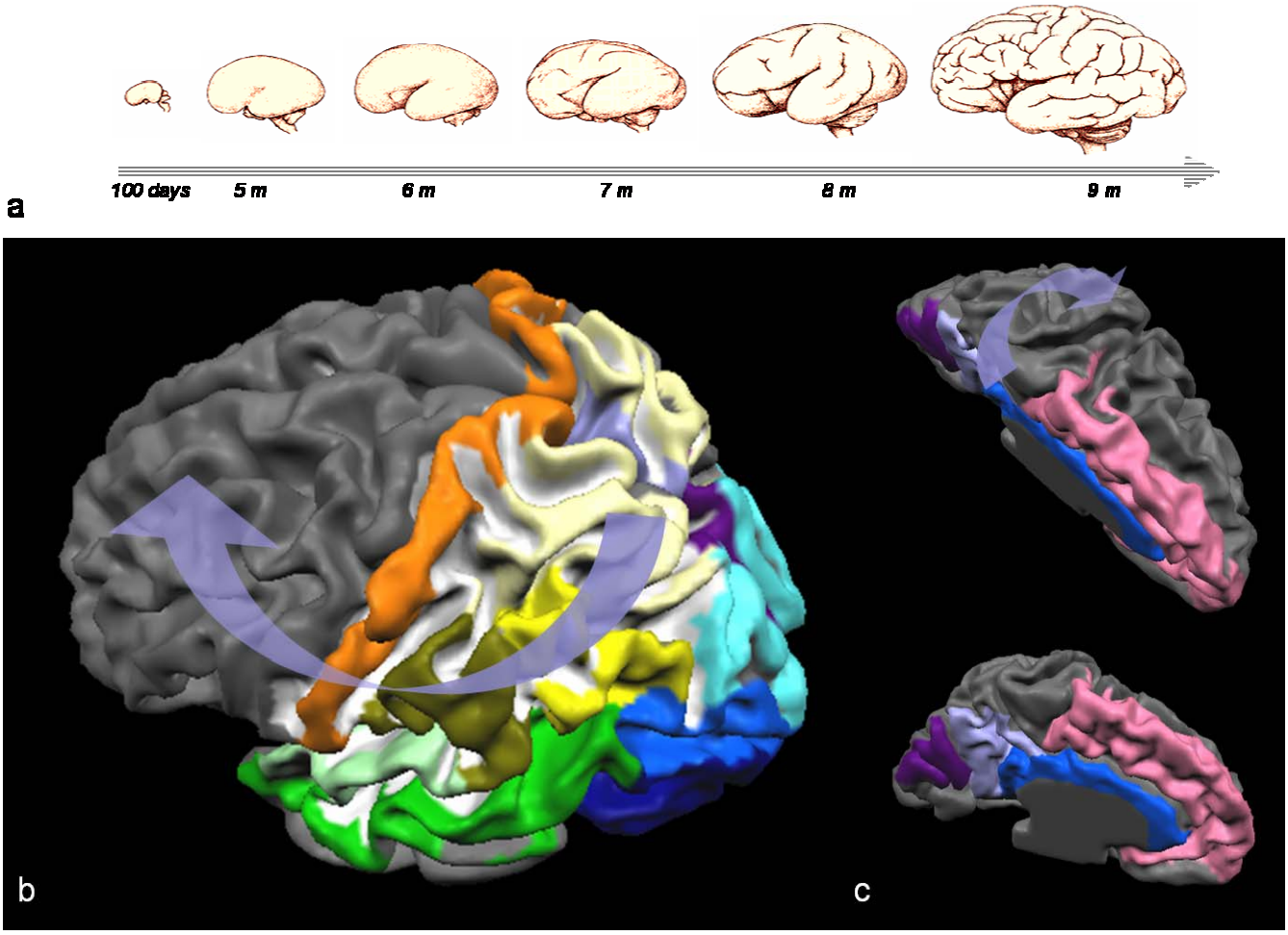

Figure 2. Gyral and sulci temporal development. a) Ontogenesis of the nervous system; b) posterior-anterior trend; c) mediolateral trend. *Image sources*: a) http://www.brainmuseum.org/location-use/index.html; b & c) BrainVoyager program. *Abbreviation*: m, months of gestation.

such as voxel-based morphometry have the capacity to show subtle structural brain alterations.

Diffusion anisotropy provides an early assessment of brain maturation and precedes the information of conventional T1-weighted images (Wimberger et al., 1995; Takeda et al., 1997). Diffusion tensor imaging uses the fractional anisotropy (FA) and the apparent diffusion coefficient (ADC) to determine brain tissue integrity and map the fiber tracks orientation (Shimony et al., 1999; Melhem et al., 2000; Kubicki et al., 2002), reflecting the microstructural measurements of brain water diffusion process *in vivo*, and giving an idea of the developmental changes in normal and abnormal maturation at different stages (Le Bihan, 2003; Miller et al., 2003a).

Major WM tracts visualization can be feasible by DTI at early stages, despite low anisotropy (Yoo et al., 2005; Mukherjee and McKinstry, 2006). First investigations of normal human brain maturation with DTI were performed in preterm and term neonates (Toft et al., 1996; Huppi et al., 1998; Neil et al., 1998; Tanner et al., 2000), in childhood samples (Mukherjee et al., 2001), and in subjects from newborn to early adulthood (Engelbrecht et al., 2002) free from brain lesions. These studies reported ADC decreases in both GM and WM and FA increases, especially in WM, with age. Factors that contribute to these results would be decreases in brain water content and formation of barriers to water mobility, and increases of WM myelination (the analysis of how exactly brain maturation influences the eigenvalues of the diffusion tensor has been described in Mukherjee et al., 2002). Decreasing ADC and increasing FA with increasing GA have also been corroborated in posterior studies of preterm newborns near term (Miller et al., 2002; Partridge et al., 2004). There has also been demonstrated a correlation between WM tissues maturation and anisotropy value changes in full term newborns (Boujraf et al., 2002). Regarding region-related FA values, some of these DTI studies of healthy preterm samples at term equivalent age reported a concrete age-related pattern of FA in motor and sensory tracts, indicating an increase of the tract-specific diffusion parameters with the increase of age (Miller et al., 2002; Schneider et al., 2004; Berman et al., 2005). A recent study from Partridge et al. (2005) estimates the diffusion tensor tractography as a good approach to obtain more details of WM maturation, allowing quantitation along the entire tract. Comparing WM maturity attending the different pathways in premature newborns seems to be a differentiation between commissural tracts and deep projections and subcortical and associative pathways, being the first two areas mature before in the brain development. No left-right hemisphere maturational asymmetries have been found (Partridge et al., 2004). For cortical GM development in healthy preterms, there seems to be a specific relationship between water diffusion coefficients and GA. In concrete, McKinstry et al. (2002) reported a decrease in diffusion anisotropy with increasing GA (from 32 GA weeks). A study in healthy at-term neonates demonstrated that FA values vary regionally showing the major WM tracts higher FA values than the GM areas (Zhai et al., 2003).

While several DTI studies have consistently showed FA increases through infancy and childhood, there are few investigations that evaluated differences in WM diffusion as a function of age in healthy children and adolescents. In normal subjects, DTI studies indicate a slow WM maturation until the young adult period, showed by increases in WM density and organization (Snook et al., 2005), that indicates a long term period of WM maturation, and then a possible reestructuration after early brain injury. Concretely, from a healthy sample between 5-18 years age, Schmithorst et al. (2002) reported a positive correlation of anisotropy and negative correlation of ADC with age in WM, reflecting brain maturation. Another investigation delineated the exact spatial development of WM pathways in normal developing children and adolescents, between 6 to 19 years, combining both a DTI and a voxel-based morphometry approaches (Barnea-Goraly et al., 2005). The authors reported positive correlations between FA and age in the prefrontal area, internal capsule, pathways extending within the basal ganglia, regions between the basal ganglia and the thalamus, cortico-thalamic and cortico-spinal tracts extending from sensory-motor regions, or in intrahemispheric tracts, among other regions. Voxel-based analysis revealed parallel WM density increases with age in some of the mentioned areas. Thus, this study demonstrated WM anisotropy changes during childhood to adolescence in regions related to attention, cognition, memory or motor abilities. Currently, there is a database of DTI images in early childhood to be used as a normal standard of reference for diagnosis of normal WM maturation or paediatric neurological abnormalities (Hermoye et al., 2006).

The majority of early MRI studies provide qualitative descriptions of T1 and/or T2-weighted images, focusing on the GM-WM contrast and degree of myelination (McArdle et al., 1987; Barkovich et al., 1988; Dietrich et al., 1988; Bird et al., 1989; Christophe et al., 1990; van der Knaap and Valk, 1990), but more recent **T1-weighted conventional MRI** studies also provide detailed information on how

the human brain changes in normal samples throughout childhood, adolescence, and into old age.

There are different examples of regional **WM** maturational changes from childhood to young adulthood. For example, in the second half of the ninety different studies focused on brain development in normal samples reported an increase in the global WM volume from ranges 4-22 years (Giedd et al., 1999a) and 5-17 years (Reiss et al., 1996), and significant positive relationships between WM density and the age of the subjects (ranged from 4 to 17 years) in the internal capsule and the left arcuate fasciculus (Paus et al., 1999). Another example of regional WM maturation depending on the age is the corpus callosum (CC). The fetal CC is an important WM fiber tract that can be considered a sensitive indicator for normal brain development and maturation. Structural changes on it can disturb a correct cognitive development. During fetal life, its fibers starts to develop at 12 weeks of gestation, the maximal growth of width and thickness is observed between 19 and 21 weeks of gestation, and by 21-22 weeks the CC is recognizable with its genus, body and splenium. It continues to grow and develops caudally during the whole gestation period (Achiron and Achiron, 2001). Thus, CC length, width and thickness increases are functions of GA, and at prematurity this normal development is interrupted. In a recent ultrasonography study in a VLBW sample, Anderson et al. (2005) reported that the CC grows at a much lower rate postnatally than in utero conditions among very premature infants. From childhood to adolescence, the rostro-caudal growth is also detected by tensor maps in young normal subjects scanned across the time (aged 3-15 years) (Thompson et al., 2000). There is also the fact that posterior part of CC seems to present continuous aged-related changes (Giedd et al., 1996a; Giedd et al., 1999b).

Formation of interhemispheric structures, such as the CC, is related with the fetal ventricular system configuration. Ventricular size has been shown to decrease with GA (Lan et al., 2000). An abnormal development of brain ventricles at fetal MRI has been related to different central nervous system anomalies at long term (Levine et al., 2002).

Some MRI studies have also been focused on the **GM** differences in brain maturation between childhood, adolescence and young adulthood (Giedd et al., 1996b; Giedd et al., 1996c; Reiss et al., 1996). In general, these studies have revealed a regional and temporal pattern of progressive cerebral changes between childhood to adolescence and adult age. More recently, brain maturational investigations by a voxel-by-voxel analysis demonstrated that dorsal-parietal and frontal cortex mature between childhood to adolescence (Sowell et al., 1999a), that after adolescence there is an increase in frontal and striatal brain maturation (Sowell et al., 1999b), an accelerated growth in frontal and lateral temporal regions, and a specific density reduction in dorsal frontal areas (Sowell et al., 2001). A previous study from Thompson et al. (2000) coincides with these results and reports that between ages 9-13 years brain growth is most pronounced in lateral parieto-temporal regions (Paus (2005) widely reviews mapping brain maturation during adolescence). Regarding cortical asymmetries during normal development, results from the same Sowell's group (Sowell et al., 2002) showed that there were some cortical asymmetries (in perisylvian cortices) that continue to develop between childhood and young adulthood, being bigger at adult stages. These differences may be related to changes in cognitive abilities and have an importance to interpret the abnormal brain development, especially in certain regions, such as the aforementioned perisylvian cortice.

In the study from Giedd et al. (1999a) the authors did not find the same global developmental increase for GM as they reported for WM. Main developmental peaks for GM were found exclusively in the frontal and parietal lobes in a sample with a mean age of 11 years. After that, they reported a decrease in GM volumes in these regions. Similar results were found by other investigators, previously cited (Sowell et al., 2001). There is an interesting study from Gogtay et al. (2004) that establishes a dynamic map of GM maturation during the pre and postpubertal period (mean age scan 1: 10 years; mean age scan 4: 17 years) during normal brain maturation. Summarizing main results, the authors found that the maturational sequence of GM cortex agrees with regionally functional development; in this sense, the parts that mature earlier are those associated with basic functions (motor and sensory brain areas), and later to mature were association areas which contains executive functions, motor coordination and attention. In addition, the authors observed temporal lobes appeared the last to mature with the exception of the temporal pole, which shows GM loss (maturation) around the same time as the frontal and occipital poles. It seems that there is an agreement across the above studies in the fact that cortical GM changes in a non-linear trend from childhood to adolescence, and that there are age-related development differences depending on the brain region. Of note here, on july 2006 is gone to be available a new multi-center public database from a

large sample aged 7 days to 18 years (> 400 subjects), including MRI/clinical and behavioural data to have a global characterization of healthy brain maturation in relation to behaviour (Evans and Brain Development Cooperative Group, 2006). In this project, the previously mentioned DTI database is included as an auxiliary project.

Previous studies of healthy children and adolescents showed age-related linear increases in brain GM and WM (Giedd et al., 1999a; Giedd et al., 1999b; Thompson et al., 2000), but in the *in vivo* study of brain development across the time, the sex can influence such differences. A study from De Bellis et al. (2001) suggests that there are age-related sex differences in brain maturation. The authors reported that girls (mean age 12 years) showed significant developmental brain changes with age but at a slower rate than boys. Boys showed bigger GM volume reductions and WM volume increases between 6 and 18 years of age compared to girls. Thus, sex should be bear in mind during observation of differences in brain maturation.

Although there are several studies reporting brain maturational changes in normal subjects, few studies have defined by T1-weighted conventional MR images the developmental changes occurring in preterm infants. A study from Childs et al. (2001) created a scoring system to assess global cerebral maturation in premature infants. All of the infants were born with a postmenstrual age < 14 days prior to the MRI (postmenstrual age is defined as the time elapsed between the first day of the last menstrual period and birth (that is GA) plus the time elapsed after birth). Results showed that a total maturational score (including measures for myelination, cortical folding, germinal matrix distribution and glial cell migration pattern) strongly correlated with postmenstrual age. Battin et al. (1998) evaluated changes in the brains of preterm infants between their birth and term age. During this postnatal extrauterine period, it seems that MRI appearance of the preterm brains was markedly different from that of term infants. The authors reported that in preterms: a) the germinal matrix was apparent on all early images and became much less obvious after 30 to 32 weeks of GA; b) the WM showed a homogeneous appearance and there were bands of increased and decreased signal intensity which were most apparent antero-posterolateral to the lateral ventricles; c) the global level of myelination was reduced compared with term infants; and d) regional cortical folding appearance was related to increases in GA. Relative content of myelinated WM has been reported as an indicator of functional brain maturation (Pujol et al., 2004). Little is known regarding the progression of myelination development in the preterm brain of subjects with a good neurodevelopmental outcome. Precisely, the study from Counsell et al. (2002) evaluated this myelination progression retrospectively in subjects born very preterm with a good outcome at 2 years (corrected age). The authors found an evident myelination in numerous GM and WM structures at $\leq$ 28 weeks. Between 30 and 36 weeks GA, there was an increase in the parts showing myelin that had been identified before 30 weeks of gestation. Of note here, there was no evident visualization of myelin in any new area from 28 until 36 gestational weeks.

Finally, it must be considered that prematurity *per se* condition results different from the intrauterine life. In this sense, there is an interesting investigation from Righini et al. (2003) that investigated GM and WM ADC values in utero in a sample of fetuses ranged from 22 to 35 weeks of gestation with a normal brain. With this, they reported information about prenatal normal brain development, avoiding the study of the preterm state. The authors found similar results that those reported in postnatal studies in preterm babies (Huppi et al., 1998; Neil et al., 1998; Tanner et al., 2000): the mean ADC value for WM was higher than that for the GM; in addition, fetuses presented a negative relationship between GM and ADC values.

It has been described GM and WM brain maturation in infant samples across the time, but emerges the question whether there is a relationship between this maturation changes and developmental changes in brain functionality. Using MRI, Huppi et al. (1996) reported that preterm infants showed a significant degree of brain development over time, nonetheless, exhibited less GM-WM differentiation and less myelination brain degree than full-term infants. In addition, behavioral performance was delayed in the preterm, suggesting that the delays in brain development were parallel in behavior. Pujol et al. (2004) concluded that WM myelination detected by volumetric MRI reflects a progression of functional brain maturation. The authors found that WM myelination progress in language-related areas in children was exponentially related to language production.

1.3.3.2. Functional analyses of the human brain development

Advances in neuroimaging made possible the *in vivo* analysis of the structural brain maturation. In addition, the MRI-based analyses of functional changes derived

from the anatomical findings, including quantitative metabolic cerebral composition and brain activation during development, appear complementary to them (Johnson, 2001). Brain functionality during development has been addressed from different approaches. Two important non-invasive techniques that let us study functional development of human brain are the proton MR spectroscopy (MRS) and functional MRI (fMRI).

Previously, WM and GM microstructure maturation by DTI analyses in normal development has been reported. But, which can be the relationship between this maturation during development and brain activity? From a progress point of view, can we talk in terms of brain activity development? There is an interesting study from Olesen et al. (2003) that gathers together brain maturation (by DTI) and brain activity (by **fMRI**) in a sample of healthy children an adolescents (mean age 12 years). The study demonstrated a correlation in several GM and WM regions between tissue maturation and functional brain activity. Concretely, the authors emphasize that FA values in fronto-parietal WM correlated with brain activity in GM near the superior frontal sulcus and the parietal lobe, and that age appears to influence these maturational network. Thus, functional activity seems to correlate with maturational changes of brain.

Proton MRS provides metabolic information complementary to the non-invasive meuroimaging structural methods availables from conventional MRI (Giedd et al., 1996b). In 1993, Kreis et al. presented the first direct quantitative spectroscopic data of human cerebral development from the neonate to the adult. Main results showed that the water content of cerebral cortex changes drastically over the first months of life; parietal and occipital water content was shown as dependent of GA, being cerebral proton MRS different with brain maturation from infancy to adulthood. For developing GM and WM, however, no differences in water content are evident below about 50 to 70 GA weeks. Regarding concrete metabolites that change during brain development, the authors found that while N-Acetylaspartate (NAA) (accepted not only as a neural integrity and cell dysfunction marker (Demougeot et al., 2001; Block et al., 2002), but also with an important role in osmoregulation and myelin formation (Baslow, 2003)), and less obviously Creatine (Cr) (related with the cell energy (Wyss and Kaddurah-Daouk, 2000)), increase, Myo-Inositol (a glial marker (Griffin et al., 2002)) and Choline (Cho) (a marker for cell membrane integrity and cell density (Gupta et al., 2000)) decrease with age. Kimura et al. (1995) confirmed increases in the NAA/Cho and NAA/Cr ratios in normal developing brain of neonates and infants, with age-dependent changes. Clinical utility of spectroscopy in paediatrics is important for a characterization and often also for diagnostic purposes of brain functionality after PB. Other papers have reported MRS of the brain up to three years of age (Huppi et al., 1995; Cady et al., 1996). These studies consistently showed strong age-related changes, with low NAA levels at birth, increasing in the first years of life, and high levels of Cho and Myo-Inositol, that decrease with age. Changes in NAA values become less pronounced after two years of age (Kreis et al., 1993; Pouwels et al., 1999). More recently, a recent combined brain volume and diffusion study reported that during developing brain and maturation, the most significant changes (brain volume increases and brain diffusion decreases) occurred within the first two years of life (Zhang et al., 2005). Horska et al. (2002) suggested small but significant regional metabolic changes for metabolite rations (but not concentrations) during childhood to adolescence in a healthy sample. The authors observed different age-related changes in the ratio NAA/Cho in GM and WM. The increase in NAA as a function of GA, reflecting neuronal development, has also been reported during perinatal period (Penrice et al., 1996; Kreis et al., 2002) and in utero conditions (Girard et al., 2006). In a large sample of normal subjects between 4 and 88 years old, Kadota et al. (2001) specified that WM NAA/Cho ratio showed a rapid growth during the first decade and reached a maximum value at 19 years old approximately. Since that moment, the authors reported a steady decrease in the WM NAA/Cho ratio continuing into old age. GM NAA/Cho ratio showed a gradual decline from childhood to old age. Moreover, regarding sex differences, the WM NAA/Cho decline was steeper in males. Proton MRS data agree, in general terms, with cognitive and functional status.

1.3.3.3. Effects of immaturity on brain development

It is well-known that PB has an impact on brain development (Inder et al, 2005a). Prematurity has been associated with a risk of the presence of an immature brain and a delayed neurodevelopment (Bhutta and Anand, 2001; Bhutta and Anand, 2002). In addition, the GM-WM contrast appearance of MR images of preterm neonates appears different than those of term newborns, partly because of the structural immaturity of the developing myelin (Miller et al., 2003a). Under some conditions preterm brain maturation occurs in environmental conditions that do not characterize the expected intrauterine state. In this sense, possible questions that emerge are whether extrauterine life provides increasing stimulus for brain development,

whether brain maturation takes place at the same rate as in utero, or whether there is an absence or normalization of preterm brains to term stages. In the present Section changes in preterms are considered from a continuous development point of view.

Previously, it has been cited that some studies of normal human brain have been done in preterm samples. But there is another approach focused on the comparison between the preterm and the term brain normal development to add new information about possible abnormal changes derived from the immature preterm brain. Quantitative MRI studies have demonstrated differences between the preterm brain at term equivalent age and term born infants, confirming a differential development post birth (Huppi et al., 1998; Peterson et al., 2000).

Huppi et al. (1996) demonstrated that brain development in preterms does not normalize at 40 weeks of postconceptional age and described less myelination and a poor differentiation between GM-WM in preterm infants at term compared with full-term infants. The study of Maalouf et al. (1999) also showed that when MR images for preterm infants at term gestation (obtained within 48 hours of birth) were compared with those of a group born at term, preterms presented brain abnormalities and had diffuse and excessive high signal intensity in the WM, possibly associated with WM disease. This maturational delay could be acquired in the period between birth and term. Similar maturational differences were found for the cerebral cortex between extremely preterm infants imaged at term and a term control sample.

A recent study from Deipolyi et al. (2005) evaluated cerebral cortex development exclusively in a group of preterms to relate the decrease in anisotropy during maturation (McKinstry et al., 2002) to gyral development. The authors found a regional heterogeneity in cortical development and concluded that distinc sensorimotor, posterior, and anterior stages of paediatric behavioural maturation may be predetermined by the temporal pattern of regional cortical development prior to term-equivalent age. In addition, though anisotropy and gyration were both dependent on GA, they considered that both variables were not correlated with each other independent of their common association with GA. In agreement with this, a study from Maas et al. (2004) demonstrated different ADC and FA characteristics in the cerebral plates that correlate with the laminar organization during human fetal brain development. A previous study from Ajayi-Obe et al. (2000) had reported a reduction in cortical surface and complexity during development in preterm newborns, suggesting that cortical development is specifically affected in these infants. Limperopoulos et al. (2005a) have recently reported that the growth of cerebellum is particularly rapid during late gestation and that the PB impedes this accelerated growth. Similar findings have been reported for CC that grows in preterm infants at only half the expected rate from birth to term equivalency (Anderson et al., 2005).

A volumetric comparison of regional cerebral lobe development in two groups of children at aged 8 years (preterm and term controls) reported disproportionately increases of frontal and parietal lobe volumes and reduced temporal lobe volumes in preterms compared to controls (Kesler et al., 2004). These findings coincide with previous studies of preterm brain morphology (Peterson et al., 2003). Counsell and Boardman (2005) have summarized main characteristics of the brain growth and development in preterm samples by MRI. Section 1.3.7.1. will widely deal with concrete structural findings in preterms.

From a functional point of view, and remembering the low weight as a predictor of bad long term outcome, there is a study from Hayakawa et al. (2003) that demonstrated a functional maturation delay of cerebral cortex in a group of infants with history of extremely low BW and undernutrition using a serial electroencephalographic approach. This agrees with another electroencephalographic-sleep study from Scher et al. (2003) that described a functional brain dysmaturity (by differences in electroencephalographic-sleep organization) in a sample of preterm neonates compared to full-term controls. In this sense, PB, in addition to other negative fetal and early neonatal factors (i.e., nutritional factors), supposes the infants to be a high-risk group for developing central nervous system impairments.

As proposed previously, spectroscopic studies reveal developmental changes in brain metabolites with age. In addition, there are several transversal studies showing that preterm subjects present brain metabolic abnormalities compared to control samples. These spectroscopic findings will be addressed in Section 1.3.7.3.1.

