# PATTERNS OF CEREBRAL GRAY AND WHITE MATTER ALTERATIONS IN PRETERM SUBJECTS BY MAGNETIC RESONANCE IMAGING

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*CERTIFIES that she has supervised and guided the PhD thesis entitled* "**PATTERNS OF CEREBRAL GRAY AND WHITE MATTER ALTERATIONS IN PRETERM SUBJECTS BY MAGNETIC RESONANCE IMAGING**", *presented by Sara Soria Pastor. She hereby asserts that this thesis fulfils the requirements to be defended for the Degree of Doctor.*

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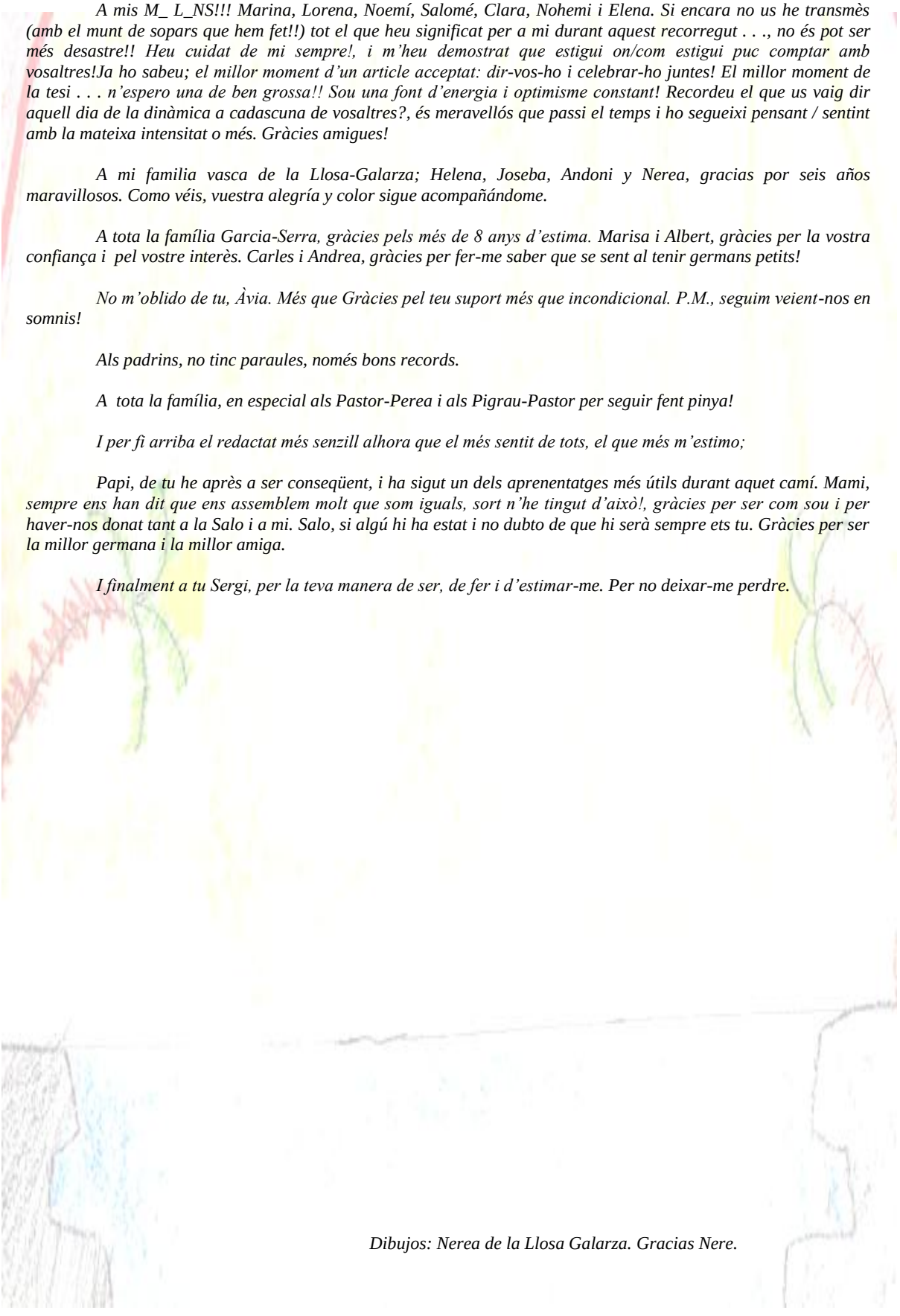

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***A l'àvia.***

***Al millor padrí.***

.