The immaturity of preterms has also to be considered in relation to the effects of their cerebral response to brain injury. Traditionally, it has been believed that the response of the premature brain to HI is immature, contributing this immaturity to the apparent vulnerability to neuronal injury. But, paradoxically the brain of the preterm is highly adapted and resistant to

asphyxial damage. Of note here, this does not mean that this resistance is absolutely beneficial for the preterm brain. Surprisingly, while the premature fetal response to hypoxia appears to be different to that at term (it has been described the brain injury in the preterms in front of HI (Rees and Inder, 2005)), the response to asphyxia is similar to that observed in mature fetuses (Bennet et al., 1998; Bennet et al., 1999). A previous MRI study from Barkovich and Sargent (1995) reported that preterm infants (<32 weeks of gestation) showed a similar (or even less extensive) injury pattern than that observed in term infants who had profound asphyxia. Paradoxically, preterms can survive longer periods under severe asphyxia than mature subjects by hypotension and hypoperfusion mechanisms (Keunen et al., 1997; Bennet et al., 1999), but precisely these hypotension and hypoperfusion mechanisms increase the risk of GM and WM injury observed in the preterm samples (Gunn et al., 2001).

In summary, neuromaturation characterization it is fundamental to grasp infant neurodevelopment, especially in preterm samples. Understanding normal neuromaturation in the fetus and preterm infants allows for the identification of abnormal brain patterns of structural and functional development (Allen, 2005). Since deficits acquired during critical periods of cerebral development may be permanent, abnormalities in brain suggest a neural substrate for the neurocognitive impairment that is frequently reported in preterm subjects.

1.3.4. Perinatal brain injury in preterm infants

The developing brain is susceptible to damage from ischaemic of inflammatory mechanisms and most of the preterm infants show evidences of brain injury on MRI in the early neonatal period (Maalouf et al., 1999). Selective cellular vulnerability in the developing brain can be defined anatomically by the differential vulnerability of developing neuronal circuits, regionally by the presence of unique cell types, and neurochemically by the expression of signalling receptors for glutamate, and biosynthetic enzymes critical to synaptogenesis. Observations of selective vulnerability often imply concrete mechanisms.

The periventricular area in premature infants is highly vulnerable to hypoxic encephalopathy due to the presence of arterial border zones in this region (Nonaka et al., 2003). Fluctuations in blood pressure are common in preterm samples and the cited region is particularly susceptible to reductions in cerebral pressure or other cerebral blood flow alterations (Volpe, 1992). Below, it is exposed the relevant paper of oligodendrocytes in the pathogenesis of the periventricular damage.

1.3.4.1. Delayed mechanisms of brain injury

Most of brain injuries in the premature infant occur in the postnatal period, and is usually that during this time no evident clinical signs of a possible brain insult appear. So, a delayed recognition of the brain insult impinges on the possibility of an early intervention. Experimental studies in immature animals exemplify the characteristics of delayed cellular injury (Puka-Sundvall et al., 2000; Northington et al., 2001a). Generally, there has been a modification in the classical differentiation between the models of cell death, which are the necrosis and apoptosis. It seems that an interaction stands out at the classical distinction between them. The mechanisms of apoptosis appear to be more important after hypoxic processes than necrosis in the immature brain, compared to mature brains (Nakajima et al., 2000). It appears a new concept, 'an apoptotic-necrotic' *continuum* with an intermediate step during which cells present both necrotic and apoptotic characteristics. In addition, the typology and predominance of neuronal death varies across the regions (Nakajima et al., 2000). Mitochondrial dysfunction plays a central role in the delayed mechanisms of brain cell injury (Puka-Sundvall et al., 2000), activating the caspase-3. The caspase-3 acts as a link between the mitochondrial actuation and the cell death, turning into an important target to incise.

1.3.4.1.1. Pathogenesis of injury to the immature oligodendrocyte

During the third trimester of pregnancy, when PB is most likely to occur, glial cells in the periventricular region are in an active stage of differentiation into specialized subtypes, such as the oligodendrocyte. Oligodendrocytes have been shown to be especially vulnerable to injury in the premature infant (Volpe, 2001b; McQuillen and Ferriero, 2004). This cell type in its immature form presents intrinsic features that underlie its vulnerability to different lesional processes such as the cerebral ischemia (Back et al., 1998). Experimental studies demonstrated that immature oligodendrocytes death by apoptosis after an HI within the first hours post-insult, especially in the subventricular areas and adjacent WM, being the mature oligodendrocytes intact (Skoff et al., 2001). The early cell death cascade after a HI has been previously proved (Fern et al., 2000). An especial

remark should be done to the anatomo-pathological study of Back et al. (2001). This study provides evidences that during the gestational period (when the infant has a high risk for brain injury) the predominant cells are those pre-myelinating immature oligodendrocytes. The authors describe three stages of oligodendrocyte development, attending the GA. Between the 24 and 32 weeks of gestation (an especially vulnerable period for a PVL), the predominant oligodendrocyte is in a pre-myelination phase. Thus, subjects with oligodendrocyte injury before 32 weeks of gestation show a failure in the posterior phase of rapid myelination, resulting in periventricular damage, and possibly present both cerebral atrophy and ventricular dilation. The periventricular brain injury is associated with either focal or diffuse GM and WM damage (i.e. affected structures can include the basal ganglia, hippocampus, the cerebellum and/or the temporal and frontal cortex) (Section 1.3.7.1).

1.3.4.1.2. The role of inflammatory processes in brain injury

Experimental studies demonstrated that HI is directly related to WM injury (Olivier et al., 2005; Meng et al., 2006), particularly in the premature brain (McQuillen et al., 2003). However, there are also evidences of a relationship between brain inflammation processes and cerebral diseases (Nelson et al., 1998). The review from Dammann et al. (2002) relates perinatal infections and inflammatory mechanisms with WM damage and cognitive outcomes in preterm samples. This point of view supposes a link between structural brain damage and cognition (relationship that is going to be developed in Section 1.3.7.2).

Thus, neural injury may also be related to immunological response of the mother to intrauterine infection (Duggan et al., 2001; Hitti et al., 2001; Toti and DeFelice, 2001; Dammann et al., 2002). In the context of maternal infection, proinflammatory cytokines are released by the mother's immune system, reaching the fetus.

Immature oligodendrocytes also appear to be prone to cytokines (Baerwald and Popko, 1998). So, as Dammann and Leviton (1997) proposed, the cytokines may be involved in the induction of WM damage. There are studies that postulate that cytokines amplify the effect of brain injury produced by HI (Kadhim et al., 2001). Brain inflammatory processes by cytokines can be produced by several reaction cascades (du Plessis and Volpe, 2002; Allan and Rothwell, 2003). Considering main complications in preterm (Section 1.3.2.2.), in spite of these cascades of events, cytokines can contribute to the occurrence of IVH (Dammann and Leviton, 1997). Figure 3 shows possible pathways describing how cytokines work on the fetal brain to produce IVH and WM damage.

This model may explain why some infants have more vulnerability to brain damage: the presence of a proinflammatory response in utero lead a high risk for cerebral lesions, predicted early after delivery (Duggan et al., 2001). This has important implications for intervention strategies prior to birth.
Two main interesting points regarding perinatal brain

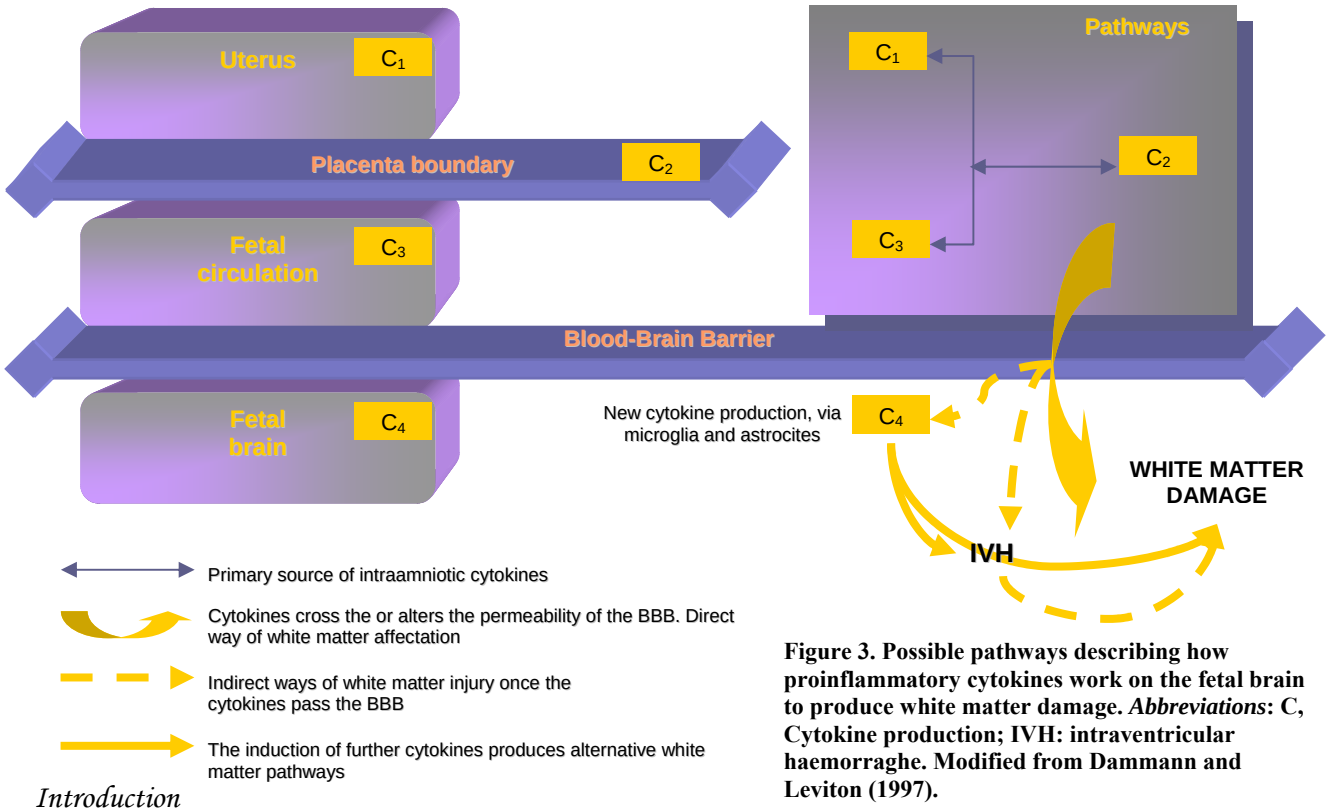

Figure 3. Possible pathways describing how proinflammatory cytokines work on the fetal brain to produce white matter damage. *Abbreviations*: C, Cytokine production; IVH: intraventricular haemorraghe. Modified from Dammann and Leviton (1997).

injury that should be mentioned are the interconnection between normal development mechanisms and injury to the immature brain, as well as the role of brain plasticity mechanisms at long term (du Plessis and Volpe, 2002).

1.3.4.1.3. Specific injury mechanisms within the context of normal development

Specific molecular mechanisms of selective vulnerability in the immature brain should be considered within the context of normal cell and systems development, and developmental differences in cellular defences.

In the immature brain, injury can be easily confused with maturational changes in the cytoarchitecture of the neurons residing there, for example the CA1 region of Ammon's horn, the least mature part of the hippocampal complex at birth (Lopez-Gallardo and Prada, 2001). The maturation of the hippocampus, for example, contributes to lead damage patterns (Towfighi et al., 1997).

Main mechanisms of selective vulnerability in the developing brain include oxidative stress (Buonocore et al., 2002; Kaindl et al., 2005), glutamate receptor-mediated calcium-dependent excitotoxicity (McDonald et al., 1988; Husson et al., 2005), and programmed cell death (Mason et al., 2006; Ueno et al., 2006) (some of the mechanisms have been dealed in McQuillen and Ferriero, 2004; Blomgren and Hagberg, 2006; Becker and Bonni, 2005).

1.3.4.2. Early human brain plasticity

It is well-known that relevant positive or negative experiences may functionally alter human brain (Anand and Scalzo, 2000; Dobrossy et al., 2000; Kaufman et al., 2001; Champagne and Curley, 2005; de Kloet et al., 2005) and it has been assumed that early injury can lead to substantial reorganization and functional recovery (Ewing-Cobbs et al., 2003). In a recent investigation, early brain injury in preterm newborns has been associated with adverse early neurodevelopmental outcome (Miller et al., 2005). Two important points should be mentioned: firstly, outcomes should be assessed longitudinally because an apparent recovery at early ages may be reversed as the brain matures; and secondly, the recovery of a function may be due to the expense of others.

1.3.4.2.1. Early experiences at prematurity

Extrauterine life is not a normal condition in preterm infants. A complete understanding of the critical role of environment at first's days of life in preterm infants in brain development might stimulate research evaluating the adaptive mechanisms of the immature developing brain. For the infant before term, the appropriate physiological environment is the uterus, where the fetus is relatively protected from external stimuli. But the premature infant is exposed to profoundly different acoustic, visual and somatosensory stimuli. With the preterm delivery, the infants are exposed to new gravitational influences, temperature changes, and nutritional alterations, each of which can be considered as a stressor in some cases. So, depending of the type of stimuli at early stage, these environmental challenges can be viewed as benign, enriched or detriments to normal development.

A recent long term investigation focused on effects of early postnatal experience on brain development showed that individual developmental care seems to promote changes in different brain structures (Als et al., 2004). The authors reported a higher relative increase in anisotropy (maturation index) in different brain areas in a preterm subgroup exposed to a high early stimulation compared to preterm infants with no individual developmental care program, as well as they presented changes in functional connectivity and they scored better than the control group at neurobehavioral outcome assessment. Other previous studies demonstrated an effectiveness of sensorial experiences in the newborn intensive care unit environments (Kleberg et al., 2002; Westrup et al., 2000). The study of Als et al. (2004) raises doubt in the classical question whether the extrauterine environment takes away preterm neonates from an appropriate and necessary stimulation (Duffy et al., 1990).

It has been well established the presence of negative effects of stress and painful situations (suctioning, skin puncture, dressing change or removal, discontinuation of intravenous line, and insertion of a nasogastric tube) in the preterm newborn (Modrcin-McCarthy et al., 1997; Grunau, 2002). The brain response to stress in preterm can suppose an increase of the possibility of brain injury and oxidative processes (Anand, 1998; Buonocore et al., 2002). Extrauterine adaptation in preterm infants seems to be more stressful than in term newborns, possibly producing changes in the regularization of the cortisol levels (Peters, 1998). Precisely, the death of brain cells can be induced by effects of cortisol, especially in some vulnerable regions, such as the hippocampus (Zhang et al., 2006).

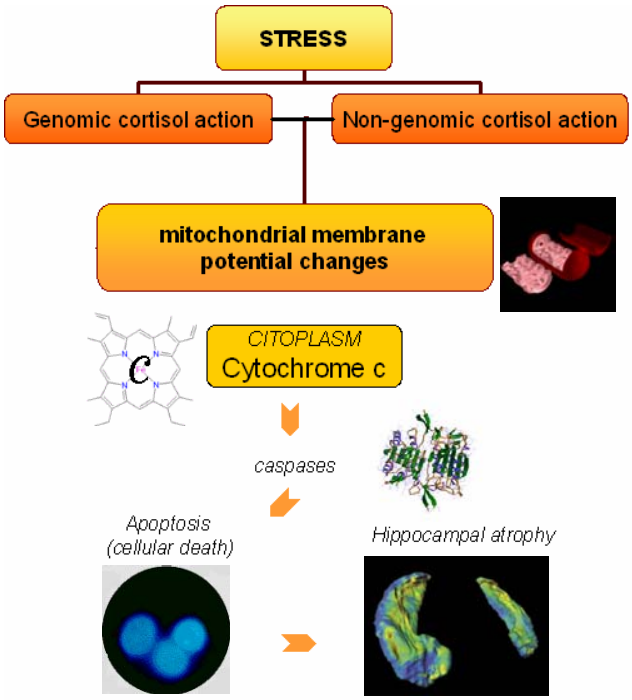

Figure 4. Role of stress-induced mitochondria membrane potential mediated by genomic and non-genomic actions of cortisol in hippocampal cell death. Stress stimuli result in elevation of cortisol. Apoptotic stimuli are transduced to mitochondria through both genomic and non-genomic cortisol action. The changes in mitochondrial membrane potential may cause cytochrome c to be released from mitochondria into the cytoplasm, where cytochrome c promotes the action of caspases and apoptotic process. Modified from Zhang et al. (2006).

Figure 4 illustrates the effects of stress in the hippocampal cell death.

In a review about brain and behaviour changes, Rosenzweig (2003) reported the existence of two different temporal models of plasticity attending differential experience: life-long plasticity and the plasticity in an early critical period. In addition, there is a number of patterns by which different measures of plasticity vary as a function of age. It seems that recovery of a function shows partially life-long plasticity, despite the existence of a critical period for the development of neural circuits and behaviour. In general, animal models have shown that the early perinatal environment and its effects on stress responses may have important consequences at developmental level as a result of plasticity in preterm and vulnerable brains; in human, i.e., a recent study of posttraumatic stress disorder demonstrated specific cerebral GM changes after brain injury (Chen et al., 2006). This fact demonstrates important repercussions on neural plasticity and brain reorganization (Post et al., 1998).

1.3.4.2.2. Brain plasticity at prematurity

Abnormal development of the brain during fetal life is now thought to contribute to the aetiology of many neurological disorders. As exposed above, the preterm brain is particularly vulnerable to damage, especially periventricular brain structures and WM. The timing, severity and nature of specific insults are critical in determining the pattern of injury and thus the extent to which neurological function will be affected postnatally. Defining the causes, patterns and mechanisms of brain injury is crucial to develop rational neuroprotective strategies to reduce the burden of altered brain growth and poor functional and behavioural outcomes (Rees and Inder (2005) review different responses to brain injury during fetal and neonatal periods). Several studies reported global neurobehavioral and cognitive deficits in preterm infants and children, partly derived from brain damage at early stages. Different brain regions continue to develop into the postnatal period (i.e., the hippocampus (Bayer, 1980)), allowing for the plasticity mechanisms of the developing brain to compensate for early damage (Holmes et al., 1998). But, despite there can be a brain reorganisation shortly after an injury, it is questionable whether these deficits persist at long term in adolescents and adult samples. Some literature has led the assumption that when damage to the brain occurs early in life the reorganizational compensatory capacity of the immature brain rescues the possible impaired functions (i.e., memory function), but an alternative view can be postulated. There is increasing evidence about damage in immature brains that interferes with the general cognitive development. Most of the studies showed the presence of selective and global cognitive impairments at long term related to specific brain injury (Section 1.3.7.2.). In this sense, there is an interesting study from Taylor et al. (2004) that demonstrated that the long term consequences of VLBW are consistent with expectations based on early brain damage, suggesting limitations to functional plasticity.

After a brain injury in the PB, several developmental courses are possible: a) development severely compromised because of an important brain damage → not recovery; b) evidence of injury but development proceeds with no sequelae; c) progressive recovery from early developmental impairment may be difficult to appear at early stage but seems to improve with increasing age; d) subtle of absent evidence of cognitive dysfunction in infancy → dysfunctions

appear with increasing age. McGrath et al. (2000) coin this late-emerging dysfunction as a "sleeper effect". The last three developmental courses come close to the concept of brain plasticity. Plasticity should be understood as a dynamic process that fluctuates across the time (Luciana, 2003).

In Section 1.3.3., the cerebral maturation was exposed as the continuum of different stages in the cellular and synaptic development. Relating this idea to the brain plasticity and the effects of PB, it should be mentioned that plasticity varies its incidence depending on the neurodevelopmental stage. In this sense, it has been hypothesized that cerebral plasticity depends on several factors (Chugani et al., 1996), such as the age at injury, size and localization of the lesion, or maturational state of the injured areas. Figure 5 synthesizes the degree of brain plasticity (recovering) following early brain injury, in relation to stages of neurodevelopment.

1.3.4.2.3. Other lesional and cerebral reorganization studies at early stages

The study of brain **language lateralization** has been widely carried out to differentiate samples with early and late lesions. Investigations of language development in children with early brain damage demonstrated cerebral plasticity, which has the capacity of relatively compensate for damage to specific areas. There is an interesting study that showed that congenital focal lesions in any of brain hemispheres determine different patterns of language organization (Brizzolara et al., 2002). The authors reported: a) that children with left lesions showed a right hemisphere superiority on dichotic listening test and that the lesion side had an incidence in the language lateralization (i.e. left lesion → marked left ear superiority → right hemisphere superiority; right lesion → marked right ear superiority → left hemisphere superiority; bilateral lesion → normal right ear values and performance comparable to the unilateral groups); b) lesion site may have contributed significantly to the interhemispheric shift (i.e., all the children who did not show an interhemispheric shift, had lesions not involving language areas and bordering the periventricular WM, whereas children with left lesions at cortical-subcortical level involving language areas presented a right language pattern); c) in children with unilateral damage, size of the lesion was significantly associated with the degree of language lateralization; d) the importance of the timing and type of insult in the language lateralization (only when the left lesions involved cortical-subcortical regions involving temporal lobe and occurred at term age language was lateralized to the right hemisphere; if lesions (in any hemisphere) involved periventricular WM and occurred at preterm stages language was lateralized to the left hemisphere). With these results it can be concluded that the type of lesion, occurring at term or preterm age, may be the primary factor to produce different neurofunctional outcomes.

There is an interesting and detailed study from Bates et al. (2001) that compares language production in unilateral brain-injured children (5-8 years) and adult ($\geq$50 years) samples. The authors showed the presence of cerebral adaptation in children in language processing after brain injury, not observed in adult samples. Adults showed more severe and contrasting profiles of language impairment than children. Children with unilateral brain injury (left or right, without distinction) had a normal language performance compared to normal ranges, and the comparison between children and adults demonstrated a better performance among the children. These results provide evidences for neural plasticity following early brain injury and for differential outcomes in children and adults.

Functional MRI investigations in lesional samples suppose an interesting approach to plasticity and brain reorganisation (Rossini et al., 2004). The clinical literature offers several theories of recovery that can be tested by fMRI (Price and Friston, 2002). There are different examples in literature about brain changes and plasticity following early injury in different kind of samples.

In the face of an **early specific brain lesion**, Cao et al. (1994) investigated the reorganization of the sensoriomotor cortical area after unilateral brain injury in the perinatal period (five of the patients had damage to the left sensorimotor cortex, while one had injury to his right sensorimotor cortex). The authors reported significant increases in fMRI signal in both hemispheres during both normal and paretic hand movements. Concretely, during normal hand task performance, brain activation was observed only in the intact hemisphere; thus, the normal hand was linked to the contralateral hemisphere. During paretic movement, the fMRI signal in the damaged (contralateral) hemisphere was distributed around the lesion, whereas the ipsilateral hemisphere showed an increase of the fMRI signal. The sensorimotor system demonstrated plasticity. The sensorimotor area in the intact hemispheres of hemiparetic patients was substantially activated by ipsilateral motor movement, suggesting a reorganization of this cortical region, despite functional signals in the damaged hemisphere

during paretic movements were also observed. Cortical reorganization of motor areas and the involvement of the undamaged hemisphere in the control of movements have also been reported (Vandermeeren et al., 2003).

There is an interesting study from de Schonen et al. (2005) in term birth children that evaluated whether the face-processing deficit is still present after age 5 years in children who sustained an early unilateral brain lesion and whether the long-term effects of the lesion depend on the period of occurrence of brain injury. Results emphasize that face processing develops poorly in children with unilateral brain lesion, independently from laterality and time of the lesion, and that there is a poor postlesional plasticity. Remembering the previous idea of language lateralization, these results contrast with some studies focused in speech development after early unilateral brain damage (Brizzolara et al., 2002; Hertz-Pannier et al., 2002; Liegeois et al., 2004).

The information provided by studies in **newborns** is important to understand possible processes of subsequent impairment and recovery. Seghier et al. (2004) presented the case of a 3-month-old infant with a left hemispheric lesion involving temporo-parieto-occipital areas. In a visual fMRI task, the infant showed consistent negative cortical responses only in the intact (right) hemisphere (occipital areas) upon visual stimulation; no significant positive responses were observed.

Left-right contralateralization of brain activity has also been reported in studies of **lesions and brain dysfunctions acquired further over perinatal and postnatal ages** (Richardson et al., 2003). Some examples point out: a) the existence of differential activation patterns compared to control samples, with the presence of hypo and hyper activation mechanisms in areas distal to the lesion in *temporal lobe epilepsy* samples (Dupont et al., 2000). This hyper activation found in patients was not efficient, because the performance in the memory task was poor. Of note here, other some studies confirm neuropsychological permanent deficits in patients with unilateral damage in areas specialized in concrete functions (i.e., right hippocampus and spatial memory) (Abrahams et al., 1997); and b) the presence of an hyper activation in ipsilateral (Pantano et al., 2002; Reddy et al., 2002) and contralateral (Pantano et al., 2002) regions in subjects with hemiparesis by *multiple sclerosis* compared to controls. Changes in brain response involved both hemispheres through two mechanisms: the use of ipsilateral corticospinal pathways and the extension of cortical areas normally dedicated to hand movement. The contribution of the ipsilateral motor pathway to the execution of movement after brain damage has been described in most of these studies. Brain reorganization of motor system has also been reported by **other methodological approaches** (apart from fMRI) in other clinical conditions, such as in patients with striatocapsular stroke (Verleger et al., 2003).