***El experimentador que no sabe lo que está buscando no comprenderá lo que encuentra.***
***(Claude Bernard)***

***Lo oscuro acabamos viéndolo; lo completamente claro lleva más tiempo.***
***(Edward Roscoe Murrow)***

## *Contents*

## *Foreword*

*This thesis, presented to obtain the degree of Doctor by the University of Barcelona, is the result of two different studies carried out 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.*

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*Study I:*

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*Study II:*

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| | |
|---|---|
| **BA** | *Brodmann Area* |
| **BW** | *Birth Weight* |
| **CBCL** | *Child Behaviour Checklist* |
| **CC** | *Corpus Callosum* |
| **CSF** | *Cerebral Spinal Fluid* |
| **DARTEL** | *Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra* |
| **DTI** | *Diffusion Tensor Imaging* |
| **ELBW** | *Extremely Low Birth Weight* |
| **EPT** | *Extremely Preterm* |
| **FA** | *Fractional Anisotropy* |
| **FDR** | *False Discovering Rate* |
| **FLAIR** | *Fluid-attenuated Inversion Recovery* |
| **fMRI** | *Functional Magnetic Resonance Imaging* |
| **GA** | *Gestational Age* |
| **GM** | *Gray Matter* |
| **ICV** | *Intracranial Volume* |
| **IQ** | *Intelligence Quotient* |
| **IUGR** | *Intrauterine Growth Restriction* |
| **IVH** | *Intraventricular Haemorrhage* |
| **LBW** | *Low Birth Weight* |
| **MNI** | *Montreal NeurologicaI Institute* |
| **MRI** | *Magnetic Resonance Imaging* |
| **NEC** | *Necrotizing Enterocolitis* |
| **PIQ** | *Performance Intelligence Quotient* |
| **PV** | *Periventricular* |
| **PVL** | *Periventricular Leukomalacia* |
| **RDS** | *Respiratory Distress Syndrome* |
| **SD** | *Standard Deviation* |
| **SGA** | *Small for Gestational Age* |
| **VBM** | *Voxel-Based Morphometry* |
| **VIQ** | *Verbal Intelligence Quotient* |
| **VLBW** | *Very Low Birth Weight* |
| **VPT** | *Very Preterm* |
| **WAIS** | *Wechsler Adult Intelligence Scale* |
| **WHO** | *World Health Organization* |
| **WISC** | *Wechsler Intelligence Scale for Children* |
| **WM** | *White Matter* |

# 1. INTRODUCTION

# 1. Introduction

Preterm birth is still a major cause of infant morbidity and mortality worldwide, although important advances in neonatology and perinatal care have significantly increased the survival rate of preterm born infants. Today, the neurocognitive and neurobehavioural outcome of children born preterm constitute one of the main issues in paediatrics. Conventional magnetic resonance imaging (MRI) has established itself as a useful tool in the study of brain lesion due to prematurity. Nevertheless, the correlation between these appearances and developmental outcome has not been investigated in depth.

## *1.1 Theoretical framework of prematurity*

### *1.1.1. Length of gestation*

Preterm birth and its consequences constitute a major health problem worldwide. In 1977, in association with the International Federation of Gynaecology and Obstetrics the World Health Organization defined preterm birth as delivery before 37 completed weeks of gestation (259 days), based on the first day of the last menstrual period (WHO, 1997) (Figure 1 summarizes the currently accepted definitions of pregnancy lengths). The lower limit of viability in preterm birth is determined by foetal organ development and advances in high-risk obstetric and neonatal intensive care. Although there are sporadic reports of survival at the lowest gestational ages (GA) (21 or 22 weeks) or birth weights (BW) (400 grams), the lower limit of viability has been defined as the GA or BW at which 50% of population survives (Alexander *et al.*, 1999; Allen *et al.*, 2000). Consistent definitions for describing the length of gestation and age in neonates are used in order to compare neurodevelopmental, medical, and growth outcomes (Engle, 2004). The conventional definitions regarding age terminology during the perinatal period are displayed in Table 1.

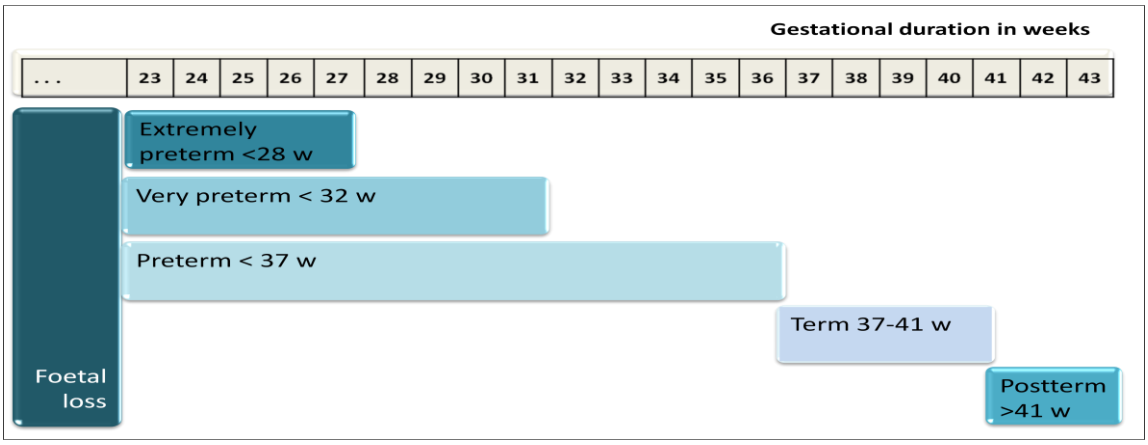



**Figure 1. Categorization of pregnancy lengths** (modified from *Tucker and McGuire, 2004*).

**Table1.** Age terminology during the perinatal period

| *Term* | *Definition* | *Units of Time* |
|---|---|---|
| *Gestational age* | *Time elapsed between the first day of the last menstrual period and the day of delivery* | *Completed weeks* |
| *Chronological age* | *Time elapsed since birth* | *Days, weeks, months, years* |
| *Postmenstrual age* | *Gestational age _ chronological age* | *Weeks* |
| *Corrected age* | *Chronological age reduced by the number of weeks born before 40 weeks of gestation* | *Weeks, months* |

Source: *Engle, 2004*.

### *1.1.2. Measures of size at birth*

Children demonstrating BWs 2 Standard Deviation (SD) below or above the mean BW for GA are referred to as appropriated for GA. Low BW is defined by the WHO as weight at birth of less than 2,500 grams (WHO, 1977). Figure 2 shows the current BW classification. Low weight at birth may be the result of preterm birth or of restricted foetal intrauterine growth. Therefore, both preterm and full-term infants may present low BW. Another BW-related condition regardless of whether the pregnancy ends at term or preterm is the "small for gestational age" (SGA) concept. SGA is defined as BW and/or length at least 2 SD below the mean for GA or less than the $10^{th}$ percentile for GA (Lee *et al.*, 2003). Although the terms SGA and intrauterine growth restriction (IUGR) are often used as synonyms, they reflect two different concepts. While SGA refers to a statistical definition, based on an auxological cross-sectional evaluation (prenatal or neonatal), and denotes a foetus or a neonate whose anthropometric variables (usually weight) are lower than a given threshold value computed from set of infants with the same GA, IUGR refers to a clinical and functional condition and denotes foetuses unable to achieve their own growth potential: a foetus with IUGR would have been larger if adverse environmental or genetic factors had not affected its growth (Bertino *et al.*, 2007). IUGR is usually assessed using ultrasound. Moreover, both SGA and IUGR conditions are considered as risk factors for adverse neurodevelopmental outcome (see Section 1.5.7.).


**Figure 2. Birth weight classification.**

### *1.1.3. Epidemiology of preterm birth*

Estimates of preterm birth rates range from 5% in developed countries to 25% in developing countries (Steer, 2005). It is obvious that, to some extent, this is due to different levels of well-known risk factors and contributors of preterm delivery, such as artificial reproductive treatment, multiple births, ethnic admixture and the varying extent to which preterm gestations are induced (Morken *et al.*, 2008). The rates of preterm birth are relatively stable in the developed world, ranging from 5% to 15% according to the social and nutritional status of the mothers (Steer, 2005). As Figure 4(A) and Table 2 show, in Spain the proportion of preterm births has risen fairly steadily, and consequently the prematurity rate has doubled in the last ten years. Specifically, the incidence of multiple births increased progressively from 1996 to 2006; for instance, the rates of twin births climbed from 4% to 7%. As can be deduced from these data, multiple births are much more likely than singletons to be born preterm. The rise in multiple births is largely because of the increased use of assisted reproduction techniques, such as drugs that induce ovulation and *in vitro* fertilization (Tucker and McGuire, 2004). In summary, the percentage of preterm birth today in Spain is ~ 8-9 % (*Instituto Nacional de Estadísitica de España*: http://www.ine.es), and 85% of the most immature neonates (<1500 gr) survive (*Sociedad Española de Neonatología*: www.se-neonatal.es).

### *1.1.4. Aetiological heterogeneity of preterm birth*

Prematurity is associated with a vast range of complex biological, psychological, and social factors which are poorly understood but interrelated, and which appear to be expressed in the common pathway of preterm birth (Bherman and Butler, 2007). Although the greatest aetiological factor worldwide is infection (mainly due to malaria and human immunodeficiency virus), in developed countries, iatrogenic delivery is responsible for almost half of the births between 28 and 35 weeks; hypertension and pre-eclampsia are the major pathologies. Other factors include multiple pregnancy, IUGR (Lackman *et al.*, 2001), maternal stress and heavy physical work (Steer, 2005). Main causes of spontaneous and medically indicated preterm labour are summarized in Figure 3.