Magnetic resonance spectroscopy also provides an approach to the evaluation of brain damage and monitoring its evolution. An example can be found in Duc et al. (1998) that observed how far hippocampal atrophy temporal lobe epilepsy contributes to reversible metabolic disturbances and neurodenegeration in ipsilateral and contralateral functionally related regions. Spectroscopic analysis revealed NAA concentration decreases in both ipsilateral and contralateral to the epileptic focus, being the ipsilateral area more affected. The NAA decrease in the ipsilateral region was related to the degree of hippocampal atrophy. After surgery, a normalization of contralateral signals has been suggested to reflect postoperative recovery of metabolism. Applying this idea to the study of preterm samples, it could be interesting to evaluate metabolic patterns and changes in these samples at long term, after an early brain injury, just to evaluate possible total or partial metabolic recovery.

Literature gives some examples about brain and cognitive reorganization following injury (Chen et al., 2002; Ewing-Cobbs et al., 2003; Levin, 2003; Stiles et al., 2005). Functional MRI and metabolic findings in preterm samples will be addressed in Section 1.3.7.3.

1.3.5. Experimental models of prematurity and immature brains

Evidences from animal models reveal that the process of brain development is robust and ongoing coincident with birth. However, there is increasing evidence from experimental animal models that maturational factors that underlie this robust development may also render the perinatal brain more susceptible to certain forms of injury. The normative sequence of early brain development appears to be similar across mammalian species, but its timing varies (Luciana, 2003). At birth, species differ considerably in terms of where they are situated in the normative sequence. Most of brain animal studies and prematurity have been done with rats. The rat is born > 3 weeks of gestation, and its neuronal migration takes place during the first postnatal week (Figure 5). In this sense, at birth, the rat

is equivalent to a preterm human fetus (approximately to a 5-month-old human fetus). A 5-postnatal day-old rat is equivalent to a human at birth. These relationships must be understood in order to evaluate the experimentally induced early brain injury and to concrete the normal brain development at different stages.

Previously, across different sections there have been succinct references to animal investigations on brain damage and reorganization at prematurity. It can be considered the presence of different focus of study in animal-related brain investigations, such as: a) normal development; b) mechanisms of preterm delivery and associated brain injury; c) models of induced early brain injury (i.e., hypoxic mechanisms have been widely studied in preterm and term samples); d) stress-induced and effects on brain; e) brain plasticity and reorganization after brain injury.

Magnetic resonance imaging is increasingly used in animal studies to provide information regarding to **brain development** in the newborn. In this sense, Inder et al. (2005b) created an unique brain development baboon model (based on conventional MRI, diffusion MRI and histopathology), including PB animals, in which cortical development and WM organization appear to be similar than those observed in human preterm infants. Conventional MRI and histopathology demonstrated similar development of gyri compared to human development (Chi et al., 1977), with the exception that baboon model did not show an evident asymmetry between hemispheres in gyral development, as Chi et al. (1977) reported in humans. Diffusion results correlated with histopathological data and demonstrated that trends in anisotropy in baboons matched those described in human infant studies. In general, this new model had a high similarity in the sequence of brain GM and WM development to that in humans.

Animal models of **early brain injury** have been useful in delineating concrete injured areas and evaluating posterior structural and functional outcomes. Hypoxic insult in the preterm infant disrupts normal development and results in significant cerebral injury. Neurological disability is observed in 51% of premature infants (<25 weeks of gestation) examined at 30 months of age (Wood et al., 2000) and persists into adulthood (Hack et al., 2002). Deficits are found in motor, perceptual, and cognitive systems (Volpe, 2001a). These widespread abnormalities of cerebral development can be measured quantitatively with human MRI, but also with animal models. Experimental studies support the presence of WM damage in immature brains, reflecting damage to WM precursor cells by known mechanisms. Prematurity contributes to myelination disturbances by disrupting

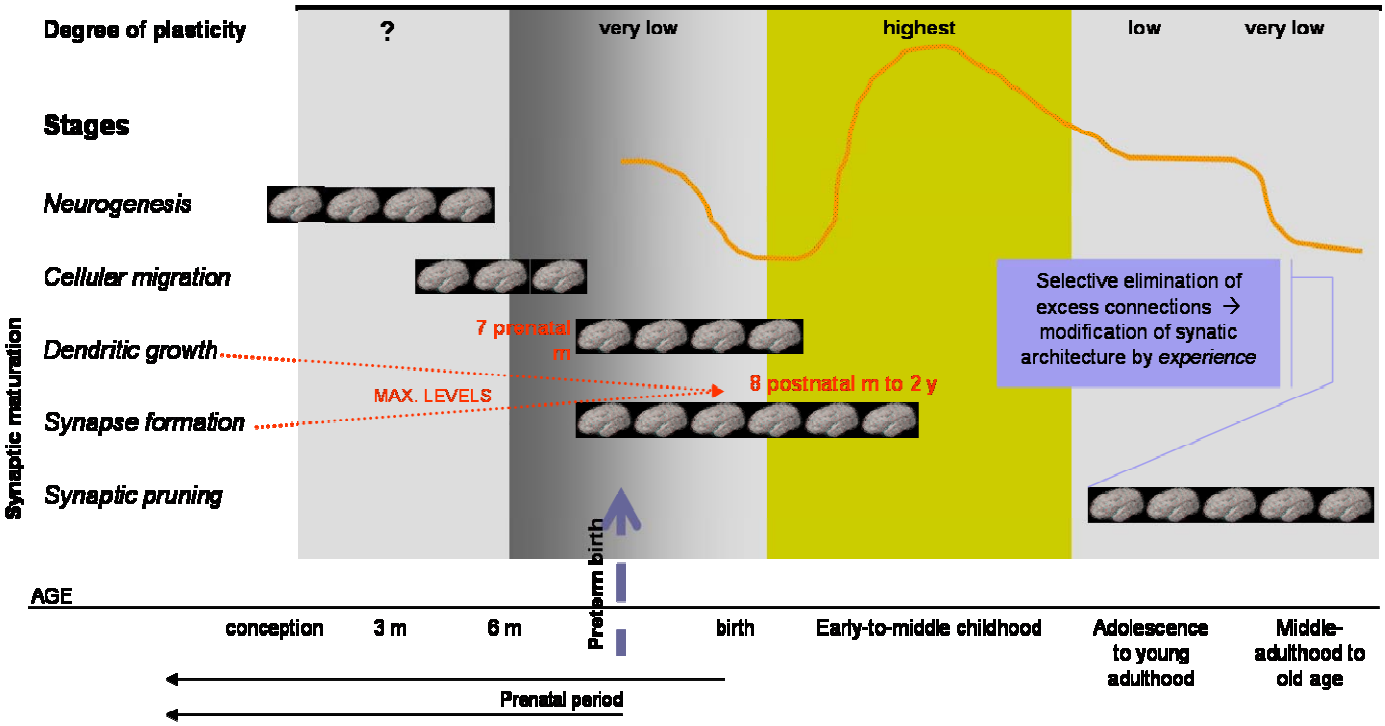

Figure 5. Plasticity attending normal neurodevelopment. Following early brain injury, the plasticity degree varies attending the precise stage of development in which the injury took place. During the second and third trimestres of pregnancy (period that include preterm births) and during the adulthood the plasticity will be very low, periods that correspond to the cell migration and a stabilization of synapsis. Bars indicate approximately the beginning and ending of the different stages in the brain cortex development. In green, the highest plasticity degree period, prior to synaptic stabilization. Orange line indicates the relative plasticity in recovery from frontal cortex injury in the rat across the different stages. Red numbers indicate the beginning of the dendritic growth (during the seventh prenatal month) and the coincidence between the maximal dendritic growth and synaptogenesis (from 8 postnatal months to 2 years). At adolescence, the individual experiences can lead differences in synaptic alterations. Abbreviation: m, months. Adapted and modified from Kolb et al. (2000) and from Luciana (2003).

the maturation of oligodendrocyte progenitors (Back et al., 2001; Back et al., 2002; Chamnanvanakij et al., 2002; Haynes et al., 2003; Back and Rivkees, 2004). Recent evidence demonstrated that vulnerability of immature brains to HI provokes an early WM damage with respect to GM damage (Meng et al., 2006). However, HI can also produce GM damage (Vannucci and Vannucci, 2005). With regard to GM, animal models of HI and infections performed in neonatal rats have shown increased neuronal necrosis in the cortex, striatum, thalamus and hippocampus (Nagata et al., 2000; Despres et al., 1998).

The most frequently used model of HI is the one developed in neonatal rats and/or mice at 7 postnatal days (analogous to the human newborn), that are extremely susceptible to hypoxic brain injury. One of the first studies focused in rats at 7 postnatal days declared that hypoxic damage in immature brains causes neuronal destruction in the same areas than adult animals, but also that the foci of myelin formation in immature brain appear especially vulnerable (Rice et al., 1981). More recent studies in 7-day-postnatal rats reported: an hippocampal delayed cell death with apoptotic-necrotic characteristics and selective to certain subregions (Sheldon et al., 2001); an early and delayed neurodegeneration in different brain areas, where the type of degeneration (apoptosis/necrosis) depends on a) the region, b) the connectivity between these regions, and c) the time of degeneration (Northington et al., 2001b); a prolonged role of apoptosis in the cell neurodegeneration after a neonatal hypoxic insult (Nakajima et al., 2000); a protective effect of Cr (Berger et al., 2004), and of hypoxic preconditioning (Vannucci et al, 1998; Jones and Bergeron, 2004), by providing an increase of glycogen (Brucklacher et al., 2002), to cerebral HI in immature rats, among other things. A recent interesting study provides further insights into the neurodegeneration and apoptotic processes in early brain development. Jiang et al. (2005) postulate that the presence of the *survivin* gene, a member of the inhibitor of apoptosis protein family (Ambrosini et al., 1997), is essential during early development for the survival of neurons, and has an impact on neural plasticity at early stages.

There are investigators that have induced injury at early stage of development of rats (0-3 day's postnatal age), equivalent to the human very preterm stage. Sizonenko et al. (2003; 2005) induced a unilateral HI in very preterm rats and showed a cortical volume reduction, an alteration in myelination, a persistent gliosis, and axonal outgrowth in preterm rats compared with more mature infant rats. These findings appear similar to some of the findings in the human premature infant with PVL. In this sense, another study from McQuillen et al. (2003) induced a neonatal rat model of preterm HI injury that produces similar features than the human PVL, and found a selective subplate neuron death and an age-dependent and region-specific injury. There are other interesting studies (Nuñez et al., 2003a; Nuñez et al., 2003b) that propose a different model of HI injury in the premature infant. They showed that muscimol (selective γ-aminobutyric $acid_A$ [$GABA_A$] receptor agonist) exposure on preterm period produced a reduction in the number of hippocampal cells (the various subregions of the hippocampus showed differential sensitivity to muscimol-induced damage) (Nuñez et al., 2003a). This goes accompanied by moderate deficits in hippocampus-dependent behaviours in the prepubescent rats (Nuñez et al., 2003b). The lack of profound behavioural deficits following a hippocampal cell reduction has been previously reported (Jeltsch et al., 2001). A long term study of sequelae of prenatal asphyxia in the aging rat showed that asphyxiated animals presented a significant impairment in relearning ability (Morris Water Maze) (Weitzdoerfer et al., 2002). In a complementary study, Nuñez and McCarthy (2003) demonstrated that in the same model of preterm infant HI, the administration of extradiol exacerbates damage subsequent to the insult. Opposite to the studies of Nuñez et al. (2003a; 2003b), and applying a model of global asphyxia in preterm rats, Scheepens et al. (2003) found a specific increase in hippocampal proliferation in the preterm rats at equivalent term age (5 postnatal days). This may be because neural proliferation is already maximally activated during early postnatal life in the rat. Schwartz et al. (2004) demonstrated that chronic exposure to hypoxia during perinatal period produces decrements in the volume of cerebral cortex and cell number. They reported different stages in the loss of cells: first, a period with a reduction of glial cells; second, a loss of cortical neurons. This suggests that alterations may depend on the stage of cell differentiation.

A study from Graulich et al. (2002) reported the effect of high and low reoxygenation modes following hypoxia. They demonstrated a larger hypoxia-induced cell injury after hyperoxic reoxygenation (defined as 85% oxygen concentration) than after normoxic reoxygenation (defined as 19% oxygen concentration). This fact indirectly indicates a neural damage effect of high reoxygenation that might be due to a reduced antioxidant capacity in newborns (Buonocore et al., 2002), and has important repercussions in newborn infants requiring assisted or artificial ventilation.

Apart from rat and mouse studies, experimental studies of ischemia in fetal sheep have demonstrated a relationship between the degree of WM injury and the maturational brain stage. Thus, it has been demonstrated an increase in the vulnerability of immature fetuses to WM damage, especially at midgestation (Reddy et al., 1998; Mallard et al., 2003). White matter affectation by systemic endotoxemia to fetus and neonates has also been reported in other species (Young et al., 1983; Yoon et al., 1997). The previously cited baboon model of prematurity (Inder et al., 2005b) also studied the pattern of cerebral damage in preterm animals, in which there was no induced brain damage to the developing brain other than that associated with standard neonatal intensive care. They found brain weights reductions, regional cell loss (in hippocampus, basal ganglia, and cortex) and an associated reactive astrogliosis in the preterm baboons compared to controls. Histological examination revealed that the most important brain damage was the WM injury and the haemorrhage. These patterns of cerebral injury had been previously reported (Dieni et al., 2004).

Animal models are also essential for investigating the pathways that promote **preterm delivery**. In this sense, the role of inflammation or infection has been widely reported to affect PB (Goldenberg et al., 2000; Yoon et al., 2001; Ustun et al., 2001; Goncalves et al., 2002; Elovitz et al., 2003; Elovitz and Mrinalini, 2004). The mechanisms leading to brain injury and the risk variables for adverse long term neurologic outcome in the preterm have been recently studied in mice (Elovitz et al., 2006). The authors investigated the activation of cytokines in rats at 79% of gestation (corresponds to about 28-29 weeks of gestation in humans) in a model that reproduces both intrauterine inflammation and preterm delivery. They found an activation of cell death pathways and an increase of neurotrophic factors by the effect of intrauterine inflammation. This fact supposed an alteration in the glial proliferation and a loss of oligodendrocyte precursors. The interest of this study is that the authors closely approximated what occurs clinically in most cases of PB.

Following a cerebral injury, the immature brain is capable of a compensatory **reorganization**. Jansen and Low (1996) induced a unilateral HI brain injury in 7-day-old rats to observe anatomical changes in the undamaged contralateral hemisphere. They reported that the contralateral hemisphere showed a hypertrophy, and that this hypertrophy was accompanied by a better sensoriomotor performance. The reorganization in the corresponding contralateral regions to a unilateral lesion has been previously reported (Ono et al., 1990; Towfighi et al., 1994). In an experimentally traumatic brain injury (by a controlled cortical impact that produced neuronal loss in the neocortex and in the underlying CC and hippocampus) in immature rats (17-day-old rats, equivalent of >1 human month), Card et al. (2005) found a plastic reorganization of neocortical and hippocampal circuitry, by the incorporation of polysynaptic circuits that project to the affected areas in the injured hemisphere.

Regarding the induced brain injury in immature brain and the presence of enriched environment conditions in postnatal ages (that are found to have positive effects on brain), some authors reported that the possibility to benefit from environmental stimulation following brain injury (by plasticity mechanisms) is relative and depens on the time after injury. Giza et al. (2005) demonstrated that immature animals with a moderate traumatic brain injury and a posterior enriched environment had disturbances in an experience-dependent behavioural plasticity and persistent deficits in both learning and memory. Moreover, animals with an enriched environment shortly after brain damage showed less benefit than animals with a delayed enriched environment after injury. These data display a possibility to state that the timing of environmental change has important implications for post-injury functional outcome.

Apart from the studies related to direct induced brain damage, there is an interesting area of study related to stress and the effects on brain damage. Some experimental studies investigate the effects of stress responses (stressful situations: maternal separations of repetitive acute or inflammatory pain) on the cognitive, behavioural and neuroendocrine responses at long term (Liu et al., 1997; Liu et al., 2000; Anand et al., 1999; Ruda et al., 2000). Basically, it seems that stressfull situations can alter the normal brain development and responses (Anand et al., 1999). A current hypothesis states that stress contributes to impairment in learning and memory (El Hage et al., 2006). A study from Poland et al. (1999) created a prenatal and postnatal stress situation and evaluated the metabolic changes in adult male rats. They found a decrease in the NAA in perinatally stressed rats compared to a control sample. This finding provides support for the perinatal stress model to have importance to the study of neurodevelopmental alterations.

In summary, animal models afford similarities to human models in terms of fetal characteristics and outcomes, biological mechanisms, brain injury, and

recovery. Based on these experiments, several predictions can be made regarding outcomes in humans with early abnormalities in the neonatal period.

1.3.6. Cognitive and neurobehavioral functions in preterm

Several studies have shown that prematurity has a negative impact on cognitive outcome. Longer term follow up studies of infants with PB have almost invariably shown a presence of behavioural and learning difficulties at school age (Marlow et al., 1993; Powls et al., 1995) (Tables 2 and 3). Even those subjects with uncomplicated neonatal courses frequently present cognitive and learning difficulties and school functional limitations (Sykes et al., 1997; Botting et al., 1998; Msall and Tremont, 2002). Results are fairly consistent, showing a wide spectrum of intellectual and behavioural impairments (Aylward, 2005).

Neuropsychological studies of premature children include deficits in global intelligence, language development, attention and visuoperceptual memory impairments and frontal lobe dysfunctions. Memory impairment appears as one of the most important cognitive deficits. In the immature brain, it may be responsible for learning disabilities during schooling.

Table 4 summarizes and simplifies some of the main neuropsychological findings from studies in preterm samples in the last ten years (there is a previous meta-analysis from 1980 to 2001 that explores the cognition and behaviour in children $\geq$ 5 years old (Bhutta et al., 2002)). Globally, the age of the studied cohorts ranges from 7 months to 20 years, being the most common sample type schoolchildren with a mean age of 9 years old. Most of studies are focused in samples with a GA $\leq$ 30 weeks. The most common pattern of neuropsychological impairment observed was of compromise of multiple areas, with IQ being reflecting this global cognitive deficit. In fact, the last two years integrate majority of studies reporting this deficit (Table 4). Moreover, preterm samples were reported to exhibit also an increased risk of impairments in specific functions such as motor and sensorial abilities, attention, language, and memory, compared to control samples.

During infancy, attention appears to be compromised and notably problems in this area contribute to apparent deficits in recognition memory (Rose et al., 2001). It seems that these deficits are more related to an inability to encode visual information in a developmentally appropriate length of time than to poor memory retrieval. As Table 4 shows, delays in the development of executive functions and motor abilities are also normative within this population (de Haan et al., 2000). The findings from de Haan et al. (2000) showed that even very healthy preterm infants may exhibit deficits in executive functions as these skills are beginning to emerge in the late stages of the cognitive development. Similarly, the study of Ross et al. (1996) reported impaired spatial working memory abilities in 2-year-old preterms.

Several studies demonstrated that deficits in infancy persist into early childhood. Thus, a 'normal' classification of preterm at infancy seems a relatively poor predictor of later functioning, because subtle neuropsychological abnormalities became evident as preterm children approached school age. As an example, Fazzi et al. (1997) showed that infants identified as normal at 24 months of age and described as having minor abnormalities at ages 5-7 years exhibited motor skills impairment relative to their verbal abilities. Dewey et al. (2000) demonstrated that preterm children, labelled as 'developing normally' at age of 3 years, at ages 6-14 years showed school difficulties, impairments in language skills, motor functions and had low IQ.

Paying attention to the functioning during preschool and school age in preterm, there are different investigations that have reported that preterm children are more likely than full-term children to encounter academic difficulties, requiring educational support (Table 3). Interestingly, deficits in global IQ are consistently found in studies that report school difficulties. Other specific domains have been widely reported to be impaired in preterm between the ages of 5 and 9 years: selective deficits in memory, language, motor skills, executive functions and visuo-perceptive abilities are emphasized.

Table 2. Behavioral and emotional disorders

	Specific findings	Preterm sample Age (GA and/ or weight)	Study
Behaviour disorders	Conduct problems, anxiety/withdrawal Premorbid adjustment Emotional maturation, hyperactivity[1], motor control, ability to accomplish a work Emotional and conduct problems	7 y (mean 28 w) 14-15 y (<33 w) Mean 5 y (mean 31 w) Mean 9 y (< 28 w or < 1000 gr) Mean 15 y (<33w)	*Horwood et al., 1998* *Stewart et al., 1999* *Torrioli et al., 2000* *Anderson et al., 2003* *Nosarti et al., 2005*
Psychopathological symptoms		Mean 20 y (mean 30 w)	*Hack et al., 2004*
Separation anxiety disorder		8 y (29 w)	*Peterson et al., 2000*
Anxiety, depressive symptoms		12 y (<1500 gr)	*Botting et al., 1997*
Simple phobias		8 y (29 w)	*Peterson et al., 2000*
Sleep-Disordered breathing		8-11 y (<36 w) Mean 10 (8-11) y (>999- <2500 gr)	*Rosen et al., 2003* *Emancipator et al., 2006*

All studies compare preterm samples with a control group.
Abbreviations: GA: gestational age, gr: grams, w: weeks, y: years.

Table 3. School difficulties

	Preterm sample Age (GA and/ or weight)	Study
School difficulties and assistance needs (extra educational support)	12 y (<1500 gr) 7 y (mean 28 w) 14 y (mean 27 w, ≤ 1000 gr) 20 y (mean 30 w) 8-11 y (mean 28 w ≤ 1000 gr) 14-15 y (≤32 w) 8 y (<30 w)	*Botting et al., 1998*** *Horwood et al., 1998* *Saigal et al., 2000* *Hack et al., 2002* *Saigal et at., 2003* *O'Brien et al., 2004** *Wocadlo & Rieger 2006*

Most of studies compare preterm samples with a control group. Exceptions:
* longitudinal comparison of preterms at 15 y compared to their performance at 8 y.
** longitudinal comparison of preterms at 12 y compared to their performance at 6 y.
Abbreviations: GA: gestational age, gr: grams, w: weeks, y: years.

[1] Here, authors frame hyperactivity as a factor related to social behaviours.

Table 4. Main neuropsychological impaired functions

	Specific findings	Preterm sample Age (GA and/ or weight)	Study
Primary functions: visual-motor functions	Global visual-motor skills	5 y (<1500 gr) 5 y (≤32 w) Mean 16 y (mean 30 w) 3-4 y (30-34 w)	*Goyen et al., 1998* *Luoma et al., 1998* *Taylor et al., 2004* *Caravale et al., 2005*
Visual abilities	 Visual impairment and stereopsis	5.5-7 y (<34 w) 11 y (26 & 29 w) Mean 5 y (mean 31 w)	*Krageloh-Mann et al., 1999* *Hack et al., 2000* *Torrioli et al., 2000*
Motor and sensorial abilities	Both fine and gross motor skills Chronic motor tics	Mean 7 y (< 30 w & < 1500 gr) 6 y (<1500 gr) 5 y (<1500 gr) 5 y (≤32 w) 12-13 y (mean 29 w) 2, 6 & 9 y (<2000 gr) 8 y (29 w) 14 y (mean 27 w) Mean 5 y (mean 31 w) 8 y (< 37 w) 20 y (mean 30 w) Mean 9 y (< 28 w or < 1000 gr) 7-8 y (<32 w) Mean 5 y (< 37 w & < 1501 gr) 14-15 y (≤32 w) 8 y (<30 w)	*Korkman et al., 1996* *Skranes et al., 1997*● *Goyen et al., 1998* *Luoma et al., 1998* *Cooke & Abernethy, 1999* *Pinto-Martin et al., 1999* *Peterson et al., 2000* *Saigal et al., 2000* *Torrioli et al., 2000* *Yliherva et al., 2001* *Hack et al., 2002* *Anderson et al., 2003* *Foulder-Hughes & Cooke, 2003* *Bohm et al., 2004* *O'Brien et al., 2004** *Wocaldo & Rieger 2006*
Attention (& processing speed)			
Attention deficit with or without hyperactivity	Attention impairment Inattention/hyperactivity Related to recognition memory impairment Processing speed	12 y (<1500 gr) 8 y (31 w) 7 y (mean 28 w) 12-13 y (mean 29 w) 5.5-7 y (<34 w) 8 y (mean 29 w) 5, 7 & 12 months (<1750 gr) 15-16 y (<31 w & < 1500 gr 5, 7 & 12 months (<1750 gr) 7-8 y (<32 w) 11 y (mean 29 w) 3-4 y (30-34 w) 7 months & 2-3 y (mean 30 w)	*Botting et al., 1997* *Olsen et al., 1998* *Horwood et al., 1998* *Cooke & Abernethy, 1999* *Krageloh-Mann et al., 1999* *Peterson et al., 2000* *Rose et al., 2001* *Abernethy et al., 2002* *Rose et al., 2002* *Foulder-Hughes & Cooke, 2003* *Nagy et al., 2003* *Caravale et al., 2005* *Rose et al., 2005*

Continue...