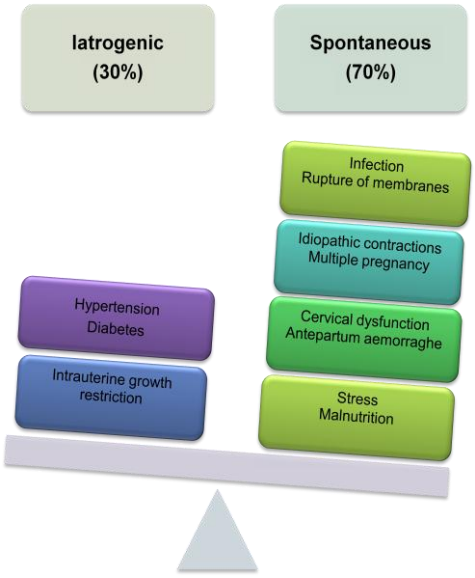



**Figure 3. Preterm birth: summary of causes**
(Adapted from Steer, 2005).

**Table 2.** Number of preterm births and percentual increases in Spain during the last 10 years

| | All labours | | | Singletons | | | Twins | | | Triplets or higher-order multiple births | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Year** | ***Total*** | ***Term*** | ***Preterm*** | ***Total*** | ***Term*** | ***Preterm*** | ***Total*** | ***Term*** | ***Preterm*** | ***Total*** | ***Term*** | ***Preterm*** |
| **1996** | 359,309 | 342,255 | 17,054 | 354,729 | 339,289 | 15,440 | 4,433 | 2,922 | 1,511 | 147 | 44 | 103 |
| **1997** | 365,564 | 341,932 | 23,632 | 360,743 | 339,230 | 21,513 | 4,649 | 2,675 | 1,974 | 172 | 27 | 145 |
| **1998** | 361,393 | 337,062 | 24,331 | 356,378 | 334,283 | 22,095 | 4,820 | 2,759 | 2,061 | 195 | 20 | 175 |
| **1999** | 375,683 | 349,925 | 25,758 | 370,003 | 346,798 | 23,205 | 5,457 | 3,102 | 2,355 | 223 | 25 | 198 |
| **2000** | 392,584 | 365,511 | 27,073 | 386,336 | 362,252 | 24,084 | 5,975 | 3,231 | 2,744 | 273 | 28 | 245 |
| **2001** | 401,054 | 373,721 | 27,333 | 394,507 | 370,302 | 24,205 | 6,234 | 3,378 | 2,856 | 313 | 41 | 272 |
| **2002** | 412,753 | 383,288 | 29,465 | 405,512 | 379,661 | 25,851 | 6,929 | 3,601 | 3,328 | 303 | 26 | 277 |
| **2003** | 435,261 | 404,304 | 30,957 | 427,457 | 400,520 | 26,937 | 7,499 | 3,763 | 3,736 | 305 | 21 | 284 |
| **2004** | 447,784 | 415,866 | 31,918 | 439,806 | 411,922 | 27,884 | 7,712 | 3,927 | 3,785 | 266 | 17 | 249 |
| **2005** | 459,265 | 428,095 | 31,170 | 450,831 | 423,886 | 26,945 | 8,225 | 4,193 | 4,032 | 209 | 16 | 193 |
| **2006** | 475,635 | 442,233 | 33,402 | 466,913 | 437,885 | 29,028 | 8,510 | 4,335 | 4,175 | 212 | 13 | 199 |
| ***Percentual increases 1996-2006*** | *+32.4%* | | *+95.9%* | *+31.6%* | | *+88%* | *+92%* | | *+176.3%* | *+44.2%* | | *+93.2%* |

Source: *Instituto Nacional de Estadística de España* (INE): www.ine.es

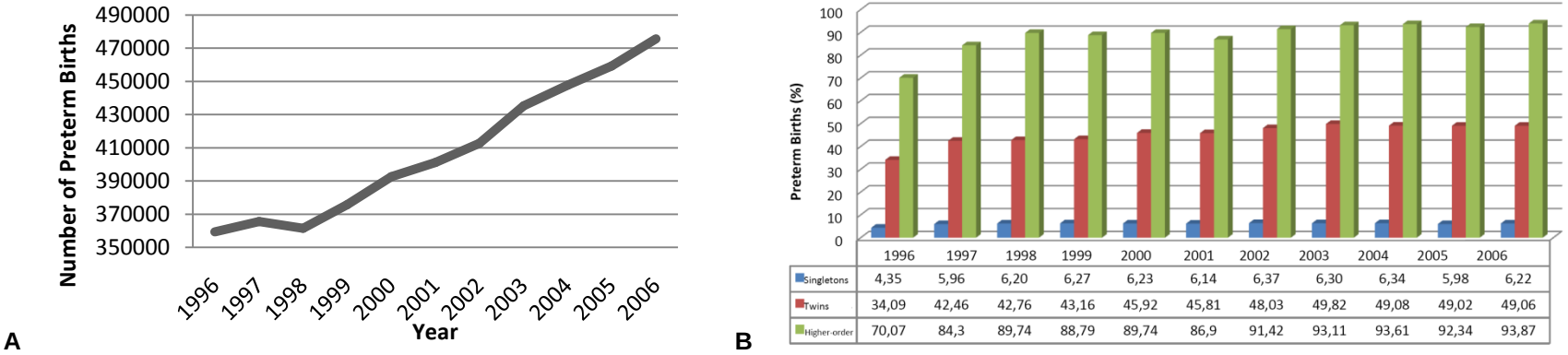



**Figure 4.** Graph (**A**) illustrates the tendency in the number of preterm births according to the natural movement of the Spanish population from 1996 to 2006. Graph (**B**) detailes the percentages of preterm births according to singleton and multiple pregnancies. Source: *Instituto Nacional de Estadística de España* (INE): www.ine.es

Goldenberg *et al.*, 2008 have recently detailed three obstetric precursors leading to preterm birth: (1) delivery for maternal or foetal indications, in which labour is either induced or the infant is delivered by prelabour caesarean section, (2) spontaneous preterm labour with intact membranes and (3) preterm premature rupture of the membranes, irrespective of whether delivery is vaginal or by caesarean section. Figure 5 shows the percentages of these obstetric precursors of preterm birth.

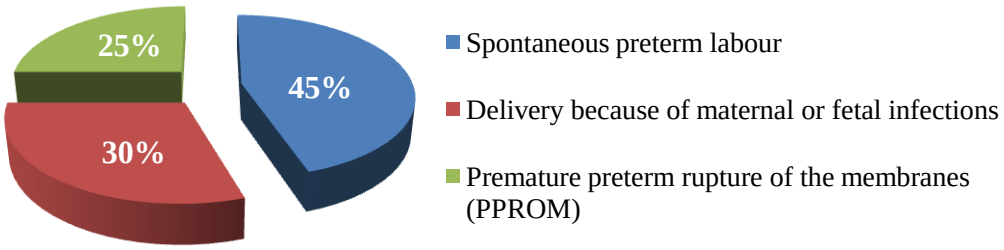



**Figure 5. Obstetric precursors of preterm birth** (Adapted from Goldenberg *et al.*, 2008).

Risk factors for spontaneous preterm births include a previous preterm birth, poor socioeconomic background of the mother black race, periodontal disease and low maternal body-mass index (Tucker and McGuire, 2004). Short cervical length and a raised cervical-vaginal fetal fibronectin concentration are the strongest predictors of spontaneous preterm birth (Goldenberg *et al.*, 2008). Therefore, preterm born infants are not a homogeneous group. They have all been exposed to different biological conditions resulting in preterm birth and consequently to different neonatal complications *(see Section 1.1.6.)* and medical interventions.

### *1.1.5. Mortality and morbidity after preterm birth*

Preterm delivery is a serious global health problem and one of the leading causes of child death worldwide (Bryce *et al.*, 2005). Compared with infants born at term, preterms have a much greater risk of death and disability. Approximately 75 % of perinatal deaths occur in infants born prematurely (Slattery and Morrison, 2002). Despite these elevated perinatal mortality rates, preterms' survival has improved over recent decades. In fact, at present, the advances in medical technologies and therapeutic perinatal and neonatal care have led to improved rates of survival among preterm infants, including those born with a GA of only 23 weeks. However, surviving infants have a higher risk of morbidity. Morbidity is inversely related to GA; however, there is no GA, including term, that is wholly exempt (Saigal and Doyle, 2008). Although the group of infants with the greatest morbidity and mortality are those who are born at less than 32 GA weeks, infants born between 32 and 36 GA weeks represent the

greatest number of preterm births (Bherman and Butler, 2007). Interventions to reduce the morbidity and mortality of preterm birth can be primary (directed at all women), secondary (aimed at eliminating or reducing existing risk), or tertiary (intended to improve outcomes for preterm infants). Although these measures have reduced perinatal morbidity and mortality, the incidence of preterm birth is still increasing. According to the experts, advances in primary and secondary care will be needed to prevent prematurity-related illness in infants and children (Iams *et al.*, 2008).

### *1.1.6. Neonatal complications following preterm birth*

Most premature infants born at <32 weeks gestation remain in the newborn intensive care units until close to term to allow sufficient organ maturation. The complications of preterm birth arise, then, from immature organ systems that are not yet prepared to support life in the extrauterine environment (Ward and Beachy, 2003). As Figure 6 illustrates, the developmental immaturity of preterm newborns affects a wide range of organs and systems.

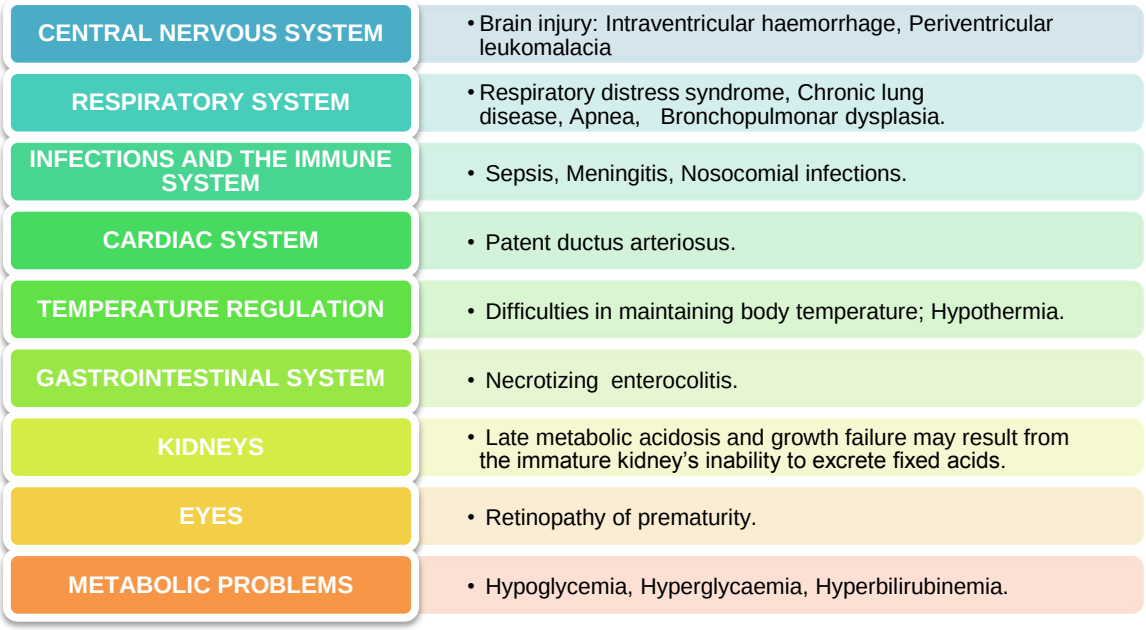



**Figure 6. Neonatal complications following preterm birth.**

Neubauer *et al.*, 2008 conducted a ten years follow-up study to identify the perinatal and neonatal factors associated with adverse cognitive and neurological outcomes. They concluded that some neonatal complications were important risk factors for long-term neurodevelopmental deficits, particularly necrotizing enterocolitis (NEC), respiratory distress syndrome (RDS) severe intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL).