Freedom for distractibility	Sustained concentration	Mean 7 y (< 30 w & < 1500 gr) Mean 13 y (≤30 w) Mean 9 y (< 28 w or < 1000 gr)	*Korkman et al., 1996* *Isaacs et al., 2000* *Anderson et al., 2003*
Global executive functions		7-9 years (mean 30 w) Mean 9 y (< 28 w or < 1000 gr) Mean 5 y (< 37 w & < 1501 gr) Mean 16 y (mean 30 w) 3-4 y (30-34 w) 7 months & 2-3 y (mean 30 w)	*Luciana et al., 1999* *Anderson et al., 2003* *Bohm et al., 2004* *Taylor et al., 2004* *Vicari et al., 2004* *Rose et al., 2005*
Visual-perceptive abilities	Visual-spatial functions	5 y (<1500 gr) 8 y (31 w) 15 y (≤30 w) 3-4 y (30-34 w)	*Goyen et al., 1998* *Olsen et al., 1998* *Isaacs et al., 2003a* *Caravale et al., 2005*
Language	Reading Female superior than male in hearing and speech Vocabulary delays Verbal fluency Verbal fluency Picture vocabulary	3-4 y (≤32 w) 14-15 y (<33 w) 2 y (mean 27 w) 14-15 y (<33 w) 5 y (≤32 w) 14-15 y (<33 w) 8 y (< 37 w) Mean 9 y (< 28 w or < 1000 gr) 8-11 y (mean 28 w ≤ 1000 gr) Mean 5 y (< 37 w & < 1501 gr) Mean 16 y (mean 30 w) 3-4 y (30-34 w) Mean 10 y (8-11) (>999- <2500 gr)	*Briscoe et al., 1998* *Stewart et al., 1999* *Hindmarsh et al., 2000**** *Allin et al., 2001* *Briscoe et al., 2001* *Rushe et al., 2001* *Yliherva et al., 2001* *Anderson et al., 2003* *Saigal et al., 2003* *Bohm et al., 2004* *Taylor et al., 2004* *Caravale et al., 2005* *Emancipator et al., 2006*
Calculation	Arithmetic and coding Mathematics reasoning and numerical operations Mathematical skills	8 y (31 w) Mean 13 y (≤30 w) 14 y (mean 27 w) Mean 15 y (≤30 w & ≤ 1500 gr) Mean 9 y (< 28 w or < 1000 gr) 8-11 y (mean 28 w ≤ 1000 gr)	*Olsen et al., 1998* *Isaacs et al., 2000* *Saigal et al., 2000* *Isaacs et al., 2001* *Anderson et al., 2003* *Saigal et at., 2003*
Memory	Invisible displacement task (Piaget: remembering an itinerary and in the object discrimination reversal (memory for location and on ability to change response set) Elicited imitation of action sequences Everyday memory Recognition problems related to attention Verbal and visual memory	2 y (28-32 w) 8 y (31 w) 3-4 y (≤32 w) 19 months corrected age (≤ 37 w)◊ 12 & 16 y (26 & 33 w)† Mean 13 y (≤30 w) 5 y (≤32 w) 5, 7 & 12 months (<1750 gr) Mean 14 y (<31 w) Mean 16 y (mean 30 w) 3-4 y (30-34 w) 7 months & 2-3 y (mean 30 w)	*Ross et al., 1996* *Olsen et al., 1998* *Briscoe et al., 1998* *de Haan et al., 2000* *Gadian et al., 2000* *Isaacs et al., 2000* *Briscoe et al., 2001* *Rose et al., 2001* *Isaacs et al., 2003b* *Taylor et al., 2004* *Caravale et al., 2005* *Rose et al., 2005*

Global cognitive measures	Overall cognitive impairment	6 y (< 26 w) Mean 10 (8-11) y (>999- <2500 gr)	*Marlow et al., 2005* *Emancipator et al., 2006*
Low IQ	Low verbal, performance and full-scale IQ	Mean 7 y (< 30 w & < 1500 gr) 12 y (< 1500 gr) 7 y (mean 28 w) 8 y (31 w) 12-13 y (mean 29 w) Mean 13 y (≤30 w) 8 y (29 w) 14 y (mean 27 w) 15-16 y (<31 w & < 1500 gr) 20 y (mean 30 w) Mean 9 y (< 28 w or < 1000 gr)	*Korkman et al., 1996* *Botting et al., 1998*** *Horwood et al., 1998* *Olsen et al., 1998* *Cooke & Abernethy, 1999* *Isaacs et al., 2000* *Peterson et al., 2000* *Saigal et al., 2000* *Abernethy et al., 2002* *Hack et al., 2002* *Anderson et al., 2003*
	Low verbal, performance and full-scale IQ	7-8 y (<32 w) Mean 14 y (<31 w) 14-15 y (≤32 w)	*Foulder-Hughes & Cooke, 2003* *Isaacs et al., 2003b* *O'Brien et al., 2004**
	Decline of IQ over the time	8-11 y (mean 28 w ≤ 1000 gr) Mean 5 y (< 37 w & < 1501 gr) 7 & 15 y (<31 w) 8 y (mean 28 w) 10 y (< 36 w) Mean 16 y (mean 30 w)	*Saigal et al., 2003* *Bohm et al., 2004* *Isaacs et al., 2004* *Reiss et al., 2004* *Schermann & Sedin, 2004* *Taylor et al., 2004*
	Global developmental index	3-4 y (30-34 w) Mean 3 y (mean 27 w) 7 months & 2-3 y (mean 30 w) 8 y (<30 w)	*Caravale et al., 2005* *Klamer et al., 2005*▲ *Rose et al., 2005* *Wocadlo & Rieger 2006*
Deterioration of cognitive measures		12 y (< 1500 gr)	*Botting et al.,1998***
Mental retardation		5.5-7 y (<34 w)	*Krageloh-Mann et al.,1999*

Most of studies compare preterm samples with a control group. Exceptions:
* longitudinal comparison of preterms at 15 y compared to their performance at 8 y.
** longitudinal comparison of preterms at 12 y compared to their performance at 6 y.
*** gender differences between a preterm group.
† this case-report study is focused on 3 full term subjects and 2 preterm. The table only shows the preterm data.
● follow-up evaluation of preterm children at 6 years.
▲ IQ avaluation by a new questionnaire (validation questionnaire).
◊ results found in preterm from 27 to 34 weeks of gestation.
Abbreviations: GA: gestational age, gr: grams, IQ: Intelligent Quotient, w: weeks, y: years.

As in infancy and school age, cognitive impairments characterize adolescent samples with PB. As it can be shown in Table 4, most important impairments at adolescence are found in global IQ, memory and language functions. Some of these impairments observed in adolescence were also previously found in the same children when they were tested before. Opposite to this, a study from Tideman (2000) in a healthy preterm sample compared to controls reported that cognitive differences observed at age 4 were not evident at ages 9 and 19, when some sociodemographic characteristics (such as maternal education) are controlled, suggesting positive effects of environmental enrichment.

In last years, the unique study focused in ages > 19 years was reported by Hack et al. (2002). Main goal of this investigation was to combine descriptions of cognitive functioning, social and risk-taking behaviours at 20 years of age. Compared to controls, despite 20-year-old subjects with PB showed more school difficulties, the authors reported lower levels of risk behaviours in the preterm sample (i.e. rates of sexual activity or pregnancy). Considering that some level of risk behaviour represents the social norm, a failure in the development of them can be partially interpreted as a delay in areas of potential biological significance.

There is a relationship between the increment of educational demands and an increase of problems at school (D'Angio et al., 2002). McCormick et al. (1996) considered that environmental factors, as the socio-economic status, may be partly responsible of the preterm neurobehaviour and well-being of children. A study from Fawer et al. (1995) goes in the same way reporting a strong effect of the socio-economic status on the general intellectual functioning at 5 years. A study assessing whether medical complications or early socio-economic environment mediates the relationship between birth status and developmental outcome, Miceli et al. (2000) analyzed a preterm sample at 4, 13, and 36 months. The authors showed that maternal distress was associated with behaviour in children at 36 months. In a group of 6-years-old preterms, Taylor et al. (1998) found that although neonatal medical risk was the most important predictor of behaviour, social risk factors also contributed to the prediction of global IQ and verbal skills. Taking into account that environmental enrichment influences brain synapses, it is not surprising that environment becomes more important as a determinant of outcome as preterm infants reach school age. However, a report from Ment et al. (2003) indicated that the majority of preterm children at age of 14 years require no special assistance needs at school. This indicator can hide more subtle dysfunctions that persist in adolescence.

Nonetheless, despite some studies indicate that the environmental factors seem to influence more than perinatal factors as the infant grows up (Fawer et al., 1995), other investigations identified the periventricular brain region as responsible of poor performance. Thus, D'Angio et al. (2002) found that IVH was directly influenciating the neurologic, cognitive and educational outcome in adolescents with history of prematurity.

A very interesting study from Rose et al. (2005) postulates different paths by which later cognition in preterm samples is influenced. The authors state that infant information processing mediates the effect of PB on later outcomes and that deficits in this infant processing have implications for global cognitive performance in childhood. In addition to information processing at early stages, a perspective on the cerebral injuries to which preterm samples are susceptible has made possible to establish links between cerebral damage, volume reductions, behavioural disorders and cognitive outcome.

1.3.7. Brain imaging: structural and functional studies of the preterm brain

Magnetic resonance imaging provides a good approach for imaging the developing brain and allows a considerable detection of cerebral pathology and subtle abnormalities in the immature brain (Counsell et al., 2003). Structural or functional MRI may shed light on which brain areas are the most vulnerable to damage in the preterm infant. For now it can be considered that, in subjects born prematurely, even minor risk may be associated with different kinds of brain injury.

The majority of neuroimaging studies in the 80s and 90s in preterm children have been done qualitatively and with poorly controlled samples, combining different types of brain lesions. In general, these reports consistently seem to indicate that subjects born prematurely have high incidence of anatomical brain abnormalities (Ment et al., 2000). Most recent MRI approaches have provided new quantitative insights into the brain injury in preterm. Thus, volumetric and voxel-based analyses have demonstrated specific regional reductions in cortical and subcortical brain areas in preterm.
In addition to the study of the anatomy, chemical and functional investigations provide new and complementary insights into the brain neurofunctioning in preterm. Magnetic resonance

spectroscopy has been widely used to assess in vivo tissue biochemistry. Particular neurochemical metabolites are of clinical relevance in healthy and diseased brain. Metabolic concentrations can appear altered in a defined and reproducible way in diseased brain (Castillo et al., 1998). Accordingly, abnormal brain spectra can be recognized and compared to healthy samples. The metabolic changes have been related to different cognitive outcomes in pathology and in normal human brain (Jung et al., 1999a; Jung et al., 1999b; Ross and Sachdev, 2004).

Functional imaging has generated considerable evidence about the relationship between structure and function in the normal human brain (Mulkern et al., 2006). Functional MRI uses the haemodynamic responses to neural activity that underlie the blood-oxygen-level-dependent (BOLD) signal, that are often assumed to be driven by energy use in a concrete brain region (Logothetis et al., 2001; Attwell and Iadecola, 2002). This approach is complementary to the injury-based method. However, despite the two study lines can produce converging evidence of systems involved in neurodevelopmental and neuropsychological behaviours, fMRI studies of brain damaged can provide information that is not available from structural neuroimaging, behaviour assessments or fMRI in normal subjects. In addition, the task performance following brain abnormalities can indicate alternative mechanisms that can mediate recovery and brain reorganisation (Price and Friston, 2002).

1.3.7.1. Structural findings

In general, prematurity has been shown as a high risk focus for different complications and brain abnormalities (Krageloh-Mann et al., 1999; Stewart et al., 1999; Dammann et al., 2002; Nosarti et al., 2002; Santhouse et al., 2002; Inder et al., 2003a; Isaacs et al., 2003a; Isaacs et al., 2003b; Ward and Beachy, 2003). Main MRI structural findings in prematurity include decreased whole brain volumes (Nosarti et al., 2002), cortical anormalies (Isaacs et al., 2003a), periventricular WM damage (Cooke and Abernethy, 1999; Krageloh-Mann et al., 1999; Inder et al., 2003a), involving CC reductions (Cooke and Abernethy, 1999; Stewart et al., 1999; Santhouse et al., 2002), medial temporal lobe injury involvement, particularly hippocampal volume reduction (Isaacs et al., 2000; Isaacs et al., 2003b; Peterson et al., 2000), ventricular dilatation (Cooke and Abernethy, 1999; Felderhoff-Mueser et al., 1999; Stewart et al., 1999; Isaacs et al., 2000), and other subcortical brain region involvement, including the cerebellum (Peterson et al., 2000; Allin et al., 2001; Argyropoulou et al., 2003), basal ganglia (Peterson et al., 2000; Abernethy et al., 2002) and thalamus (Barkovich and Sargent, 1995; Krageloh-Mann et al., 1999; Ricci et al., 2006). Several of these studies suggested that these brain lesions might predict poor neurodevelopmental outcome.

Next sections revise and synthesize the literature regarding structural findings in preterm samples by ultrasonography and MRI approaches. Peterson et al. (2003) suggested that morphological abnormalities depending on the brain tissue type and region are present soon after birth in preterm samples. The authors also found that these brain abnormalities correlated with cognitive outcome. So, structural abnormalities could be predictors of long term impairments (Section 1.3.7.2.).

1.3.7.1.1. Gray matter abnormalities

Most findings in premature samples provide objective evidence that brain development in preterm and term subjects is different. Cortical and subcortical GM abnormalities have been shown in preterm. Table 5 summarizes some of the main structural GM abnormalities found in subjects born prematurely by T1 and T2-weighted conventional images and ultrasonography (Tables 5, 6 and 7 are based exclusively on investigation works in last ten years avoiding revisions, and are focused on visual and volumetric approaches compared to control samples. In the case of volumetric studies tables only show significant atrophies or reductions.).

As it is shown, most of studies have been done from birth to adolescence. Apart from whole brain GM volume reductions, literature also reports basal ganglia, hippocampal and thalamic abnormalities. Cortical atrophy also appears affected in preterm samples.

1.3.7.1.2. White matter abnormalities

During the preterm period, axonal brain connectivity is developed but there is a high vulnerability to cerebral WM damage (Follett et al., 2000; Back et al., 2001; Chamnanvanakij et al., 2002; Dalitz et al., 2003; Graham et al., 2004; McQuillen and Ferriero, 2004). Various insults to the preterm human brain can result in predominantly WM injury that later may be reflected in loss of GM as the brain matures (Inder et al., 1999; Ment et al., 1999).

Table 5. Classification of main structural gray matter findings

	Technique/ Approach : Qualitative (◊) ; Quantitative (●) → type	Specific findings	Preterm sample Age at scan (GA and/ or weight)	Study
Global GM abnormalities	MRI ● → Automatic volumetric analysis	Global GM volume reduction	16 d & 39-41 w (<32 w)	*Inder et al., 1999*
	MRI ● → VBM	Decreases in parieto-occipital GM*	15 y (<31 w)	*Isaacs et al., 2004*
	MRI ● → Semiautomatic volumetry	Increase in the parietal and the frontal GM	Mean 9 y (mean 28 w)	*Kesler et al., 2004*
	MRI ● → Semiautomatic volumetry	Global GM volume reduction	8 y (mean 28 w)	*Reiss et al., 2004*
Lesions/atrophy hippocampus	MRI & Histopathology ◊	Abnormalities in hippocampus	MRI: mean after birth 20 d; histopathology: mean 3 d after MRI (<29 w)	*Felderhoff-Mueser et al., 1999*
	MRI ● → Volumetry & VBM	Bilateral reduction†	12 & 16 y (33 w & 26 w) *[N=2]*	*Gadian et al., 2000*
	MRI ● → Volumetry	Bilateral reduction	Mean 13 y (≤30 w)	*Isaacs et al., 2000*
	MRI ● → Manual volumetry (ROIs)	Bilateral amygdala and hippocampus reductions	8 y (29 w)	*Peterson et al., 2000*
	MRI ● → Stereology	Bilateral reduction	Mean 15 y (<33 w)	*Nosarti et al., 2002*
	MRI ◊	Bilateral reduction	Mean age 15 (≤30 w & ≤1500 gr)	*Isaacs et al., 2003a*
	MRI ● → Semiautomatic volumetry	Bilateral reduction	Mean 14 y (<31 w)	*Isaacs et al., 2003b*
	MRI ◊ & ● → Manual volumetry & VBM	Reduction of hippocampus*	15 y (<31 w)	*Isaacs et al., 2004*
Lesions/atrophy basal ganglia or thalamus	MRI ● → Area measurements	Reduction of the caudate area (mid-coronal section)	15-17 y (mean 29 w)	*Cooke & Abernethy, 1999*
	MRI & Histopathology ◊	Abnormalities in basal ganglia and thalami	MRI: mean after birth 20 d; histopathology: mean 3 d after MRI (<29 w)	*Felderhoff-Mueser et al., 1999*
	MRI ◊	Thalamic lesions	5.5-7 y (<34 w)	*Krageloh-Mann et al.,1999*
	MRI ● → Manual volumetry (ROIs)	Bilateral basal ganglia reductions	8 y (29 w)	*Peterson et al., 2000*
	MRI ◊	Basal ganglia and thalamic lesions	<10 y (<37 w)	*Sie et al., 2000*
	MRI ● → Semiautomatic volumetry	Bilateral caudate nuclei reductions	15-16 y (<31 w & < 1500 gr)	*Abernethy et al., 2002*
	MRI ● → Manual volumetry (ROIs)	Bilateral caudate nuclei reductions‡	7 y (<32 w)	*Abernethy et al., 2004*
	MRI ◊	Thalamic abnormalities	Mean 15 y (<33 w)	*Ricci et al., 2006*
	MRI ● → Stereology	Caudate reductions	12-14 months (<36 w)	*Nosarti et al., 2005*
Lesions/atrophy cortical GM	MRI ● → Automatic volumetric analysis	Reduced cortical GM	16 d & 39-41w (<32 w)	*Inder et al., 1999*
	MRI ● → Cortex convolution and surface indexes	Reduction of global cortical surface and complexity	38-42 w (<30 w)	*Ajayi-Obe et al., 2000*
	MRI ● → VBM	Reduction of parietal lobe	Mean 15 y (≤30 w & ≤ 1500 gr)	*Isaacs et al., 2001*
	MRI ● → Stereology	Reduced cortical GM	Mean 15 y (<33 w)	*Nosarti et al., 2002*
	MRI ◊	Gyral abnormalities & enlargement of subarachnoid space (suggestive of GM atrophy)	At term (<33 w)	*Inder et al., 2003b*
	MRI ● → VBM	Decreases of GM in the extrastriate cortex	Mean age 15 (≤30 w & ≤1500 gr)	*Isaacs et al., 2003a*
	MRI ● → Semiautomatic segmentation and manual anatomic divisions of brain subregions	Sensorimotor, parieto-occipital and inferior occipital cortices reductions	Near birth PMA preterm: mean 35 w (29 w)	*Peterson et al., 2003*
	MRI ● → Gyrification index	Increased temporal lobe gyrification	8 y (mean 28 w & <1500 gr)	*Kesler et al., 2006*

* in a group with a large IQ decline across the time compared to a preterm group with a small decline.
† one of the cases (*16 y; 26w)* has been also studied in *Maguire et al., 2001*
‡ reductions in a preterm sample IQ<80 compared to a preterm sample IQ ≥80.
Abbreviations: d: days, GA: gestational age, GM: gray matter, gr: grams, MRI: magnetic resonance imaging, ROI: region of interest, VBM: voxel based morphometry, w: weeks, y: years.

Table 6. Classification of main structural white matter findings

	Technique/ Approach : Qualitative (◊) ; Quantitative (●) → type	Specific findings	Preterm sample Age at scan (GA and/ or weight)	Study
Global WM abnormalities	MRI ● → Automatic volumetry	Total brain myelin volume reduction	16 d & 39-41w (<32 w)	*Inder et al., 1999*
	MRI ◊	Occipital WM reduction	5.5-7 y (<34 w)	*Krageloh-Mann et al.1999*
	MRI ◊	Abnormal WM signal	Mean 2 d (<30 w)	*Maalouf et al., 1999*
	Ultrasonography ◊	Ischemic WM injury	2, 6 & 9 y (<2000 gr)	*Pinto-Martin et al., 1999*
	MRI ◊	Reduced WM volume and/or abnormal signal	14-15 y (<33 w)	*Stewart et al., 1999*
	MRI ◊		At term (<33 w)	*Inder et al., 2003b*
	Ultrasonography & MRI ◊	Moderate reduction in WM volume Hyperintensities within 1 to 2 cm of the ventricles	Mean postconcept. age: 32 w & 37 w (<36 w)	*Miller et al., 2003b*
	MRI ● → Semiautomatic segmentation and manual anatomic divisions of brain subregions	Global WM reductions	Near birth PMA preterm: mean 35 w (29 w)	*Peterson et al., 2003*
	MRI ● → VBM	Increases in frontal WM*	15 y (<31 w)	*Isaacs et al., 2004*
	MRI ● → Semiautomatic volumetry	Global WM volume reduction	8 y (mean 28 w)	*Reiss et al., 2004*
	MRI ◊	WM injury	After birth, mean 32 w postgest. (mean age 28 w postgest.)	*Miller et al., 2005*
Periventricular WM lesions (PVL) (…)	Ultrasonography ◊		Serial postnatal scans : 3, 5, 7, 10, 21, 30 d & every 15 d until discharge	*Fazzi et al., 1997*
	MRI ◊	Periventricular gliosis (centrum semiovale & central occipital WM)	8 y (mean 31 w; <1750 gr)	*Olsen et al., 1997*
	MRI ◊	Periventricular and subcortical WM injury	6 y (<1500 gr)	*Skranes et al., 1997●*
	MRI ◊		8 y (mean 31 w; <1750 gr)	*Olsen et al., 1998*
	MRI ◊		15-17 y (mean 29 w)	*Cooke & Abernethy, 1999*
	MRI & Histopathology ◊		MRI: mean after birth 20 d; histopathology: mean 3 d after MRI (<29 w)	*Felderhoff-Mueser et al., 1999*
	Ultrasonography & MRI ◊		Ultr.: 72h, 7,28 & 42 d; MRI: 16 d & 39-41w (<32 w)	*Inder et al., 1999*
	MRI ◊		5.5-7 y (<34 w)	*Krageloh-Mann et al.,1999*
	MRI ◊		<10 y (<37 w)	*Sie et al., 2000*

Continue...