Prematurity remains the most consistent risk factor for NEC and its risk is inversely related to BW and GA (Lin and Stoll, 2006). NEC is an inflammatory disorder of the gastrointestinal tract that is more frequently in premature infants or those SGA at birth than in term neonates (Ward and Beachy, 2003).Despite decades of research, its pathogenesis remains unclear (it is associated with decreased intestinal blood flow and invasion of bacteria into the intestinal wall), diagnosis can be difficult and treatment is challenging (Linn *et al.*, 2008).

Severe neonatal lung disease due to surfactant deficiency, structural immaturity, and infection remains a frequent neonatal problem (Ward and Beachy, 2003). The lack of surfactant makes the lung non-compliant and the infant is at risk of developing RDS, a condition which requires continuous positive airway pressure or mechanical ventilation to ensure adequate gaseous exchange. The chronic lung disease, that sometimes follows RDS in preterm infants, is also called bronchopulmonary dysplasia; it is a chronic disorder that results from inflammation, injury and scarring of the airways and the alveoli (Dammann *et al.*, 2005).

IVH or haemorrhage into the germinal matrix tissues of the developing brain with possible rupture into the ventricular system and parenchyma remains a major problem in preterm neonates and has been attributed to alterations in cerebral blood flow to a damaged germinal matrix capillary bed (Duncan and Ment, 1993). IVH is a common neonatal morbidity among premature infants which is diagnosed by cranial ultrasound in the newborn special care unit. Although very preterm (VPT) infants are more likely to experience the highest grades of hemorrhage, a number of perinatal and postnatal events have been shown to be associated with its occurrence (Vohr and Ment, 1996). Another cerebro-vascular lesion is PVL. PVL may occur in premature infants of less than 32 weeks gestation due to their unique anatomical features; the WM of these infants is poorly vascularised and contains oligodendrocyte progenitors (pre-oligodendrocytes), which are sensitive to the effects of ischaemia and infection (Blumenthal, 2004) (*for more details about IVH and/or PVL see Sections 1.3.1.1 and 1.3.1.2., respectively*).

It is important to note that cerebral WM injury, mainly following IVH and PVL, is the most significant problem contributing to neonatal mortality and to long-term neurologic deficits in the premature infant (Perlman, 1998; Volpe, 2003).

## *1.2. Human brain development*

The development of the human brain is a process that commences early in gestation and continues into adulthood following a series of precise and genetically predetermined stages (de Graaf-Peters and Hadders-Algra, 2006). Prenatal life is usefully divided into embryonic and foetal periods. The embryonic period is characterized by the rapid appearance of new features, whereas the foetal period is more concerned with the elaboration of existing structures. The embryonic period, however, is particularly important because the vast majority of congenital anomalies arise during that time (O'Rahilly and Müller, 2008). Neurulation, differentiation of cerebral vesicles and neurogenesis occur especially during the first half of gestation (Encha-Razavi and Sonigo, 2003). The second half is characterized by the tremendous growth of the cerebral hemispheres; this is the major period of glial cell proliferation, programmed cell death (de Graaf-Peters and Hadders-Algra, 2006) and the settlement of gyral formation (Encha-Razavi and Sonigo, 2003). Axon and dendrite sprouting and synapse formation bloom during the last trimester of gestation and the first postnatal year (de Graaf-Peters and Hadders-Algra, 2006). To summarize, the basic stages in the cell development are: neurogenesis, cellular migration, dendritic growth and synapse formation (Kolb *et al.*, 2000). The time course of critical events in the determination of human brain morphometry is detailed in Figure 7. Therefore, the final size of the brain is determined by the rate of production of neurons and glial cells and the programmed cell death (Encha-Razavi and Sonigo, 2003). Many developmental processes, such as myelination, synapse formation and synapse elimination continue throughout childhood and adolescence (de Graaf-Peters and Hadders-Algra, 2005).