(...) Periventricular WM lesions (PVL)	Ultrasonography & MRI ◊ Ultrasonography & MRI ◊ MRI ◊ MRI ◊ Ultrasonography ◊ MRI ◊ MRI ◊ MRI ◊ MRI ◊ & ● → Semiautomatic measurements MRI ◊		Mean postconcept. age: 21 d, 31 w & 37 w (≤33 w) Ultr.: first 48h life, 5-7 d, 4-6 w of age; MRI: at term (mean 28 w; < 1500 gr) At term (<33 w) Near birth PMA preterm: mean 35 w (29 w) Daily for the first 5 d of life; then weekly until discharge (<33 w) 7 y (<32 w) 15 y (<31 w) At term, mean postconcept. age 40w (≤37 w) Mean 15 y (<34 w) 12-14 months (<36 w)	*Debillon et al., 2003* *Inder et al., 2003a* *Inder et al., 2003b* *Peterson et al., 2003* *Vollmer et al., 2003* *Abernethy et al., 2004* *Isaacs et al., 2004* *Limperopoulos et al., 2005a* *Pavlova et al., 2006* *Ricci et al., 2006*
Lesions/atrophy Corpus Callosum	MRI ◊ & ● → Area measurements MRI ◊ MRI ● → Manual volumetry (ROIs) MRI ◊ MRI ● →Area measurements (ROIs) MRI ◊ MRI ◊ MRI ◊ MRI ◊ MRI ● → Area measurements (4 ROIs) MRI ◊	Reduction and thinning of CC Thinning or atrophy of CC Reduction of CC Thinning or atrophy of CC Reduction of the CC area Thinning of CC Thinning of CC in the genu and body Thinning of CC Reduction of CC Reduction in the global CC area, and in the posterior and mid-posterior quarter Thinning of CC	15-17 y (mean 29 w) 14-15 y (<33 w) 8 y (29 w) 14-15 y (<33 w) Mean age 1.4 y (≤36 w) At term (<33 w) Mean age 15 y (≤30 w & ≤1500 gr) 7 y (<32 w) 15 y (<31 w) Mean age 15 y (<33 w) 12-14 months (<36w)	*Cooke & Abernethy, 1999* *Stewart et al., 1999*□ *Peterson et al., 2000* *Santhouse et al., 2002*□ *Argyropoulou et al., 2003* *Inder et al., 2003b* *Isaacs et al., 2003a* *Abernethy et al., 2004* *Isaacs et al., 2004* *Nosarti et al., 2004* *Ricci et al., 2006*
Internal capsule, optic radiation	MRI & Histopathology ◊ MRI ◊	Abnormalities in the posterior limb of the internal capsule Abnormalities in optic radiation	MRI: mean after birth 20 d; histopathology: mean 3 d after MRI (<29 w) 12-14 months (<36 w)	*Felderhoff-Mueser et al., 1999* *Ricci et al., 2006*
Lesions/atrophy cortical WM	MRI ● → VBM MRI ● → Semiautomatic segmentation and manual anatomic divisions of brain subregions	Increases of WM in the extrastriate cortex Parieto-occipital WM reductions	Mean age 15 (≤30 w & ≤1500 gr) Near birth PMA preterm: mean 35 w (29 w)	*Isaacs et al., 2003a* *Peterson et al., 2003*

***** in a group with a large IQ decline across the time compared to a preterm group with a small decline.
♦ infants with qualitative abnormalities were all of them ≤32w.
● follow-up evaluation of preterm children at 6 years.
□ both studies used a common sample.
Abbreviations: CC: corpus callosum, d: days, GA: gestational age, gr: grams, MRI: magnetic resonance imaging, PMA: postmestrual age, postconcept: postconceptional age, postgest: postgestational age, PVL: periventricular leucomalacia, ROI: region of interest, VBM: voxel based morphometry, w: weeks, WM: white matter, y: years.

Most **DTI** analyses in preterm samples have focused on intra-group description, studying the evaluation of diffusion changes in long term investigations (Section 1.3.3.). However, an aforementioned study formally addressed differences of anisotropy between premature and mature infants at the same post-conceptional age (Huppi et al., 1998). The study demonstrated delayed brain maturation in some brain regions in preterm newborns at term-equivalent age as compared with term born infants. Concretely, Huppi and co-workers (1998) found that relative anisotropy was significantly lower in posterior limb of the internal capsule in preterm infants at term-equivalent age as compared with term born infants, suggesting that preterm infants have delayed brain maturation.

More recently, there is an interesting long term study from Nagy et al. (2003) that reports that preterm children have disturbances of WM at 11 years in the CC and in the internal capsule that are not repaired or compensated before this age. The authors demonstrated WM probability and FA reductions in the posterior CC, just as WM volume reductions in this area. This could be related to one or the combination of reduced axon diameter, fewer axons or poorer myelination. Huppi et al. (2001) compared preterm subjects with and without WM at term and found that anisotropy in the internal capsule was lower in those with WM injury. The study from Huppi et al. (1998) even showed that in uncomplicated preterm samples the developing brain takes a different course from those of full term samples.

1.3.7.1.3. Other brain findings

Just as previously it has been mentioned, the presence of WM damage has been described as PVL, WM injury or other different terms. Table 7 exposes other brain damage found in preterms and injury terminology than can be associated to WM damage, such as parenchymal lesions, ventricular enlargement or the presence of IVH which is often accompanied by periventricular WM damage due to the rupture of the ventricles wall. Terminology in literature may vary based on different research teams. For example, the researchers led by Dr. Paneth often refer to WM damage as parenchymal lucencies (Paneth, 1999; Qiu et al., 2003), compared to the group of Dr. Volpe, who refer to WM damage as PVL (Volpe, 2001b). Murphy et al. (2002) introduced the term of progressive ventricular dilatation.

Ventricular system has been widely studied. Several researchers demonstrated ventricular dilatations and ventriculomegaly in preterm (Table 7). Some of these findings have been related to the presence of IVH.

The trend in structural neuroimaging has been to emphasize the study of the brain, excluding the hindbrain (the area of the brain comprising the pons, medulla and cerebellum). However, classically the cerebellum has been reported to have an important role in cognitive and motor functions (Leiner et al., 1993; Paulin, 1993) that have been found to be impaired in preterm samples. Table 7 shows some of the studies that found reductions of this structure.

The abnormalities found on MRI during neonatal period and later in childhood and adolescence may be indicating that brain damage occur in critical periods of development disrupt maturation (Inder et al, 1999; Maalouf et al., 1999). Most of imaging studies have focused on specific brain regions and have been inspired by current hypotheses. Linking with the cognitive consequences, some studies suggested that these regional brain lesions might explain the neurocognitive and neurodevelopmental outcome (Stewart et al., 1999).

1.3.7.2. Relationships between neurodevelopmental, neurobehavioral, cognitive outcomes and structural magnetic resonance imaging findings in the preterm

Without the use of MRI techniques it is difficult to establish brain-cognition inferences. Since deficits acquired during critical periods of brain development may be permanent, these results suggest a neural substrate for the neurocognitive impairment that is frequent among preterm. Associations between cognitive, neurobehavioral functions and brain injury have been found in the neuroimaging literature regarding samples with PB (Hack and Taylor, 2000).

Some studies have shown abnormalities in GM and WM of preterm neonates (Maalouf et al., 1999; Inder et al, 1999), and there are other studies that found specific links between these MRI findings and neurobehavioral abnormalities (Krageloh-Mann et al, 1999). A first approach from Luciana et al. (1999) used the Cambridge Neuropsychological Test Automated Battery (CANTAB) in a 7 to 9 years-old preterm sample. The authors reported deficits in recognition memory, memory span, and motor speed that were consistent with damage to periventricular regions. When CANTAB scores were correlated with a composite measure of neonatal medical risk, high risk was significantly associated with some of the neuropsychological measures.

Table 7. Classification of other structural findings

	Technique/ Approach : Qualitative (◊) ; Quantitative (●) → type	Specific findings	Preterm sample Age at scan (GA and/ or weight)	Study
Whole brain volumes	MRI ● → Stereology	Reduction of the whole brain volume	Mean 15 y (<33 w)	*Nosarti et al., 2002*
	MRI ● → Semiautomatic volumetry	Reduction of the total cerebral volume (GM & WM)	Mean 9 y (mean 28 w)	*Kesler et al., 2004*
	MRI ● → Automatic segmentation	Reduction of the whole brain volume (GM & WM)	At term, mean postconcept. 40 w (≤37 w)	*Limperopoulos et al., 2005a*
Specific lobar, regional and/or hemispheric atrophy (including both GM & WM)	MRI ● → Area measurements	Reductions of left and right area of brain hemispheres	15-17 y (mean 29 w)	*Cooke & Abernethy, 1999*
	MRI ● → Manual volumetry (ROIS)	Bilateral reductions in regional brain volume: premotor, subgenual, sensorimotor, midtemporal and parieto-ocipital	8 y (29 w)	*Peterson et al., 2000*
	MRI ● → Semiautomatic volumetry	Decrease in the temporal lobe	Mean 9 y (mean 28 w)	*Kesler et al., 2004*
	MRI ◊	Abnormalities in the occipital lobes	12-14 months (<36 w)	*Ricci et al., 2006*
Lesions cerebellum/ brain stem	Ultrasonography & MRI ◊	Cerebellar atrophy and haemorrhage	7 months to 8 y (≤33 w)	*Mercuri et al., 1997*
	MRI & Histopathology ◊	Abnormalities in brain stem and cerebellum	MRI: mean after birth 20 d; histopathology: mean 3 d after MRI (<29 w)	*Felderhoff-Mueser et al., 1999*
	MRI ◊	Cerebellar atrophy	5.5-7 y (<34 w)	*Krageloh-Mann et al.,1999*
	MRI ● → Manual volumetry (ROIS)	Reduction of the left cerebellum	8 y (29 w)	*Peterson et al., 2000*
	MRI ● → Stereology	Reduction of the cerebellum	14-15 y (<33 w)	*Allin et al., 2001*
	MRI ● → Area measurements by ROI	Reduction of the pons and cerebellum	Mean age 1.4 y (≤36 w)	*Argyropoulou et al., 2003*
	MRI ● → Stereology	Reduction of the vermis and cerebellum	14-15 y (<33 w)	*Allin et al., 2005*
	Ultrasonography ◊	Cerebellar haemorrhage	First week of life & 30 d (<37 w)	*Limperopoulos et al., 2005b*
	MRI ● → Manual volumetry	Reduction of the cerebellum	At term, mean postconcept. 40 w (≤37 w)	*Limperopoulos et al., 2005a*
	MRI ◊	Cerebellar haemorrhage	After birth, mean 32 w postgest. (mean age 28 w postgest.)	*Miller et al., 2005*
	MRI ● → Manual volumetry	Smaller cerebellar volumes	At term equivalent age (<34 w)	*Srinivasan et al., 2006*
Ventricular enlargement, Ventriculomegaly/CSF (…)	Ultrasonography & MRI ◊		7 months to 8 years (≤33 w)	*Mercuri et al., 1997*
	MRI ◊		15-17 y (mean 29 w)	*Cooke & Abernethy, 1999*
	MRI ● → Automatic volumetric analysis	Increase in CSF	16 d & 39-41w (<32 w)	*Inder et al., 1999*

Continue…

(...) Ventricular enlargement, Ventriculomegaly/CSF	MRI ◊ Ultrasonography ◊ MRI ◊ MRI ● → Manual volumetry (ROIs) Ultrasonography ● → manual volumetry MRI ● → Stereology Ultrasonography & MRI ◊ MRI ◊ Ultrasonography & MRI ◊ Ultrasonography ◊ MRI ● → Semiautomatic segmentation and manual divisions of brain subregions MRI ◊ MRI ● → Semiautomatic volumetry MRI ◊ MRI ◊	Left-right ventricular assimetry*	Mean 2 d (<30 w) 40 weeks' concept. age (≤1250 gr) 14-15 y (<33 w) 8 y (29 w) 3 d & 10 d (mean 33 w) Mean 15 y (<33 w) Ultrasonography: first 48h life, 5-7 d, 4-6 w of age; MRI: at term (mean 28w; < 1500 gr) At term (<33 w) Mean postconcept. age: 32 w & 37 w (<36 w) Daily for the first 5 days of life; then weekly until discharge (<33 w) Near birth PMA preterm: mean 35 w (29 w) 7 y (<32 w) Mean 9 y (mean 28 w) At term, mean postconcept. 40 w (≤37 w) After birth, mean 32 w postgest. (mean age 28 w postgest.)	*Maalouf et al., 1999* *Ment et al., 1999* *Stewart et al., 1999* *Peterson et al., 2000* *Ichihashi et al., 2002* *Nosarti et al., 2002* *Inder et al., 2003a* *Inder et al., 2003b* *Miller et al., 2003b* *Vollmer et al., 2003* *Peterson et al., 2003* *Abernethy et al., 2004* *Kesler et al., 2004* *Limperopoulos et al., 2005a* *Miller et al., 2005*
Parenchymal haemorrhage, IVH	Ultrasonography ◊ Histopathology & MRI ◊ Ultrasonography ◊ Ultrasonography & MRI ◊ MRI ◊ MRI ◊ Ultrasonography ◊ Ultrasonography ◊ MRI ◊ MRI ◊		Serial postnatal scans : 3, 5, 7, 10, 21, 30 d & every 15 d until discharge MRI: mean after birth 20 d; histopathology: mean 3 d after MRI (<29 w) 40 weeks' concept. (≤1250 gr) Mean postconcept.: 21 d, 31 w & 37 w (≤33 w) At term (<33 w) Near birth PMA preterm: mean 35 w (29 w) Daily for the first 5 days of life; then weekly until discharge (<33 w) First week of life & 30 d (<37 w) At term, mean postconcept. 40 w (≤37 w) After birth, mean 32 w postgest. (mean age 28 w postgest.)	*Fazzi et al., 1997* *Felderhoff-Mueser et al., 1999* *Ment et al., 1999* *Debillon et al., 2003* *Inder et al., 2003b* *Peterson et al., 2003* *Vollmer et al., 2003* *Limperopoulos et al., 2005b* *Limperopoulos et al., 2005a*♦ *Miller et al., 2005*

* asymmetry partially affected by head position

♦ infants with qualitative abnormalities were all of them ≤32w

Abbreviations: CSF: cerebral spinal fluid, d: day, GA: gestational age, GM: gray matter, gr: grams, IVH: intraventricular hemorraghe, MRI: magnetic resonance imaging, PMA: postmestrual age, Postconcept: postconceptional age, Postgest: postgestational age, ROI: region of interest, w: weeks, WM: white matter, y: years.

Terms used in each investigation have been maintained in tables, establishing a differentiation between WM damage and parenchymal and ventricular pathologies.

To emphasize here, in an attempt to associate poor global cognitive performance with brain volume reduction there is a work from Peterson et al. (2000) that was the first to correlate these cognitive impairments in PB samples with quantitative regional brain abnormalities. They reported cognitive and visual-motor integration impairment in a preterm sample at 8 years old. In addition to this, preterm children showed lower regional brain volumes in the cortex, basal ganglia, amygdala, hippocampus and CC compared to a control sample. These regional cerebral reductions were associated with low global IQ. Thus, the authors provided an anatomical basis for the cognitive abnormalities long known to exist in PB. Interestingly, this study strongly related MRI findings with cognitive outcomes, more than with perinatal risk factors (such as hypoxia, haemorrhages, or demographic factors).

Other investigations have also reported brain abnormalities associated with IQ scores. Two studies from Abernethy et al. found a relationship between IQ and the caudate nuclei (Abernethy et al., 2002; Abernethy et al., 2004) and the hippocampal volume (Abernethy et al., 2002), independent of other brain changes; similar results were found by Isaacs et al. (2003b) regarding the hippocampus itself. In a whole brain study, Reiss et al. (2004) demonstrated a positive correlation between cortical GM/whole brain volume ratio and IQ in preterm at 4.5 and 8 years of age. They found a sex effect, being the correlation significant only for girls. Isaacs et al. (2004) reported that IQ correlated with GM and WM changes with a regional specificity. Concretely, the authors demonstrated a negative correlation between GM and verbal and performance IQ in a parietal lobe region (angular gyrus) and a positive correlation between WM and verbal IQ in an adjacent parietal region. An additional negative correlation between GM and performance IQ was found in the temporal lobe (including fusiform gyrus). Curiously, they found that frontal and temporal lobe regions were associated with a decline in verbal IQ, while occipital and temporal lobe regions were associated with decline in performance IQ. In previous studies, Isaacs et al. also demonstrated relationships between cortical areas and calculation and visual-spatial skills. In a sample of preterm born before 31 weeks of gestation, the authors reported a correlation between GM reductions in the left parietal lobe (intraparietal sulcus) and calculation ability impairments measured by the Wechsler Objective Numerical Dimensions Test (Isaacs et al., 2001) and between GM-WM abnormalities (volume decreases and increases, respectively) and impaired performance on the visuospatial processing, measured by line orientation tasks (Isaacs et al., 2003a).

Reports in older children with a history of PB have shown smaller cerebellar volumes compared with those of term-born children (Table 7), in addition to deficits in motor skills, traditionally ascribed to cerebellar injury. However, recently it has been pointed out the role of the cerebellum in non-motor functions such as cognition, language, and social function (Leiner et al., 1993). Some studies have directly associated cerebellar reductions with poor scores on global cognitive measures (Allin et al., 2001) and verbal, performance and global IQ (Peterson et al., 2000). Recently, Allin et al. (2005) proposed a causative relationship between impaired cerebellar growth in certain regions and specific cognitive deficits in premature infants. The authors reported cerebellar reductions more pronounced in the lateral regions than the midline regions, which were associated with impairments in executive, visual-spatial and language skills. The absence of vermis abnormalities in PB samples has been previously reported (Argyropoulou et al., 2003).

As Dammann et al. (2002) synthesize, WM injury is one of the MRI findings more related to long term cognitive, behavioural and neuromotor impairments in preterm. The study of neurodevelopment in preterm reveals the role of WM injury and ventricular-related areas in abnormal outcomes even in newborns (Peterson et al., 2003; Miller et al., 2005). Fazzi et al. (1997) emphasize the importance of neonatal scans diagnosis of periventricular damage to evaluate posterior long term neurodevelopment impairments in preterm. Ventricular and periventricular lesions have also been associated with IQ decline and poorer performance in certain abilities. A study from Ross et al. (1996) concluded that preterm children (aged 2 years) with Grade I or II IVH showed specific cognitive deficit on a measure of memory for location and on ability to change response set, being visual attention preserved. The impaired ability is related to subcortical areas (i.e., caudate, thalamus) and to the frontal cortex, and IVH has been shown to affect the connections between these regions. Posteriorly, Ment et al. (1999) associated the presence of ventriculomegaly with adverse motor development and higher incidence of low verbal, performance and full scale IQ at 4 years. Recently, Pavlova et al. (2006) reported that PVL provokes disturbances in functioning of the visual perceptual system, with restrictions on the brain's compensatory plasticity, measured by psychophysics methodology. In relation to the aforementioned motor skills, a study from Pinto-

Martin et al. (1999) reported that children with brain abnormalities indicative of ischemic WM injury showed poorer motor performance than subjects without, with a preservation of cognitive abilities. In a follow-up study focused only in preterm subjects (BW< 1500 grams), Skranes et al. (1997) evaluated the relationship between cerebral MRI findings to neurodevelopment at six years. Children with myelin abnormalities in the centrum semiovale and in the central occipital WM showed parallel both fine and gross motor impairment. More recently, Abernethy et al. (2004) showed a relationship between minor motor impairments and total brain volume in a group of preterm children, being more common in subjects with evidence of thinning in posterior parts of CC.

There are some investigations that were unable to found relationships between cognitive development and brain structure. In this sense, there are studies that can not correlate cognitive impairments with conventional markers of perinatal brain injury. In 1995, Fawer et al. emphasized the absence of a clear relationship between the presence/absence of periventricular lesions, diagnosed by ultrasound, and the presence of neuropsychological deficits. The authors reported that cognitive abilities did not differ between preterm with a) normal scans, b) periventricular haemorrhage and c) PVL; however, they reported the presence of an increase in the neuromotor anomalies of preterm with periventricular lesions compared to preterm without. Posteriorly, Olsen et al. (1998) found that preterm subjects without PVL showed impairments in verbal, performance and global IQ compared to control samples. In constrast, subjects with PVL only showed a weak relationship between MRI findings and visual-spatial impairment. The study from Krageloh-Mann et al. (1999) reported that mental retardation was highly significantly associated with cerebellar atrophy and extensive WM reduction, but the authors did not observe any relationship between morphological brain lesions and minor cognitive disabilities (such as intelligence or motor skills), with the exception of the presence of attention deficit observed in preterm with mild MRI abnormalities. Despite it has been found that brains of PB adolescents show evident WM damage, a study from Stewart et al. (1999) did not observe a clear relationship between general functional development (assessed by different tests including the Schonnel Reading and Spelling Test or the Rutter Behavioural Scale) and structural brain abnormalities by MRI (establishing classifications as normal or abnormal MRI, attending especially WM visual inspection), although 65% of their sample had neurological abnormalities. To amplify these partial results, the same group conducted a posterior study to relate detailed neuropsychological outcome at adolescence and brain structure (Rushe et al., 2001). The authors reported that a preterm sample only differed from controls in a measure of verbal fluency and that MRI abnormalities did not predict poor performance on it. In a recent study, Kesler et al. (2004) were unable to find a relationship in a PB sample between cognitive and neuroanatomical variables (presence of IVH and subcortical development), although the correlation between subcortical GM and performance IQ approached significance. Some studies of adolescents born prematurely emphasize a relatively normal neuropsychological outcome despite persistent brain abnormalities (Cooke and Abernethy, 1999; Rushe et al., 2001).

The negative results can arise from the neuroimaging analysis used. Several studies used a qualitative approach, classifying the MRI as 'normal' or 'abnormal' by visual inspection. Other possible explanation can be the brain plasticity and environmental factors such as maternal education or early experiences that can compensate the early mild brain damage.

Probably some of the impaired neuropsychological functions found in PB samples can be related to global brain growth and the development of key structures, such as the hippocampus or thalamus. In some cases, neurological examination is normal and visual inspection of MRI scans does not reveal consistent abnormalities that correlate with functional deficits. However, recent studies demonstrate subtle neural abnromalies associated with specific cognitive deficits. A number of quantitative magnetic resonance techniques have been used in an attempt to identify relatively subtle pathology that might not be obvious on visual inspection. The follow-up studies of preterm to childhood and adolescence revealed cerebral abnormalities that were not discernible on earlier neonatal ultrasound studies. We can find different examples of it.

There are preterm samples without WM injury that show immaturity-related neuronal damage. Just as periventricular structures, the different regions of hippocampus are especially vulnerable to HI (Kreisman et al., 2000), so it is probably to find that measures dependent on this structure are compromised. Isaacs et al. (2000) reported a significant relationship between the volume of the hippocampus and scores in an everyday memory (including prospective memory, immediate and delayed route finding and orientation) test in children with VLBW. Thus, mean hippocampal

volume appeared as a predictor of everyday memory scores. Consistent with these findings, in a study from Maguire et al. (2001) that reported a case of a 22-year-old man born prematurely (after 26 weeks of gestation) who had bilateral hippocampal atrophy, the authors showed that this atrophy was accompanied by episodic memory impairment. Other studies report the same relationship between hippocampal reductions and memory impairments in preterm subjects (Gadian et al., 2000; Isaacs et al, 2003b). Nosarti et al. (2005) related externalizing behavioural and conduct problems observed in preterm boys with caudate volume reductions.

The CC is a WM structure widely studied because is easy to quantify. An investigation from Nosarti et al. (2004) related CC area and its subregions with verbal skills. The authors found that subjects with very PB had a smaller CC area compared to controls, and there was a relationship between these decreases and verbal skills. In concrete, the authors reported positive relationships between verbal fluency and total CC area in a mid-sagittal plane and to the size of the posterior CC quarter. Verbal subtest from the IQ also correlated with the size of the mid-posterior CC quarter. The authors interpreted these findings according to the possible role of CC in high-order cognitive processes, such as language.

Language processes have also been related to cortical development. In a recent study, Kesler et al. (2006) reported cortical developmental abnormalities in the temporal lobe in 8 years old subjects born prematurely. The authors showed a relationship between a gyrification index (a higher index, less GM in the temporal lobe) and language functions: the higher the index, the greater the language impairment.

Tables of the Section 1.3.7.1. showed structural abnormalities found by ultrasonography and conventional T1 and T2-weighted images. But there are also some DTI studies that related behavioural and cognitive outcome with imaging data. As an example, the previously mentioned study from Nagy et al. (2003) reported disturbances of WM at 11 years in the CC and in the internal capsule in preterm subjects with attention deficit.

Volumetric and MRI-related neuropsychological outcomes agree with the idea that there are persistent processing impairments following early brain injury, despite the existence of a developmental plasticity, suggesting abnormal brain development after damage that is responsible for cognitive deficits in preterm children. However, it is possible that a degree of cognitive functional recovery occurs despite the fact that structural changes persist. The extent to which postnatal effects contribute to an abnormal cerebral development is unclear, but it can be established the coexistence of multiple internal and external perinatal factors that contribute to cognitive impairments in PB (Figure 6). Counsell and Boardman (2005) summarized the literature reporting preterm brain development, emphasizing on the morphological changes related to poor outcome.

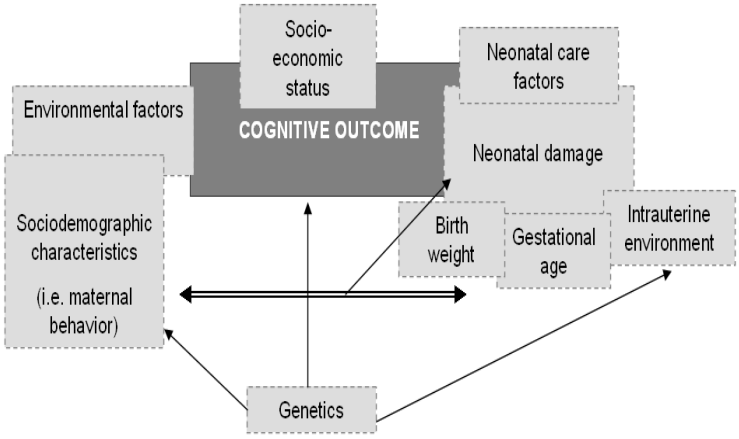

Figure 6. Sources of influence on cognitive development in the preterm infant.

1.3.7.3. Metabolic brain composition and functional findings in preterm birth samples

1.3.7.3.1. Spectroscopic analyses: brain metabolic findings

In normal human brain, proton MRS studies have addressed the regional distribution of several brain metabolite concentrations (Wang et al., 1998; Helms et al., 1999; Mader et al., 2002). This data can be useful to establish normal metabolic content and, in consequence, to know possible developmental anomalies (pathological *versus* normal samples) of brain metabolic values.

Current knowledge about the neurofunctional abnormalities of preterm brain partly comes from spectroscopy. The application of MRS in paediatric samples was mainly extolled in the 1980s (Leonard et al., 1985). In the course of time, spectroscopy has

demonstrated the potential to explore the brain and its wide applicability in paediatric samples, with and without perinatal complications (Cady et al., 1983). In Section 1.3.3., the normal metabolic development of the term and preterm brain is well developed, but there are some studies that evaluate the differences between mature, immature and injured brains. Present Section checks most of the studies in any age PB samples.

Most of the studies in preterm subjects have been mainly focused on healthy samples. During early human brain development, **healthy preterm** and full term brains have been compared by spectroscopy. The previously cited study from Huppi et al. (1995) (Section 1.3.3) apart from establishing normal brain metabolic development also compared brain metabolic concentrations between preterm and term infants by autopsy and by in vivo MRS. The authors reported decreases in the preterm group in the NAA and Cr compared to control values only by autopsy, especially in basal ganglia and thalamus. Vigneron et al (2001) found regional metabolic differences in preterm neonates compared to controls. The authors reported depletions in NA (*N*-acetylaspartate and other *N*-acetyl containing compounds)/Cho in basal ganglia and thalamus, in NA/Cr in thalamus, and increases in Cho/Cr in basal ganglia and thalamus.

Nevertheless, the study from Huppi et al. (1995) showed no significant differences in metabolites between both groups evaluated by *in vivo* spectroscopy. In this sense, a study from Kreis et al. (2002) also reported that metabolite values in moderately premature infants at term were similar than those of full-term infants. This may indicate that prematurity may normalize, especially during perinatal period. However, there is a study that showed NAA/Cho depletion in preterm newborns (Penrice et al., 1996). In addition, a study comparing small and appropriate-for-GA samples showed that concentrations of lactate was higher in the immature brain of prematures compared to term subjects in the striate region, and that is more elevated in the small-for-GA infants (Leth et al., 1995). Similar results with lactate metabolite have been reported in preterm samples with haemorrhagic lesions (Toft et al., 1997). However, a posterior study from Roelants-van Rijn et al. (2004) could not be able to demonstrate differences in cerebral metabolism between small and appropriate-for-GA preterm neonates.

An interesting approach evaluating metabolic patterns in immature brain is the use of antenatal proton MRS. Heerschap et al. (2003) reported that trends in metabolite signals as a function of fetal age were similar to those observed in 'preterm' babies (Kreis et al., 1993; Kreis et al., 2002); thus, the increase in the NAA signal appears as an indicator of the maturational process.

Most of previous studies are focused on perinatal healthy samples, and an interesting point would be to evaluate possible abnormalities of metabolic values at long term. Isaacs et al. (2000) demonstrated that a small group of adolescents with PB had temporal NAA/Cho+Cr decreases compared to full-term subjects, suggesting a persistent deficit.

In **lesional studies**, an early investigation from Groenendaal et al. (1995) reported the cases of 3 full-terms and one preterm subject with neonatal unilateral cerebral infarct. In all cases, a decrease in NAA/Cho ratio was observed within the region of infarction. This NAA/Cho depletion has also been observed in adult samples with stroke (Barker et al., 1994). In this sense, it seems that immature damaged brain showed similar metabolic values to those observed in full-term newborn and adult injured brains. Toft et al. (1997) demonstrated that metabolic abnormalities (in lactate, NAA and Cho) in a preterm sample with haemorrhagic lesions seem to persist a certain period. Kimura et al. (1995), in a sample combining both preterm and term subjects, stated that metabolic changes appeared to be helpful for discriminating between subjects with normal develop and subjects with neurological deficits and brain damage. A more recent study reported that preterm infants with early WM damage showed a different metabolic pattern at term than those observed in term infants after perinatal HI (Robertson et al., 2000).

Some investigators suggest that metabolic changes associated with cognitive dysfunction in certain diseases may lie on a continuum with the normal variations in cognition of healthy subjects. In this sense, there are two interesting papers that found strong correlations between metabolic concentrations and cognition in normal adult brain (Jung et al., 1999a; Jung et al., 1999b). Concretely, the authors reported a positive relationship between NAA and overall neuropsychological performance, in a battery comprising cognitive domains such as attention, verbal and visual memory, language, visual-spatial skills, motor abilities, and frontal executive functions (Jung et al., 1999a). Moreover, the same group reported that NAA and Cho were independently associated with IQ scores. N-Acetylaspartate was found to be positively correlated to verbal, performance and global IQ, whereas Cho was found to be correlated negatively to verbal and performance IQ (Jung et al., 1999b). These

findings should also be probed in the developing brain, since studies in ageing brain have already been done (Ferguson et al., 2002; Pfefferbaum et al., 1999).

The establishment of the metabolic-related brain functioning in normal subjects as a reference allows us to test abnormalities in the damaged brain (Ross and Sachdev, 2004). It should be mentioned that in patient samples, however, sometimes it is quite difficult to establish relationships between metabolites and cognition, despite the existence of metabolic abnormalities. As an example, the study of Isaacs et al. (2000) reported an absence of a relationship between a temporal decrease in NAA/Cho+Cr ratio values and memory scores. Possible explanations could be the difficulty to directly relate spectroscopic values in an isolate region with complex cognitive abilities when values are situated in a narrow range distribution.

1.3.7.3.2. Functional magnetic resonance imaging findings

Functional brain mapping allows investigations to evaluate in vivo cerebral activity associated with a particular task (motor, sensorial or cognitive superior functions). A common approach is the fMRI, a technique with a high spatial resolution to observe regional changes in brain activity. Despite the are studies that validate the feasibility of comparing children at different developmental stages between them and with adults (Kang et al., 2003), in the use of this approach in children and adolescent samples, different technical (i.e., head movements, normalisation of brains to adult spaces) and conceptual variables (i.e. execution of the functional task) should be bear in mind before establishing conclusions (Gaillard et al., 2001; Davidson et al., 2003; Wilke et al., 2003).

Price and Friston (2002) reported that fMRI studies in pathological samples or in subjects with suspicions of cerebral abnormalities provide a characterisation of the damage in a way that can not be deduced from structural scans (i.e., residual responsiveness within the regions of partial brain damage, or abnormal responses distant to the brain damaged area). Functional MRI in brain damaged samples can reveal cognitive responses that may not be accessible using behavioural measures, but also provides joined data to neuropsychological outcome. Previously, brain lesional studies and functional reorganisation have been quoted in different samples (Section 1.3.4.2.). An approach to all fMRI studies carried out exclusively in preterm samples let us see that just as there is a wide range of structural studies focused on these PB samples, little fMRI literature exists in the study of prematurity. Before the published results of this thesis, there have been three fMRI studies focused on preterm with brain damage and one studying preterm subjects without cerebral injury.

Maguire et al. (2001) studied the effects of hippocampal damage on fMRI activation in a single case with history of prematurity and evidence of perinatal hypoxia. The authors reported that despite the subject had a bilateral hippocampal volume reduction of 50%, retrieval in this subject was associated with increased activation in hippocampus compared to controls. An altered pattern of effective hippocampal-cortical connectivity was found in this patient compared to a control sample during a memory retrieval task. Both controls of the study (individually) and the patient showed activation in the medial frontal cortex, the temporal pole, the left parahippocampal gyrus, and in the hippocampus, among other structures, with left predominance. However, statistical differences between groups demonstrated that the preterm subject showed a hyper activation of the temporal region, especially in the hippocampus, and more right-sided activated regions compared to controls. In addition, comparing the activation in the retrieval of 'autobiographical events' remembered by the preterm subject with the activation in the 'autobiographical events known', the hippocampus was more responsive to personal events he remembered experiencing (this was not showed for the control group). As regards the concrete effective connectivity between regions, although the preterm subject showed a similar activation pattern than controls, the first one required an extra interaction between the hippocampus and the retrosplenial cortex, and also increased extra-hippocampal interaction between retrosplenial and medial frontal cortex. These results agree with the idea of brain plasticity. The use of bilateral brain regions and altered functional connectivity patterns may be indicating memory dysfunctions. The question is whether this plasticity is reflecting changes in the network supporting memory function in the immature brain or alterations derived from the hippocampal atrophy. Although the findings from Maguire et al. (2001) are unique to one individual, they provide some basis for a general view of changes in functional brain activity in front of cerebral damage.

The other two lesional studies in young adults with PB come from a London group and were focused on the evaluation of the effect of perinatal CC injury on functional visual-auditive and language tasks (Santhouse et al., 2002; Rushe et al., 2004). In both

studies the preterm subjects presented radiological evidence of thinning or atrophy of the CC and no other focal brain abnormalities. In the first study, three groups were compared: preterm subjects with callosal damage, preterm subjects without CC injury and controls (Santhouse et al., 2002). Very preterm subjects showed different activation patterns in a visual and an auditive paradigm requiring callosal transfer compared to a group of preterm without callosal injury and a control group. In the visual task, preterm subjects with CC damage showed an increase in the brain activity in the right dorsolateral prefrontal cortex compared to the other two groups. No other differences were found between the three groups. In the auditory task, both preterm groups showed more activation in the right superior temporal gyrus compared to controls, being the activation of the damaged callosum group significantly greater than the other two groups. The CC damaged group also showed more brain activity in the right precentral gyrus and left precentral gyrus than the rest of the groups. These results seem to provide evidences that callosal damage affects functional activity in early adulthood. The authors showed the presence of two kind of compensatory mechanisms: a) left or bilateral auditive representation (rather than the right hemisphere specialization of controls), and b) the activation of the dorsolateral prefrontal cortex, probably because the visual task required the use of working memory mechanisms to compensate for the impaired callosal function. The observation of the task-related performance results showed that preterm with callosal damage used alternative strategies to compensate for perinatal damage, but that these strategies were insufficient to produce performance similar to those observed in controls.

The second study in young adults with callosal damage investigated the effects of the CC lesion in language function. Rushe et al. (2004) reported that six subjects with radiological evidence of thinning of the CC showed abnormal lateralization of language function. During a task involving phonological processing (rhyming words) preterm showed significantly lower activation than controls in the left hemisphere, including the peristriate cortex, the cerebellum, and the right parietal association area. An increased activation relative to controls was seen in the right precentral gyrus and in the right supplementary motor area.

There is one fMRI study that has been done to demonstrate abnormal functional brain activity during phonologic and semantic processing in preterm children without a preconceived brain lesion (Peterson et al., 2002). The authors showed that preterm subjects deactivated more in the semantic than in the phonetic processing task; this was the opposite pattern found in a control group. In addition, the authors reported regional-related differences attending the task. In general, regional activation during semantic processing in preterm children was similar to the activation during phonologic processing in controls, involving mainly the Brodmann's Area 9 and 23, the dorsal cerebellum and the globus pallidus. In addition, brain activity during semantic processing correlated with verbal comprehension IQ scores only in preterm children. The authors suggested that probably preterm children processed semantic material using the same network as those used for phonological processing in term children. These findings contribute to increase evidences that PB is associated with long term abnormalities in brain functionality.

Finally, despite the evidences of explicit and everyday memory impairments in preterm samples, till this thesis there is no published study using the common face-name learning as declarative memory fMRI paradigm in preterm samples. Of note here, a new paper has recently appeared studying functional neuroanatomy of two structures associated with memory (the hippocampus and the caudate nucleus) in a group of adolescents with PB by declarative and spatial memory task paradigms (Curtis et al., 2006). The authors reported no significant differences between the preterm and the control groups on fMRI behaviour outcome, with all participants performing better than chance. In addition, no differences were found in the hippocampal brain activity during fMRI declarative memory tasks, whereas the differences were found in the caudate nucleus activation during a spatial memory span task. In general, the trend was that during the encoding phase of the spatial fMRI tasks, preterm showed greater significant right caudate activation change than the control group; during the test phase, the controls were who showed greater activation in the same brain structure, bilaterally. With this work, the authors emphasize the lack of behavioural performance differences between the two groups on memory tasks, with similar brain activity in hippocampus and differences in caudate nucleus depending the phase of fMRI task. The existence of good task performance, but differences in brain activity during an fMRI task in preterm subjects has also been recently reported by Nosarti et al. (2006) in a motor response inhibition task. It is difficult to account for these differences attending the task phase, as they both involve the same perceptual and motor activity. The authors speculate that perhaps during encoding preterm subjects use a neural network involving the head of caudate nucleus, whereas at test phase they use an alternate network that did not involve the head of

caudate nucleus. Thus, in this case caudate differences between groups suggest the existence of different functional mechanisms to obtain an outcome similar to that observed in control samples.

1.4. Functional magnetic resonance approach: the face-name associative learning, a declarative memory task

The ability to encode and remember associations between unrelated elements is an essential aspect of the declarative memory task. The face-name association appears as everyday learning involving declarative memory mechanisms. There are some studies appeared in last years that evaluated brain functional substrate by positron emission tomography and fMRI approaches of novel face-name association encoding, specifically, in healthy young adults and old persons (Small et al., 2001; Sperling et al., 2001; Sperling et al., 2003a; Sperling et al., 2003b; Zeineh et al., 2003; Kirwan and Stark, 2004; Rand-Giovannetti et al., 2006), in Alzheimer disease samples (Pariente et al., 2005) and in samples with a pharmacologically induced memory impairment (Sperling et al., 2002; Sperling et al., 2003b).

Learning the names of novel faces is an essential aspect of everyday memory learning and the aforementioned studies reported the involvement of the hippocampus, among other brain regions, in this associative encoding (of note here, the hippocampus has been related not only with the relational memory, but also with episodic memory encoding and retrieval (Lepage et al., 1998; Cohen et al., 1999; Schacter and Wagner, 1999). Pair-associate learning is a fundamental feature of hippocampal function, contributing the hippocampus to the binding of the individual items (Bunsey and Eichenbaum, 1996). It has been widely reported that preterm subjects have impairments in memory, both in laboratory memory tests and in everyday memory measures (Section 1.3.6.). In addition, there are evidences of hippocampal atrophy in preterm, by qualitative and volumetric approaches (Section 1.3.7.1.1.). So, the evaluation of the brain activity during the everyday face-name association task in PB samples is an interesting study focus. The functional brain activity in this declarative memory task in preterm samples remains unknown, both involving encoding and retrieval processes.

In general, just as there is a wide range of investigations that evaluated separately the effect during word and face encoding tasks, there are less functional studies focused on the face-name **encoding** task specifically. Regarding the characteristics of the face-name encoding, studies in healthy samples agree about other regions apart from the hippocampus are activated during this learning. Thus, different authors emphasize other medial temporal lobe areas (i.e. parahippocampal cortex, perirhinal cortex) (Sperling et al., 2001; Kirwan and Stark, 2004; Rand-Giovannetti et al., 2006), the fusiform region (Sperling et al., 2001; Sperling et al., 2003a; Sperling et al., 2003b), the putamen (Sperling et al., 2003a; Sperling et al., 2003b), the caudate (Sperling et al., 2001; Sperling et al., 2003b), the pulvinar (Sperling et al., 2001), the thalamus (Sperling et al., 2003a; Sperling et al., 2003b; Rand-Giovannetti et al., 2006), the frontal and prefrontal areas (Sperling et al., 2001; Sperling et al., 2003a; Sperling et al., 2003b; Rand-Giovannetti et al., 2006), the cingulated gyrus (Sperling et al., 2003a; Sperling et al., 2003b), the insula (Sperling et al., 2003a), the parietal region (Sperling et al., 2001; Sperling et al., 2003b; Rand-Giovannetti et al., 2006), and the occipital region (Rand-Giovannetti et al., 2006). All these findings suggest that the encoding of novel face-name pairs depends on a distributed functional network of cerebral regions, where the activation of hippocampus appears to be basic. Brain abnormalities in these areas may suppose some functional compensation mechanisms, such as hyper or hypo activations or contra lateralization processes.

Other activation studies focused on the associative or relational declarative memory encoding have used different associated stimuli. As an example it can be cited the following materials: word related pairs (Kapur et al., 1996), learning category-exemplar word pairs (Dolan and Fletcher, 1997; Fletcher and Dolan, 1999), face-house (Henke et al., 1997), two line drawing of objects-corresponding nouns (Rombouts et al., 1997), detailed and complex scenes by attending main features and their relationships (Montaldi et al., 1998), face pairs (Killgore et al., 2000), intra-items association in geometric patterns (Gron et al., 2001), complex visual scenes-face (Fransson et al., 2001), pairs of concrete-related pictures, concrete-unrelated pictures and couples of abstract pictures (Iidaka et al., 2001), relational or item-based processing of word triplets (Davachi and Wagner, 2002), professional category-face (Henke et al., 2003), and word pairs (Jackson and Schacter, 2004), among other things. Most of them have demonstrated similar activation patterns than those found by face-name stimuli.

The face-name learning study has generated complementary investigations. Kikyo and Miyashita (2004) evaluated the feeling-of-knowing induced by face-name associations in a healthy sample. The

authors concluded that the feeling-of-knowing has an important role within the posterior effective retrieval condition. In this sense, although brain activity has been slightly studied with fMRI and positron emission tomography during face-name encoding tasks compared to simple word and face encoding tasks, **retrieval** functional analyses after the associative face-name learning have been even less commonly reported. Three of the above works studying the face-name encoding also analyzed the activation underlying the retrieval. Kirwan and Stark (2004) reported that the activation during retrieval of the association of face-name pairs was greater than those found during the retrieval of face-name pairs in which the components were remembered without an association. Small et al. (2001) found that recalling names when cued elicited a similar pattern found during the pairing of stimuli in hippocampus. In addition, the authors reported that association of face-names generated more activation than those observed during retrieval of isolate faces or names. Zeineh et al. (2003) studied the hippocampal activation exclusively during the face-name and concluded that the activation during retrieval was associated with posterior parts of the hippocampus, whereas the encoding was more associated with anterior parts. This anterior-posterior division in the hippocampal activation during memory task has been previously reported in positron emission tomography studies (Lepage et al., 1998) though there are authors that questioned this fact (Schacter and Wagner, 1999).

Contrary to the studies of encoding, a positron emission tomography study from Campanella et al. (2001) showed that retrieval did not suppose any hippocampal activation. The authors reported activation during retrieval in parietal and frontal areas. However, in an fMRI study Paller et al. (2003) grant an important role of hippocampus triggering retrieval of associations between faces and names. In this sense, Tsukiura et al. (2003; 2006) reported the activation of the anterior temporal lobe areas in the retrieval of names (previously associated with faces).

In view that prematurity is associated with hippocampal and medial temporal lobe abnormalities and memory impairments, these structural deficits should display brain functional compensation mechanisms in a declarative memory task such as the face-name everyday learning task. The study of these mechanisms may provide new insights into the brain adaptation and plasticity in samples with early brain injury.

2. METHODOLOGY

The present thesis consists of six studies examining neuroanatomical and neurofunctional basis of brain characteristics in adolescents with history of prematurity and an additional brain metabolic study in a control sample. For that, we have used different neuropsychological and MRI approaches. Each paper details the methodology used and the studied samples.

Following *neuropsychological* tests were used in the present thesis:

* For verbal memory, a modified version of the Auditory Verbal Learning Test was used (Lezak et al., 2004).

* Visual memory ability was evaluated with the Rey's Complex Figure test (Rey, 1980).

* The IQ was evaluated by the Wechsler Intelligence Scales. Either Wechsler Intelligence Scale for Children-Revised (WISC-R) or the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) was used depending on the age of the subjects (Lezak et al., 2004).

* The evaluation of verbal fluency was done through two tasks: a) a phonetic fluency task comprising a modified version of the Controlled Oral Word Association Test (Artiola i Fortuny et al., 1999). Subjects were instructed to verbally generate words that began with the letters P, M, and R in three separate trials; b) a semantic fluency task, generating words when cued with a particular category.

Regarding the *structural MRI approaches* used in the present thesis:

* A voxel-based morphometry approach was used to evaluate structural brain differences between the groups of study, by unmodulated and modulated images. In all cases, we used the optimized method proposed by Good et al. (2001). The automated image processing was done using SPM99 and SPM2 softwares, running in Matlab (MathWorks, Natick, MA).

* Individual volumetric stereological measurements of hippocampus were done through the ANALIZE software (in its different versions). We followed the protocol proposed by Sheline et al. (1996), a procedure reported to improve hippocampal measurements.

* Cortical measurements (sulci volume and depth) were automatically done by the "Anatomist/BrainVisa 3.0.1" package (Riviere et al., 2002; Mangin et al., 2004).

Finally, *brain functionality* study supposed the analysis of neurochemistry and brain activity during a face-name learning task:

* Brain metabolic analyses involved a change in the type of approach depending on the study. In the first spectroscopic study in controls the spectra were analyzed using the manufacturer-supplied spectroscopy software package for the MR scan system. In the second spectroscopic investigation we introduced a novel analysis by the use of the Linear Combination Model-Fitting program version 6.1-4A (Provencher, 2001). With this, we could obtain a quantification of the absolute brain metabolic concentrations, expanding the studies focused only in neurochemical ratios.

* For the brain activity, the fMRI approach based on Blood Oxigen Level Dependent response was used. Subjects were asked to attend inside the MR scan a face-name declarative memory learning task, modified from Sperling et al. (2001).

Throughout the studies, the samples have been changing according to the objectives and requirements for each investigation. A detailed description of the samples characteristics and methodological approaches (neuropsychological tests and MRI methodology) can be found in each concrete study.

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3. HYPOTHESES OF THE THESIS

The hypotheses raised for study in the present thesis are the following:

Hypothesis I

Preterm children demonstrate memory deficits and structural abnormalities in different subcortical gray matter brain regions, such as hippocampus and thalamus. Both structures have been previously related to declarative memory. We postulate that the memory impairment in premature children will correlate with volume decreases of these both brain structures in a preterm sample at adolescence.

Hypothesis II

Verbal fluency is frequent sequelae of thalamic lesions because the prefrontal lobe connectivity of this subcortical region. Considering the presence of thalamic abnormalities in preterm subjects, they will have verbal fluency impairment and the thalamic volume will show correlations with this neuropsychological performance.

Hypothesis III

Periventricular white matter damage by visual magnetic resonance imaging inspection has been widely reported in preterm samples. However, adolescents with history of prematurity and no evidences of white matter injury on magnetic resonance imaging also will show a more diffuse white matter disturbance that will be detected and quantified by a voxel-based morphometry approach. Moreover, according to previous experimental data performed in rats, gestational age will be related to white matter abnormalities.

Hypothesis IV

Cortical brain gyrification depends on gestational age. Most preterm subjects are born at the early stages of the development of the secondary sulci. They will show abnormalities in the immature gyri at birth.

Hypothesis V

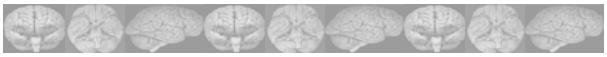
Previous studies have shown that preterm subjects show metabolic brain alterations at early stages. Medial temporal lobe is a region especially susceptible to brain damage. Adolescents with history of preterm birth and no evidences of brain injury by visual inspection of magnetic resonance imaging will show neurochemical brain abnormalities that are not reversible during childhood. These anomalies will be accompanied by structural brain changes and will demonstrate positive relationships with gestational age.

Hypothesis VI

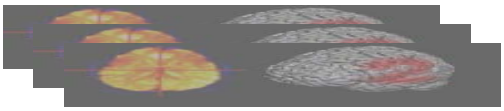
Preterm samples show volumetric abnormalities in the hippocampus, a structure related to declarative memory. Probably, the hippocampal damage characterisation will alter brain activity during a declarative memory task in a way that preterm will show an increase in cerebral activation to compensate for this brain injury.

4.- RESULTS

4.1. Neuroanatomical results



4.2. Neurofunctional results



5. GENERAL DISCUSSION

As previous manual volumetric investigations in PB samples (Isaacs et al., 2000; Peterson et al., 2000; Nosarti et al., 2002), the present work quantitatively demonstrates the presence of volumetric abnormalities in the hippocampus (Gimenez et al., 2004a). This finding goes along with neuropathological studies that showed the presence of necrosis in the same area (Felderhoff-Mueser et al., 1999). This hippocampal atrophy was related to different neuropsychological measures, such as verbal learning and long-term retention, remaining visual memory preserved. The discrepancy between visual and verbal memory has been previously reported (Isaacs et al., 2003). In a previous study, the same group also found verbal memory impairment and bilateral hippocampal reductions, but the authors did not find a significant relationship between the neuropsychological and structural findings (Isaacs et al., 2000).