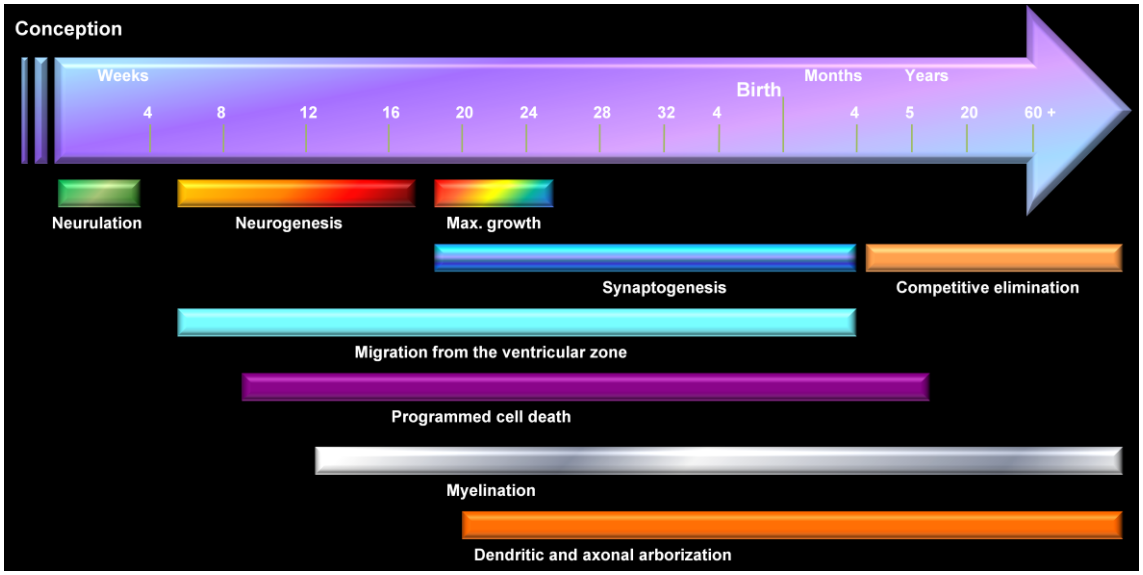



**Figure 7. Time course of critical events in the determination of human brain morphometry** (Adapted from *Lenroot and Giedd, 2006*).

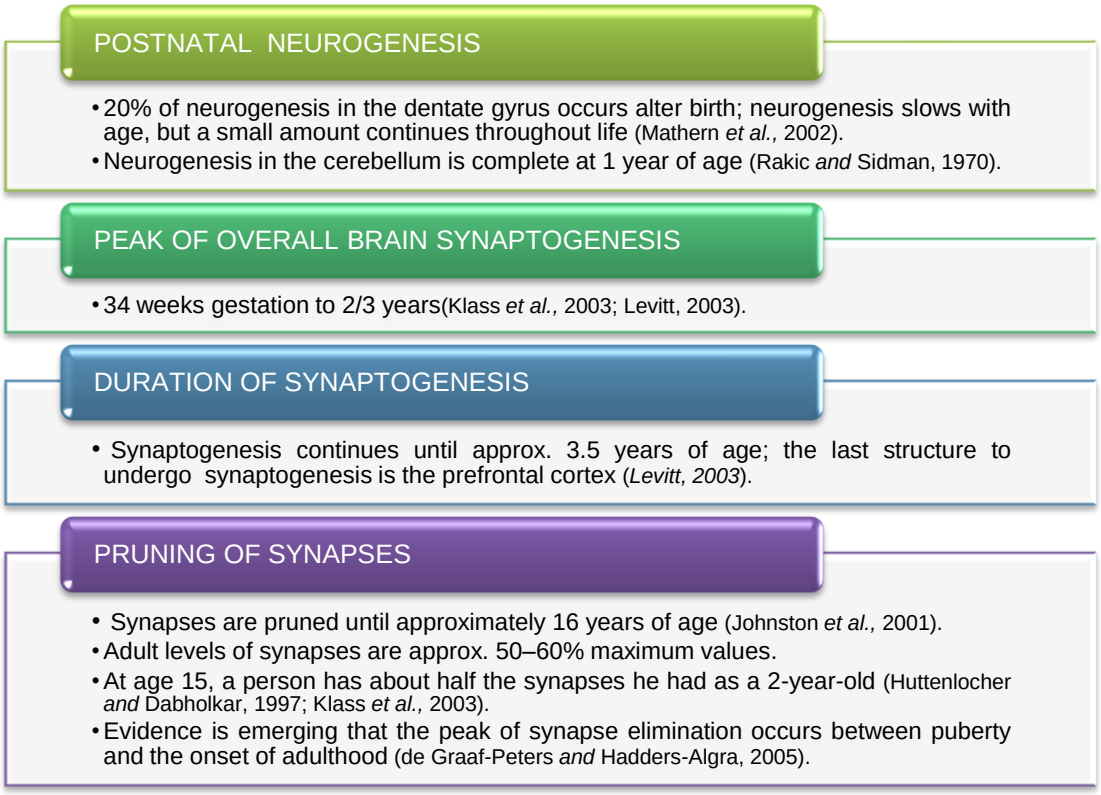
### *1.2.1. Cell proliferation and neuronal migration*

The first key event in the development of the central nervous system is the formation of a specialized fold of ectodermal tissue called the neural tube. From 4 to 12 weeks the neural tube differentiates into what will become various components of the nervous system. The forebrain and facial structures develop at one end, and the spinal cord at the other. The hollow center of the tube in the region that will become brain will eventually form the ventricles. Regions form near the ventricles, called proliferative zones, give rise to young neurons (Lenroot and Giedd, 2006). From 12 to 20 weeks these neurons multiply and migrate from their origins to destinations in the cortex, moving along a scaffolding of glial cells (Rakic *et al.,* 1994). As different neurons become postmitotic in sequence, their laminar location depends on the time when they differentiate (McKay, 1997). This migration is followed by a period of rapid cell death, reducing the neural number by half from 24 weeks of gestation to 4 weeks after birth. The cell bodies of the neurons are primarily found in the gray matter (GM) of the brain and their myelinated axons form the white matter (WM) (Lenroot and Giedd, 2006). The formation of glia begins at four and a half post-fertilization weeks and continues postnatally. Glial cells develop in the ventricular and subventricular layers of the prosencephalon; from the mesencephalic, rhombencephalic, and spinal neural crest, and from haematopoietic mesenchyme. As mentioned above, the glia is essential for the migration of neurons (O'Rahilly and Muller, 2008). Experiments from the laboratories of Sperry, Benzer, Nieuwkoop, and Le Douarin confirm that, important features of brain organization are a consequence of events that occur early in development, long before synapses form (McKay, 2000).