In the analysis of an anterior or posterior hippocampal predominance of volume reductions, our results showed that the preterm had posterior predominance, and that this specific area correlated with verbal memory impairment in PB group. This result coincides with previous findings in normal samples (Fernandez et al., 1998).

In addition to the hippocampal reductions, this work is the first to demonstrate bilateral quantitative reductions in thalamus in 22 adolescents who were born prematurely. This finding agrees with a previous investigation that showed histopathological thalamic abnormalities (Krageloh-Mann et al., 1999). The first study of this thesis could not find a correlation between thalamic volume and any declarative memory measure, despite this cerebral region has been involved in memory networks (Van der Werf et al., 2003). Probably, the main region found to be involved in the volumetric atrophy (the pulvinar) affects the absence of a relationship, because the pulvinar has been more related to attention and visuospatial functions (Parent and Carpenter, 1996).

As previously reported, in a wide sample of preterms the second study of this thesis also found thalamic volume reductions (Gimenez et al., 2006a). Considering that the thalamic lesions cause deficits in verbal fluency (Ravnkilde et al., 2002; Vitali et al., 2005), in this second investigation the study of thalamus was related with such function. Only one previous study evaluated this verbal ability in preterm and was related to CC size (Nosarti et al., 2004). We demonstrated positive correlations between both semantic and phonetic fluency performance and the volume of thalamus, especially in the preterm group. In the specific analysis of the thalamic nuclei volume we found that semantic and phonetic fluency showed differential thalamic-related patterns. Despite both controls and preterm showed significant correlations between the phonetic fluency and some nuclei, the correlational pattern was less extensive than that of semantic fluency in the preterm group (there were no relationships between semantic scores and thalamus for the controls). These results coincide with studies that postulate that semantic fluency requires greater brain functionality than phonetic fluency in pathological samples (Kubota et al., 2005) and that there is an overlapping between semantic and phonetic cerebral patterns (Crosson, 1999; Vitali et al., 2005).

Apart from GM abnormalities, most studies in PB samples reported that immature brain is particularly vulnerable to brain WM damage (Blumenthal, 2004; Deguchi et al., 1999; McQuillen and Ferriero, 2004; Volpe, 2001). In general, the WM damage involves the periventricular region (Huppi et al., 2001; Miller et al., 2002; Counsell et al., 2003; Inder et al., 2005). Our third study (Gimenez et al., 2006b) demonstrated the presence of not only periventricular injury, but also of other distal subtle WM brain abnormalities in 50 very preterm adolescents without visual evidence of WM damage. This has been mainly possible by the use of a differential approach through the analysis of both WM concentration and volume. These new results support the evidence that preterm samples show WM damage further over the classical periventricular damage and provide new argument to the notion of a more generalized WM injury in immature samples. Our findings seem to involve intrahemispheric association fiber tracts (Mori et al., 2005), such as the superior and inferior longitudinal fasciculus, the superior occipitofrontal and the uncinate fasciculi. These subtle brain abnormalities could be partly related to impairments in different neuropsychological findings previously found in part of this sample (Gimenez et al., 2004a), because of the associational role of most of the altered tracts. In the same way, we found lesions in WM areas into which these fibers project. In this third study we also detected some cortical and subcortical GM reductions in the very PB adolescent sample (Gimenez et al., 2006b), but there was no a direct relationship between the two kind of tissue-related lesions.

Finally, the WM integrity at adolescence seems to be related to GA and gestational weight. This agrees with previous reports in newborns (Larroque et al., 2003).

The fact that these relationships are maintained at adolescence demonstrated the persistence of brain injury at long term.

A good example of the brain development depending on GA is gyral formation. Data on sulci and gyri development demonstrated that in preterm the cortex appears lissencephalic at birth (Ajayi-Obe et al., 2000). Through studies that demonstrate different cortical brain maturation trends attending the GA stage (Chi et al., 1977; van der Knaap et al., 1996; Ruoss et al., 2001), one can speculate the presence of an interruption of sulci and gyri maturation in the premature birth. In this sense, considering that gyrification in the frontal lobe occurs later than other cortical regions (Ruoss et al., 2001; van der Knaap et al., 1996) the study of sulci and gyri development in this region in very PB samples could provide data contrasting the cortical development of preterm and term subjects at long term. Until now, the impact of very PB on sulcal depth development at adolescence remains unknown. There is only one study that evaluated cortical abnormalities in the temporal lobe associated with prematurity (Kesler et al., 2006). The authors showed that temporal cortex development was especially impacted by PB, with an increase in gyrification. They also demonstrated a negative relationship between the temporal lobe gyrification and the GM volume in the same region. In our four study (Gimenez et al., 2006c) we could demonstrated that orbitofrontal secondary sulci depth (developed at late gestational stages) was altered by a very premature birth. In contrast, the olfactory primary sulcus depth (developed at 16 weeks' gestation) was similar in the preterm and control group. Interestingly, the sulcal depth alteration was related to cortical GM reduction in the same region (Gimenez et al., 2006c). These results provide evidences of an alteration in the normal sulci and gyri development that is not reversible during childhood.

In addition to the study of neuroanatomy, the evaluation of neurofunctionality provides useful information regarding the relationships between behaviour brain and performance. In a study in adolescent controls (Gimenez et al., 2004b) we demonstrated a correlation between NAA/Cho in the temporal lobe and memory performance. Most of metabolic studies in preterm samples have been done in newborn and infant subjects (Huppi et al., 1995; Penrice et al., 1996; Vigneron et al., 2001). The study of brain metabolic patterns in adolescent samples with PB history has a great interest to evaluate if some of the metabolic abnormalities found in newborn samples normalize at adolescence. There is only one study reporting that a small subsample of adolescents with PB had temporal NAA/Cho+Cr decreases compared to full-term subjects, suggesting a persistent deficit (Isaacs et al., 2000). In the aim to broad the study of metabolic cerebral characteristics in a healthy sample of preterm with normal MRI we conducted a sixth investigation (Section 4.2.2.). On it, a metabolic depletion pattern in the preterm group in the medial temporal lobe was found compared to controls, just as hippocampal volume reductions. As cited previously, these volumetric alterations have been reported in preterm (Isaacs et al., 2000; Peterson et al., 2000; Nosarti et al., 2002). Our metabolic and volumetric findings in the preterm sample were related to GA. The positive relational finding between GA and N-Acetyl compounds and Cr is partially in agreement with a study in preterm infants (Kreis et al., 2002), who demonstrated positive relationships between GA and N-Acetyl compounds and Cr in different cerebral regions, but a negative correlation between Myo-Inositol and GA.

With this, we demonstrated long term neurochemical alterations in adolescents with PB and normal standard MRI, maybe providing support for either neuronal dysfunction or neuronal loss in the medial temporal lobe region. Further studies should try to elucidate if these neurofunctional brain abnormalities are directly related with cognitive impairment observed in these subjects. In some pathological samples sometimes it is difficult to establish relationships between metabolites and cognition, despite the presence of neurochemical abnormalities. A possible example is the aforementioned study from Isaacs et al. (2000) that showed an absence of a relationship between a temporal decrease in NAA/Cho+Cr ratio values and memory scores.

Apart from metabolic analyses, fMRI studies in samples with suspicions of cerebral abnormalities provide a characterisation of the injury importance in a way that can not be evaluated from structural information (Price and Friston, 2002). In this sense, we designed a study to evaluate the brain activity in a declarative memory task in adolescents with PB and hippocampal damage, with left predominance (Gimenez et al., 2005). Our results showed a greater activation in preterm subjects compared to controls exclusively in the right hippocampus. This activation was related with the volume of the right hippocampus and with the recognition test of the fMRI task in the premature group. One can speculate if this increased activation in right hippocampus may reflect a contralateral functional reorganization of the most impaired left hippocampus. This argument is in

agreement with other studies evaluating activation in the preserved regions and/or hemispheres compared to the damaged one, which showed similar results (Cao et al., 1994; Vandermeeren et al., 2003). In a functional study in a sample with left hippocampal atrophy Richardson et al. (2003) reported an increased activation in the right hippocampus in a word-encoding task. Despite the fact that premature subjects in our study showed greater right hippocampal activation than controls, this activations was not sufficient to reach controls performance, suggesting a deficiency in the compensatory mechanism and corroborating the presence of learning deficits reported in different studies of prematurity (Isaacs et al., 2000; Anderson et al., 2003).

There is growing evidence that abnormal development of the brain in prematurity contributes to behavioural, neurological and psychological anomalies that manifest throughout different life stages. As a whole, the integration of the seven studies presented in this thesis demonstrates that long term follow-up of infants born prematurely from different methodological points of view is necessary to determine neurodevelopmental and neuropsychological outcomes related to brain neuroanatomical and neurofunctional findings, particularly because in infant and children ages most reports describe specific deficits in motor, visuomotor integrative skills, IQ, academic achievement, language, executive function, and attention, that persist into adolescence. The timing, severity and type of brain damage are critical in determining the characteristics of the outcome.

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6. CONCLUSIONS

I) Adolescents with history of prematurity show volume reductions in two subcortical brain structures related to declarative memory, the hippocampus and thalamus. Verbal memory deficits observed in the preterm group correlated with hippocampal atrophy. We take such brain structural abnormalities as evidence of brain-related learning disabilities in preterm subjects.

II) Very preterm birth subjects show volume reductions in thalamus that go accompanied by anomalies in phonetic and semantic fluency performance. Verbal fluency did not correlate with frontal lobe gray matter, being thalamic volume changes more related to verbal fluency impairment. The analysis of correlations shows a more extensive correlational pattern between thalamic nuclei volume and semantic performance than that found for phonetic fluency.

III) Voxel-based morphometry approach is sensitive to detect white matter damage in very preterm birth samples without evidence of any injury on conventional magnetic resonance imaging visual inspection of T2-weighted images. Apart from the classical periventricular white matter injury, we found a more subtle and diffuse white matter tissue disturbance. So, we have extended the well-known existing periventricular white matter injury, classically mentioned, to the idea of more extensive white matter damage in preterm samples. The white matter integrity at adolescence is related to gestational age in agreement with experimental data.

IV) Our results show the first evidence of the impact of very preterm birth on cortical sulcal depth development at adolescence. Subjects with very preterm birth show abnormalities in the sulcal depth in the secondary orbitofrontal sulci compared to the development of the primary olfactory sulcus. These results provide evidences of an alteration in the normal sulci and gyri development that is not reversible during childhood.

V) Healthy preterm adolescents without perinatal complications and normal magnetic resonance images show neurochemical brain alterations in the medial temporal lobe, as well as volumetric reductions in the hippocampus. These observed metabolic alterations may reflect neuronal dysfunction or neuronal loss. Metabolic and hippocampal values were also related to gestational age.

VI) Subjects with history of prematurity and hippocampal damage, with left predominance, show an increased brain activity compared to controls in the right hemisphere during a declarative memory task. This suggests a cerebral compensatory mechanism, but that is not sufficient to reach normal neuropsychological performance.

We bring this thesis to an end by facing up future work directions through the following open issues:

- The study of frontal-related neuropsychological functions to be related to cortical development in this region. Further studies should try to elucidate the functional correlates of the frontal cortical development abnormality, because it may be that social and behaviour impairments in adolescents with preterm birth are related to these cerebral sequelae.
- The functional study of brain activity with tasks involving associative tracts to compare preterm birth samples with different kinds of white matter injury. Related to white matter study, there are no integrative studies joining diffusion tensor, voxel-based morphometry and functional approaches in prematurity.
- At present, most of studies in prematurity have been done in child and adolescents. Future directions should consider the possibility of doing follow up studies to evaluate neuroanatomical changes and neurofunctional performance in adult samples with history of prematurity.

7.- SUMMARY OF THE THESIS

Summary of the thesis

(Resumen de la tesis)

Bases neuroanatómicas y neurofuncionales de los déficit cognitivos en adolescentes con historia de prematuridad. Estudio de resonancia magnética estructural y funcional

Introducción

Los niños nacidos prematuramente tienen un alto riesgo de sufrir déficit cognitivos y tener un bajo rendimiento escolar (Rose y cols., 1996; Olsen y cols., 1998; Rushe y cols., 2001; Bohm y cols., 2002; Cooke y cols., 2003; Foulder-Hughes y Cooke 2003; Anderson y cols., 2003). A pesar de los avances en las técnicas de cuidado perinatal, la incidencia de problemas del neurodesarrollo entre los niños que sobreviven a los cuidados intensivos es ciertamente alta. En la actualidad, la tasa de partos prematuros en España se sitúa entorno al 8% (*Instituto Nacional de Estadística de España:* www.ine.es), existiendo un incremento del 13% de los niños con bajo peso en los últimos cuatro años (*Sociedad Española de Neonatología:* www.se-neonatal.es). La etiología del parto prematuro aparece como multifactorial y se relaciona con trastornos en el feto o en la madre, aunque en casi la mitad de los casos la etiología se desconoce.

En términos generales, la prematuridad se considera un riesgo importante para el desarrollo de trastornos neurológicos, incluyendo la parálisis cerebral (O'Shea y cols., 1998; Wheater y cols., 2000; Takahashi y cols., 2005). Los recientes avances en técnicas de neuroimagen permiten investigar el origen de las disfunciones neuropsicológicas descritas ya desde los años 70 en muestras de niños nacidos de parto prematuro. Las alteraciones cognitivas y conductuales mostradas por los niños prematuros son en gran parte reflejo de las lesiones cerebrales subyacentes o del escaso desarrollo cerebral asociado a la inmadurez. Son diversas las técnicas de neuroimagen que pueden identificar de forma relativamente fácil el daño cerebral estructural macroscópico (Krageloh-Mann y cols., 1999; Stewart y cols., 1999; Peterson, 2003). No obstante, el acercamiento de los estudios volumétricos cuantitativos puede evidenciar anomalías sutiles no visibles mediante inspección visual. Estas anomalías estructurales parecen estar ya presentes durante el periodo perinatal, pudiendo persistir a largo plazo a pesar de la plasticidad del sistema nervioso central durante la infancia (Peterson y cols., 2000; Peterson y cols., 2003; Nosarti y cols., 2002). Los avances más importantes en el estudio de las bases neurales que subyacen al déficit cognitivo de estos niños se han llevado a cabo gracias a las mejoras en la resonancia magnética, en sus vertientes estructural (volumetría por resonancia magnética y análisis basados en el estudio voxel a voxel del cerebro) y funcional (espectroscopia por resonancia magnética y resonancia magnética funcional).

Hasta la publicación de los trabajos que conforman la presente tesis, pocos son los estudios que relacionan los datos cerebrales volumétricos con la ejecución neuropsicológica en adolescentes con parto prematuro (Peterson y cols., 2000; Isaacs y cols., 2000; Allin y cols., 2001; Isaacs y cols., 2001; Isaacs y cols., 2003a; Isaacs y cols., 2003b; Abernethy y cols., 2002). En este sentido, el conjunto de los trabajos aquí mostrados proporciona nuevos datos de carácter neuroanatómico y neurofuncional, a través de aproximaciones metodológicas no utilizadas hasta en momento en el estudio del cerebro y las anomalías cognitivas en muestras de adolescentes que nacieron prematuros. Con ello, los actuales datos contribuyen al conocimiento sobre la posible plasticidad cerebral a largo plazo derivada del daño de cerebros inmaduros, siendo un primer paso para futuros acercamientos terapéuticos en este tipo de muestras.

Objetivos de la tesis

El interés general de la tesis radica en estudiar las bases cerebrales subyacentes a los déficit cognitivos descritos en adolescentes con historia previa de parto prematuro. Para este propósito, se han utilizado técnicas de análisis y evaluación estructural, funcional y metabólica, así como una aproximación neuropsicológica.

Desde un punto de vista **estructural**, cabe constatar que son pocos los estudios que han correlacionado datos cuantitativos a través de resonancia magnética con la ejecución neuropsicológica. En este sentido, nuestro primer objetivo fue realizar un estudio estructural mediante un análisis voxel a voxel del cerebro para analizar los posibles correlatos cerebrales estructurales de los déficit de memoria en una muestra de adolescentes que nacieron prematuros. Todo ello focalizado en dos estructuras cerebrales: el hipocampo y el tálamo (Sección 4.1.1.).

En segundo lugar, una vez observadas que las reducciones talámicas del estudio anterior no estaban

directamente relacionadas con disfunciones de memoria, y teniendo en cuenta que se han descrito las disfunciones de fluencia verbal como una secuela frecuente de las lesiones talámicas, en el segundo estudio investigamos si la atrofia talámica observada en los prematuros podría explicar los problemas de fluencia verbal descritos en este tipo de muestras (Sección 4.1.2.).

Avances recientes de neuroimagen aportan datos que sostienen que, paralelamente a la existencia de lesiones periventriculares de la sustancia blanca (caracterizados por necrosis celular, daño axonal y/o activación microglial), se pueden observar daños difusos en la sustancia blanca en otras áreas cerebrales. El objetivo del tercer estudio (Sección 4.1.3.) consistió en examinar y cuantificar a través de la técnica de la *voxel-based morphometry* el daño a largo plazo en la sustancia blanca en una amplia cohorte de adolescentes con historia de parto prematuro sin evidencias de daño cerebral en dicho tejido a través de la inspección visual de los datos de resonancia. Junto a esto, un segundo objetivo consistió en caracterizar la influencia de la edad gestacional y el peso en la pérdida de integridad de la sustancia blanca.

Finalmente, es ampliamente conocido el desarrollo secuencial de los surcos y hemisferios cerebrales atendiendo a la edad gestacional. El cuarto estudio se diseñó con el objetivo de abordar si el nacimiento prematuro produce un desarrollo anormal a largo plazo de los surcos cerebrales que maduran de forma tardía, y relacionar las características sulcales con el volumen cortical próximo (Sección 4.1.4.).

Desde un punto de vista **funcional**, considerando las reducciones del tamaño del hipocampo descritas en muestras de prematuros, hipotetizamos que los adolescentes con historia de prematuridad mostrarán anomalías funcionales cerebrales asociadas. En este sentido, se han diseñado dos nuevos estudios.

La prematuridad se ha asociado con daños estructurales cerebrales y posiblemente el estudio de los metabolitos cerebrales pueda aportar nuevos datos a la información estructural. Una vez establecido el estado metabólico en una muestra de adolescentes sanos controles a través del estudio cerebral por espectroscopía (Sección 4.2.1.), examinamos la existencia de un posible patrón metabólico anómalo en una muestra de adolescentes con historia de parto prematuro comparado con un grupo control (Sección 4.2.2.). Este trabajo se realizó en una muestra de prematuros sanos sin complicaciones perinatales.

Por ultimo, cabe constatar la ausencia de estudios de resonancia magnética funcional previos al publicado en la presente tesis en muestras de adolescentes nacidos de parto prematuro. En la Sección 4.2.3. analizamos si el daño structural del hipocampo altera el patrón de activación cerebral durante una prueba de memoria declarativa. Nuestro estudio trata de examinar si el daño hipocampal es compensado por una hiperactivación cerebral o un mecanismo de activación compensatoria en el hemisferio preservado.

Metodología

La presente tesis consiste en seis estudios que examinan las bases neuroanatómicas y neurofuncionales en adolescentes que nacieron prematuramente. Además, se presenta un séptimo estudio sobre las características metabólicas del lóbulo temporal medial en una muestra de sujetos sanos. Para la realización de todos los estudios se han utilizado diversas aproximaciones neuropsicológicas y de resonancia magnética. Cada trabajo publicado detalla la metodología utilizada y las muestras estudiadas en cada caso.

Para la **evaluación neuropsicológica** de las muestras se utilizaron los siguientes tests: **a)** memoria verbal: versión modificada del '*Auditory Verbal Learning Test*' (Lezak y cols., 2004); **b)** memoria visual: 'Test de la Figura Compleja', de Rey (Rey, 1980); **c)** cociente de inteligencia: '*Wechsler Intelligence Scales*'. Se usó el WISC-R o el WAIS-III según la edad de los sujetos (Lezak y cols., 2004); **d)** fluencia verbal: *d.1.)* tarea de fluencia fonética, a través de la versión modificada del '*Controlled Oral Word Association Test*' (Artiola i Fortuny y cols., 1999). Los sujetos fueron instruidos para que generaran verbalmente palabras que empezaran con las letras P, M y R, en ensayos separados; *d.2.)* tarea de fluencia semántica, a través de la generación de palabras a partir de una consigna categórica (animales).

En relación a las **técnicas de neuroimagen** empleadas en la presente tesis, cabría señalar: **a)** técnicas estructurales: *a.1.)* técnica de la '*voxel-based moprhometry*' para evaluar diferencias grupales volumétricas y de densidad, tanto en la sustancia gris cerebral como en la blanca. En todos los estudios se utilizó el procedimiento optimizado propuesto por Good y cols. (2001). El procesamiento automático de los datos se realizó a través de los softwares SPM99 y SPM2; *a.2.)* análisis estructurales del hipocampo mediante estereología, a través del software ANALIZE (en sus diversas versiones). Para ello, se siguió el

protocolo establecido por Sheline y cols. (1996); *a.3.)* las mediciones del los surcos cerebrales se realizó a través del paquete "*Anatomist/BrainVisa 3.0.1*" (Riviere y cols., 2002; Mangin y cols., 2004); **b)** *técnicas de análisis funcional*: *b.1.)* análisis de los metabolitos cerebrales a través del software de la resonancia magnética y a través del programa '*Linear Combination Model-Fitting*', versión 6.1-4A (Provencher, 2001); *b.2.)* análisis de la actividad cerebral, basándonos en la respuesta BOLD (*Blood Oxigen Level Dependent*) durante una tarea de memoria declarativa, modificada de Sperling y cols. (2001).

A través de los diversos estudios, las muestras han ido modificándose atendiendo a los objetivos y requerimientos de cada estudio. La descripción detallada de las mismas se puede encontrar en cada estudio.

Hipótesis

Las hipótesis de los estudios que forman la presente tesis son las siguientes:

Hipótesis I

Los niños con antecedentes de parto prematuro muestran déficit de memoria y anomalías estructurales en diferentes regiones subcorticales de sustancia gris, tales como el hipocampo o el tálamo. Ambas estructuras se han relacionado previamente con pruebas de memoria declarativa. Hipotetizamos que las disfunciones de memoria en los niños prematuros correlacionarán con el decremento del volumen de dichas estructuras cerebrales en adolescentes que nacieron de un parto pretérmino.

Hipótesis II

La fluencia verbal es una secuela frecuente de las lesions talámicas, debido a la conexión de dicha estructura con las regiones cerebrales prefrontales. Considerando la presencia de reducciones talámicas en los prematuros, éstos mostrarán déficit en la fluencia verbal, y el volumen del tálamo correlacionará con dicha ejecución neuropsicológica.

Hipótesis III

Los estudios de prematuridad han mostrado daño periventricular de la sustancia blanca cerebral a través de la inspección visual de la resonancia magnética. Pero los adolescentes que nacieron prematuros y sin evidencias de daño a través de la evaluación de la imagen de resonancia magnética también mostrarán un daño difuso de la sustancia blanca cerebral, cuantificado a través de la comparación voxel a voxel del cerebro. Además, atendiendo a estudios experimentales previos, la edad gestacional correlacionará con las anomalías en la sustancia blanca.

Hipótesis IV

El desarrollo de los surcos y circunvoluciones del córtex cerebral es dependiente de la edad gestacional. Muchos de los sujetos prematuros nacen en los primeros estadios del desarrollo de los surcos cerebrales secundarios. Estos prematuros mostrarán anomalías en los surcos que permanecen inmaduros en el momento del nacimiento.

Hipótesis V

Estudios previos han demostrado que las muestras de niños prematuros presentan alteraciones metabólicas cerebrales en los estadios iniciales del desarrollo. El lóbulo temporal medial aparece como una región especialmente susceptible al daño cerebral. Los adolescentes con historia de parto prematuro, y sin evidencias visuales de daño cerebral, mostrarán un patrón neuroquímico alterado, que no será reversible durante la infancia. Esta anomalía del metabolismo cerebral se verá acompañada por cambios cerebrales estructurales y estará relacionada con la edad gestacional.

Hipótesis VI

Los sujetos nacidos prematuramente muestran reducciones volumétricas del hipocampo, una estructura relacionada con la memoria declarativa. Probablemente, la presencia de un hipocampo reducido alterará la activación cerebral durante una prueba de memoria declarativa, de forma que los prematuros mostrarán un incremento de la activación cerebral para compensar la lesión cerebral.

Resultados

El **primer estudio** demuestra diferencias significativas entre un grupo de 22 adolescentes con historia de parto prematuro y 22 sujetos controles en las puntuaciones de aprendizaje y reconocimiento en la prueba modificada del "*Rey Auditory Verbal Learning Test*", siendo significativamente inferiores las puntuaciones del grupo de prematuros (P = 0,020, P = 0,005, respectivamente); sin embargo exste una similitud entre grupos en la ejecución de la tarea con componente de memoria visual (P = 0,234).

A través del uso de la técnica '*voxel-based morphometry'* se observan reducciones del volumen del hipocampo izquierdo (P < 0,0001), así como reducciones bilaterales del tálamo (P < 0,0001) en el grupo de prematuros. El análisis del volumen del hipocampo mediante estereología corrobora la atrofia de esta estructura, con predominio izquierdo, cuando se corrige su volumen por el volumen intracraneal (hipocampo izquierdo: P = 0,038; hipocampo derecho: P = 0,073)

Este estudio demuestra correlaciones significativas entre las reducciones del volumen del hipocampo izquierdo (mediante la '*voxel-based morphometry*') y las puntuaciones de aprendizaje y el porcentaje de pérdida de memoria verbal (P = 0,001, P = 0,033) en los prematuros. Complementariamente, el análisis estereológico pone de manifiesto la presencia de una relación significativa entre el aprendizaje verbal y el volumen de la parte posterior del hipocampo izquierdo corregido por el volumen intracraneal (P = 0,047).

En segundo lugar, los adolescentes con historia de parto muy prematuro presentan diferencias significativas en pruebas de fluencia semántica y fonética (P < 0,0001, P = 0,044, respectivamente).

El análisis a través de la '*voxel-based morphometry*' muestra una atrofia bilateral del tálamo en el grupo de prematuros (izquierdo: P = 0,001, derecho: P = 0,002).

El estudio correlacional entre los diversos núcleos talámicos y la fluencia verbal (semántica y fonética) demuestra relaciones positivas significativas en el grupo de prematuros entre las puntuaciones en los dos tipos de fluencia y la reducción volumétrica de los diversos núcleos talámicos, bilateralmente (P < 0,001, a nivel de voxel). La ejecución en fluencia semántica se relaciona significativamente con el volumen de más núcleos talámicos que los que aparecen relacionados con las puntuaciones en la fluencia fonética.

En el **tercer estudio**, la evaluación de las características de la sustancia blanca cerebral en adolescentes que nacieron muy prematuros sin lesiones aparentes en la resonancia magnética muestra la presencia de anomalías significativas, tanto mediante el análisis de las imágenes de densidad como de volumen de la sustancia blanca en diversas regiones, que incluyen todos los lóbulos cerebrales. Los análisis de las imágenes de densidad identifican principalmente daño periventricular, así como la afectación de diversos fascículos longitudinales, mientras que los análisis de las imágenes de volumen detectan decrementos de sustancia blanca en regiones distales al sistema ventricular. Además, encontramos una correlación significativa entre los decrementos de sustancia blanca cerebral y la edad gestacional y el peso en el grupo de prematuros (P < 0,001 a nivel de voxel, en todos los análisis).

En el **cuarto estudio** estructural, los adolescentes nacidos antes de las 32 semanas de edad gestacional muestran una reducción de la profundidad de los surcos secundarios órbitofrontales (desarrollados más allá de la semana gestacional 32) comparados con adolescentes nacidos de un parto a término, manteniéndose similar la profundidad del surco olfativo primario (desarrollado a partir de la semana gestacional 16) en ambos grupos (Análisis de la Varianza para la profundidad, con la inclusión del tipo de surco y la variable grupo como factores: P = 0,024). El análisis de las posibles reducciones de la sustancia gris y blanca cerebrales colindantes a estos surcos órbitofrontales demuestra la reducción exclusivamente del volumen de la sustancia gris cerebral de la región próxima a los surcos secundarios (P = 0,026).

En relación a los **estudios metabólicos cerebrales**, una vez establecida la relación significativa en una muestra de adolescentes controles entre la ratio de N-Acetilaspartato/Colina en el lóbulo temporal medial y diversas medidas de memoria, en el estudio 6 se observa un patrón cerebral metabólico en el lóbulo temporal medial significativamente diferente en un grupo de prematuros comparado al presentado por sujetos controles. Los adolescentes con historia de parto prematuro sin complicaciones perinatales presentan un patrón metabólico cerebral caracterizado por reducciones en la concentración de Mioinositol (P = 0,018), Creatina (P = 0,001) y de los componentes N-Acetil (P < 0,0001) en el lóbulo temporal medial izquierdo. Los datos volumétricos del hipocampo izquierdo mediante estereología muestran una pérdida de volumen de dicha estructura en el grupo de prematuros, comparado con un grupo control (P < 0,0001).

El análisis correlacional entre la edad gestacional, los datos metabólicos y los volumétricos muestra correlaciones positivas significativas entre la edad gestacional y la concentración de Creatina ($P = 0{,}002$), Mioinositol ($P = 0{,}002$) y los componentes N-Acetil ($P < 0{,}0001$) para el conjunto de la muestra (prematuros y controles). Además, en el grupo de prematuros se observan correlaciones significativas entre la edad gestacional y la Creatina ($P = 0{,}012$) y la edad gestacional y los componentes N-Acetil ($P = 0{,}005$).

El estudio de la relación entre los datos metabólicos del área temporal medial izquierda y los datos volumétricos del hipocampo izquierdo (valores directos) señala la existencia de una relación positiva entre los componentes N-Acetil y el volumen del hipocampo ($P < 0{,}0001$), y entre la concentración de Creatina y el volumen hipocampal ($P = 0{,}001$), para el total de la muestra.

Finalmente, el análisis de la activación cerebral en una prueba de memoria declarativa (paradigma de asociación cara-nombre) en una muestra de adolescentes prematuros que presentan una reducción del hipocampo de predominio izquierdo muestra una hiperactivación del hipocampo derecho duante la ejecución de dicha tarea, comparado con un grupo control ($P = 0{,}002$). Además, se observa la presencia de una correlación significativa entre la activación del hipocampo derecho y la puntuación de reconocimiento de los pares estimulares en el grupo de prematuros ($P < 0{,}0001$). Sin embargo, los resultados del proceso de aprendizaje de los pares cara-nombre muestran diferencias entre prematuros y controles tanto en las puntuaciones de recuerdo libre de los nombres como en las de reconocimiento de la cara que pertenece a un nombre dado ($P = 0{,}011$ y $P = 0{,}027$, respectivamente), puntuando los sujetos prematuros en ambos casos por debajo de los controles. Los datos volumétricos del hipocampo derecho se muestran relacionados con la activación del mismo en el grupo de prematuros ($P < 0{,}0001$).

Discusión general

Al igual que estudios previos de análisis volumétricos manuales en muestras de prematuros (Isaacs y cols., 2000; Peterson y cols., 2000; Nosarti y cols., 2002), la presente tesis demuestra la existencia de reducciones hipocampales a través de técnicas cuantitativas en adolescentes con historia de parto prematuro (Gimenez y cols., 2004a). Este hallazgo coincide con los estudios neuropatológicos que demuestran necrosis en la misma área cerebral (Felderhoff-Mueser y cols., 1999). La atrofia del hipocampo se ha mostrado relacionada con diversas medidas neuropsicológicas, como el aprendizaje verbal y la retención a largo plazo, permaneciendo preservada la memoria visual. Previamente, Isaacs y cols. (2003a) también han constatado la discrepancia entre la memoria visual y verbal.

En un estudio previo, el mismo grupo también encontró una alteración de la memoria verbal y reducciones del hipocampo de forma bilateral, sin que hubiera una correlación significativa entre los hallazgos estructurales y neuropsicológicos (Isaacs y cols., 2000).

En el análisis del tipo de reducción hipocampal, de predominio anterior o posterior, nuestros resultados mostraron que los prematuros tenían una dominancia posterior, correlacionando esta parte del hipocampo con la alteración en la memoria verbal. Este resultado coincide con hallazgos previos en muestras de sujetos controles (Fernandez y cols., 1998).

Además de las reducciones volumétricas del hipocampo, la presente tesis es la primera en demostrar reducciones cuantitativas bilaterales en el tálamo en una muestra de 22 adolescentes que nacieron prematuros. Este resultado corrobora datos histopatológicos que apuntan la presencia de anomalías talámicas en este tipo de muestra (Krageloh-Mann y cols., 1999). El primero de los trabajos que componen esta tesis no mostró correlaciones entre el volumen del tálamo y diversas medidas de memoria declarativa, pese a que esta región cerebral se ha relacionado con redes de memoria (Van der Werf y cols., 2003). Probablemente, la región talámica principalmente afectada en nuestra muestra (el núcleo pulvinar) incide en la ausencia de correlación, ya que el pulvinar se ha visto más relacionado con la atención y con las funciones visoespaciales (Parent y Carpenter, 1996).

En una muestra más amplia de sujetos prematuros, el segundo estudio corrobora la presencia de reducción del volumen del tálamo en este tipo de muestra (Gimenez y cols., 2006a). Teniendo en cuenta que las lesiones talámicas se relacionan con déficit en la fluencia verbal (Ravnkilde y cols., 2002; Vitali y cols., 2005), en esta segunda investigación el volumen del tálamo se vio relacionado con dicha función. Tan sólo un estudio previo ha evaluado esta habilidad verbal en sujetos nacidos pretérmino, relacionándola con el cuerpo calloso (Nosarti y cols., 2004). Nuestro estudio demuestra correlaciones positivas entre el volumen del tálamo y dos tipos de fluencia, la semántica y fonética, especialmente en el grupo de prematuros. En el análisis

específico de cada núcleo talámico, encontramos que ambas fluencias mostraban patrones diferenciales en lo concerniente a su relación con el volumen de los núcleos del tálamo. Pese a que ambos grupos (prematuros y controles) mostraron correlaciones entre la ejecución en una prueba de fluencia fonética y el volumen de algunos núcleos talámicos, el patrón correlacional fue menos extenso para este tipo de fluencia que para el encontrado con la fluencia semántica en el grupo de prematuros (no se observaron relaciones significativas entre la ejecución semántica y el volumen de los núcleos del tálamo en el grupo control). Estos resultados coinciden con los estudios que postulan que la fluencia semántica requiere de un uso cerebral funcional más extenso que el necesitado para la fluencia fonética, en muestras patológicas (Kubota y cols., 2005) y que existe una superposición entre los patrones cerebrales que rigen las fluencias semántica y fonética (Crosson, 1999; Vitali y cols., 2005).

Más allá de las anomalías en regiones de sustancia gris cerebral, divrsos estudios en muestras de prematuros han demostrado que el cerebro inmaduro es especialmente susceptible al daño en la sustancia blanca (Blumenthal, 2004; Deguchi y cols., 1999; McQuillen y Ferriero, 2004; Volpe, 2001). En general, el daño en la sustancia blanca cerebral se relaciona con áreas periventriculares (Huppi y cols., 2001; Miller y cols., 2002; Counsell y cols., 2003; Inder y cols., 2005). En una muestra de 50 adolescentes que nacieron muy prematuramente y sin evidencias aparentes de lesión cerebral mediante inspección visual de la resonancia magnética, nuestro tercer estudio demuestra la presencia no sólo de lesión periventricular, sino también la existencia de daño en la sustancia blanca sutil y distal de las áreas periventriculares (Gimenez y cols., 2006b). Este hallazgo ha sido posible a través del uso de acercamientos diferenciales a los datos, a través del análisis tanto de las imágenes moduladas como de las no moduladas, mediante la técnica de la '*voxel-based morphometry*'. Estos nuevos resultados respaldan la evidencia de presencia de daño en la sustancia blanca más allá del clásico daño periventricular, y proporcionan un nuevo argumento para postular la presencia de lesiones en la sustancia blanca más generalizadas en muestras de sujetos que nacieron inmaduros. Nuestros resultados parecen implicar lesiones en fibras de asociación intrahemisféricas (Mori y cols., 2005), tales como los fascículos longitudinales superior e inferior, el fascículo occipotofrontal superior o el fascículo uncinado. Las diferencias sutiles encontradas en dichas regiones podrían estar parcialmente relacionadas con diversas alteraciones neuropsicológicas previamente descritas en parte de esta muestra (Gimenez y cols., 2004a), dado el rol asociativo de muchas de las fibras afectadas.

De la misma forma, también encontramos alteraciones en áreas de sustancia blanca a las cuales dichas fibras proyectan. En este tercer estudio también encontramos algunas reducciones de la sustancia gris cerebral en zonas corticales y subcorticales de los adolescentes nacidos muy prematuramente (Gimenez y cols., 2006b), sin que se encontrara una relación directa entre los dos tipos de lesiones (de la sustancia blanca y la gris).

Finalmente, parece ser que la integridad de la sustancia blanca cerebral en la adolescencia está relacionada con la edad gestacional y el peso en el nacimiento. Este dato coincide con estudios previos en recién nacidos (Larroque y cols., 2003). El hecho de que esta relación se mantenga en la adolescencia demuestra la persistencia del daño cerebral a largo plazo.

Un buen ejemplo del desarrollo cerebral dependiente de la edad gestacional es la formación de las circunvoluciones y los surcos cerebrales. Se ha demostrado que en los sujetos nacidos prematuramente el córtex aparece lisencefálico en el nacimiento (Ajayi-Obe y cols., 2000). Teniendo en cuenta los estudios que demuestran una maduración cortical cerebral diferencial según la edad gestacional (Chi y cols., 1977; van der Knaap y cols., 1996; Ruoss y cols., 2001), puede especularse sobre la posible existencia de una interrupción de la maduración normal cortical ante un nacimiento prematuro. En este sentido, considerando que parte del desarrollo de surcos y circunvoluciones del lóbulo frontal se desarrolla más tardíamente que la de otras áreas cerebrales (Ruoss y cols., 2001; van der Knaap y cols., 1996), el estudio del desarrollo de los surcos y las circunvoluciones en muestras de sujetos que nacieron muy prematuramente podría proporcionar datos que contrasten el desarrollo cortical de sujetos pretérmino y sujetos controles a largo plazo. Hasta el momento, el impacto del nacimiento muy prematuro en la profundidad de los surcos cerebrales se desconoce. Sólo existe un estudio previo que analiza las anomalías corticales en el lóbulo temporal asociadas con la prematuridad (Kesler y cols., 2006). Los autores muestran que el desarrollo del córtex temporal se ve afectado por el parto prematuro, con un aumento de las circunvoluciones. También demuestran una relación inversa entre las circunvoluciones del lóbulo temporal y el volumen de sustancia gris cerebral en dicho lóbulo. En nuestro cuarto estudio (Gimenez y cols., 2006c), demostramos que la profundidad de los surcos órbitofrontales

secundarios (cuyo desarrollo se inicia en una etapa gestacional tardía) se ve alterada por el nacimiento muy prematuro de los sujetos. Contrariamente a este dato, la profundidad del surco olfativo primario (cuyo desarrollo se inicia hacia las 16 semanas gestacionales) es similar entre sujetos prematuros y controles. Es interesante señalar que la alteración en la profundidad de los surcos secundarios se vio relacionada con reducciones de la sustancia gris cerebral de las áreas colindantes. Estos resultados proporcionan evidencias de una alteración en el desarrollo normal de la corteza cerebral que no es reversible durante la infancia.

Además del estudio neuroanatómico, la evaluación de datos funcionales cerebrales proporciona información útil en relación a las relaciones cerebro-comportamiento. En un estudio en adolescentes controles (Gimenez y cols., 2004b) demostramos una correlación entre la ratio de N-Acetilaspartato/Colina en el lóbulo temporal medial y la ejecución en una prueba de memoria. Muchos de los estudios cerebrales metabólicos se han realizado en muestras de sujetos recién nacidos o niños pequeños (Huppi y cols., 1995; Penrice y cols., 1996; Vigneron y cols., 2001). El estudio de los patrones cerebrales metabólicos en muestras de adolescentes que nacieron prematuros tiene un gran interés para evaluar si las anomalías metabólicas encontradas en la infancia se normalizan en la adolescencia. Existe tan sólo un estudio previo en una pequeña submuestra de adolescentes nacidos prematuramente que muestra decrementos en la ratio N-Acetilaspartato/Colina+Creatina en la región temporal en dichos sujetos comparados con adolescentes controles, dato sugestivo de un déficit persistente (Isaacs y cols., 2000). Con el objetivo de ampliar los datos existentes sobre el metabolismo cerebral en una muestra sana de adolescentes con historia de parto prematuro sin complicaciones perinatales ni lesiones cerebrales aparentes (mediante inspección visual de la resonancia magnética), realizamos un nuevo estudio (Sección 4.2.2.). En este trabajo encontramos un patrón metabólico alterado (reducciones en los principales metabolitos cerebrales) en el lóbulo temporal medial izquierdo en los sujetos prematuros comparados con una muestra control, así como reducciones del volumen del hipocampo. Tal y como se señalaba anteriormente, esta atrofia volumétrica ha sido previamente demostrada en sujetos prematuros (Isaacs y cols., 2000; Peterson y cols., 2000; Nosarti y cols., 2002). Nuestros hallazgos metabólicos y volumétricos se relacionan con la edad gestacional en el grupo de prematuros. En concreto, la existencia de una relación positiva entre la edad gestacional y la concentración de metabolitos N-Acetil y de Creatina coincide con un estudio previo que demuestra correlaciones entre ambos tipos de metabolitos y la edad gestacional en diversas regiones cerebrales (Kreis y cols., 2002).

Con ello, este estudio demuestra la existencia de alteraciones cerebrales neuroquímicas en adolescentes que nacieron prematuros y que presentan una resonancia magnética sin lesiones aparentes, datos que parecen ir de acuerdo con la posible existencia de disfunciones o pérdidas neuronales en la región del lóbulo temporal medial. Nuevos estudios podrían dirigirse a elucidar si estas alteraciones neurofuncionales se relacionan directamente con las alteraciones cognitivas observadas en este tipo de muestras.

Aparte de los análisis cerebrales metabólicos, los estudios de resonancia magnética funcional en muestras en las que se sospecha la existencia de daño cerebral pueden caracterizar la importancia y tipología de la lesión, de una forma que no es fácilmente abarcable desde datos meramente estructurales (Price y Friston, 2002). En este sentido, diseñamos un estudio para evaluar la activación cerebral en una prueba de memoria declarativa en adolescentes nacidos de un parto prematuro que tenían reducciones del hipocampo, de predominio izquierdo (Gimenez y cols., 2005). Los datos de este estudio demuestran una mayor activación en el hipocampo derecho, exclusivamente, en los sujetos prematuros respecto al grupo control. Esta activación se vio relacionada en el grupo de prematuros con el volumen del hipocampo derecho y con la puntuación en el reconocimiento de nombres previamente asociados a una cara (prueba de memoria declarativa realizada dentro del escáner). Estos datos permiten especular sobre un posible mecanismo de reorganización funcional contralateral del hipocampo más dañado. Este argumento parece coincidir con otros estudios focalizados en evaluar la activación de áreas o hemisferios preservados comparados con las regiones lesionadas en los mismos sujetos (Cao y cols., 1994; Vandermeeren y cols., 2003). Richardson y cols. (2003) realizaron un estudio funcional en una tarea de codificación de palabras en una muestra de sujetos con lesión hipocampal de predominio izquierdo y demostraron un aumento de la activación en el hipocampo derecho. Pese a que en nuestro estudio los sujetos prematuros mostraron un aumento de la activación del hipocampo respecto a los controles, esta activación no fue suficiente para adquirir el nivel de ejecución de los controles en la prueba de memoria declarativa, lo cual sugiere una deficiencia del mecanismo compensatorio y corrobora la existencia de déficit neuropsicológicos, descritos previamente en los

estudios de prematuridad (Isaacs y cols., 2000; Anderson y cols., 2003).

Cada vez más, existen datos que corroboran que el desarrollo anómalo del cerebro inmaduro favorece la presencia de déficit neurológicos, comportamentales y neuropsicológicos encontrados en sujetos prematuros, en los diversos estadios de crecimiento. La integración de todos los estudios que forman la presente tesis demuestra que el seguimiento a largo plazo de los niños que nacieron prematuros desde diversas aproximaciones metodológicas se esgrime como necesario y complementario para determinar las consecuencias neuropsicológicas y del neurodesarrollo que se relacionan con hallazgos anatómicos y funcionales. El momento, severidad y tipo de daño cerebral se muestran como variables críticas para la caracterización de las consecuencias.

Conclusiones

I) Los adolescentes con historia de prematuridad muestran reducciones volumétricas de dos estructuras cerebrales subcorticales que se han relacionado con la memoria declarativa, el hipocampo y el tálamo. Los déficit en la memoria declarativa observados en el grupo nacido pretérmino correlacionan con la atrofia del hipocampo. Consideramos dichas anomalías cerebrales como una evidencia de las alteraciones en el proceso de aprendizaje dependientes de daños cerebrales en sujetos nacidos prematuramente.

II) Los sujetos nacidos muy prematuramente muestran reducciones en el tálamo que se acompañan de alteraciones en la ejecución de pruebas de fluencia fonética y semántica. La fluencia verbal no correlaciona con la sustancia gris del lóbulo frontal, siendo los cambios en el volumen del tálamo los más directamente relacionados con los problemas en la fluencia. El análisis correlacional muestra un patrón de relación más amplio entre los núcleos talámicos y la ejecución en la fluencia semántica, que entre los núcleos del tálamo y la fluencia fonética.

III) El estudio del cerebro voxel a voxel es sensible para la detección del daño en la sustancia blanca cerebral en muestras de sujetos que nacieron muy prematuramente, y sin evidencias de daño cerebral a través de la inspección visual de la resonancia magnética. Aparte del clásico daño de la sustancia blanca periventricular, encontramos un daño sutil más difuso del tejido de sustancia blanca. Con esto, hemos ampliado el conocimiento del clásicamente descrito daño periventricular en los sujetos prematuros, a la idea de un daño de la sustancia blanca de carácter extensivo a lo largo de todo el cerebro. La integridad de la sustancia blanca cerebral en la adolescencia se relaciona con la edad gestacional, siendo este dato concordante con la información proveniente de estudios experimentales.

IV) Nuestros resultados muestran la primera evidencia del impacto de un nacimiento muy prematuro en la profundidad de los surcos del córtex en la adolescencia. Los sujetos que nacieron muy prematuramente presentan anomalías en la profundidad de los surcos cerebrales secundarios del córtex órbitofrontal, comparado con el desarrollo del surco olfativo primario. Estos resultados proporcionan evidencias de una alteración en el desarrollo normal de los surcos y circunvoluciones cerebrales que no es reversible a lo largo de la infancia.

V) Los adolescentes nacidos de un parto prematuro sin complicaciones perinatales ni evidencias de daño cerebral a través de la inspección visual de la resonancia magnética presentan alteraciones neuroquímicas en el lóbulo temporal medial, así como reducciones en el volumen del hipocampo. Dichas alteraciones metabólicas parecen reflejar una disfunción o pérdida neuronal. Los valores metabólicos y volumétricos se relacionan con la edad gestacional.

VI) Los adolescentes con historia de prematuridad y daño hipocampal de predominio izquierdo muestran un aumento de la actividad cerebral en el hemisferio derecho comparado con una muestra control, durante la ejecución de una tarea de memoria declarativa. Este dato sugiere la presencia de un mecanismo cerebral compensatorio, que sin embargo no es suficiente para alcanzar la ejecución neuropsicológica de los controles.

Finalmente, y considerando los datos previamente obtenidos, futuras líneas de investigación podrían ir dirigidas a la evaluación de los siguientes campos de estudio:

- La evaluación neuropsicológica de funciones relacionadas con el lóbulo frontal y su desarrollo cortical. Cabría la posibilidad de intentar dilucidar los correlatos funcionales de las alteraciones del córtex frontal, dado que podría ser que las disfunciones sociales y comportamentales descritas en este tipo de muestras estuviesen relacionadas a largo plazo con esta secuela cerebral.
- El estudio funcional de la activación cerebral en pruebas que impliquen el paso de información a

través de fibras de sustancia blanca asociativas, para comparar muestras de prematuros con lesiones en las diversas fibras de axones. En relación con el estudio de la sustancia blanca cerebral, no existen investigaciones que combinen en una misma aproximación metodologías como el tensor de difusión, el análisis voxel a voxel del cerebro y la activación cerebral.

- Hasta el momento, muchos estudios en muestras de prematuros se han realizado en niños y adolescentes. Futuras investigaciones podrían considerar la posibilidad de hacer un seguimiento a largo plazo de amplias muestras de prematuros para evaluar los posibles cambios cerebrales estructurales y funcionales en la vida adulta.

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ANNEX

Acceptation of the paper entitled:

"Abnormal orbitofrontal development due to prematurity"

----- Original Message -----
From: <neuro_journal@urmc.rochester.edu>
To: "Carme Junque" <cjunque@ub.edu>
Sent: Wednesday, August 16, 2006 6:08 PM
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16 August 2006

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