### *1.2.3. Synaptogenesis*

Another major developmental process is the proliferation and organization of synapses, which begins slightly later, around the 20th week of gestation (Lenroot and Giedd, 2006). Synaptogenesis refers to the formation of synapses through an elaborate, precisely timed process consisting of the establishment of biochemical and morphological elements followed by competitive exclusion of inappropriate connections (Watson *et al.,* 2006). The peak of overall brain synaptogenesis, and the duration and the pruning of synapses are summarized in Table 3.

**Table 3.** Postnatal neurogenesis and synaptogenesis in the human brain




Source: Adapted from *Watson et al., 2006*.

### *1.2.4. Normal brain myelination*

Myelination occurs regionally, beginning with the brain stem at 29 weeks of gestation (Inder and Huppi, 2000) and generally proceeds from inferior to superior and posterior to anterior (see Figure 8). Thus, the brain stem myelinates before the cerebellum and basal ganglia myelinates prior to the cerebral hemispheres. Within any portion of the brain, the dorsal aspect trends to myelinate first; the dorsal brain stem (containing the medial lemniscus and medial longitudinal fasciculus) trends to myelinate before the ventral brain stem (which contains the cortico-spinal tracts). In the same way, the occipital lobes myelinate earlier than the frontal lobes (Barkovich, 2000). Another general trend in the maturation of the brain is that proximal pathways tend to myelinate before distal, sensory before motor, and projection before association (Volpe, 2000).

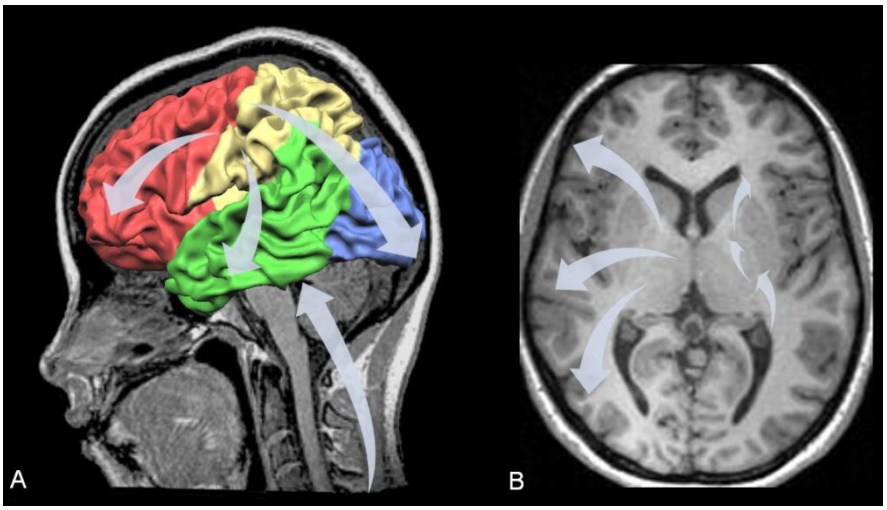



**Figure 8. MRI of the brain depicts the progression of myelination.** (**A**) Myelination progressing in a caudocranial direction from the brain stem, through the posterior limb of internal capsule and to the hemispheric white matter, proceeding to the central sulcus toward the poles. (**B**) Myelination advancing from deep to superficial and from posterior to anterior (Modified from Ballesteros *et al.*, 1993).

In many individuals, regions of WM dorsal and superior to the trigones of the lateral ventricles do not myelinate until the end of the first decade of life. At birth, the corpus callosum (CC) is thin and flat; the normal bulbous enlargements at the genu and splenium are not yet present. The CC matures from posterior to anterior. By the end of the ninth month of life, the CC should be similar in appearance to that of an adult (Barkovich, 2000). Although most major tracts are significantly myelinated by early childhood, axons within the cortex and in some regions such as the arcuate fasciculus, a white matter bundle near the temporal lobe, continue to myelinate into the second and third decades of life (Lenroot and Giedd, 2006). Similarly, the CC, the most prominent WM structure consisting of approximately 200 million myelinated fibres (most of which connect homologous areas of the left and right cortex) continues to develop throughout adolescence (Pujol *et al.*, 1993 and Rauch and Jinkins, 1994).

Diffusion-weighted and diffusion tensor images (DTI) have become a sensitive tool for monitoring WM development. Different applications of diffusion-weighted techniques provide information about remyelinating, myelinating, and postmyelinating states of WM maturation (Prayer and Prayer, 2003). In preterm newborns, WM has a lower signal intensity than GM on T1-weighted images and a higher signal intensity on T2-weighted images. The T1 and T2 relaxation rates of the neonatal brain are longer than those of the adult because of the higher water content and structural immaturity of the developing myelin sheath. Diffusion-tensor apparent diffusion coefficient images show strong GM/WM contrast because of the higher rate of diffusion in WM than in GM, but this contrast will disappear during the first year of life (Miller *et al.*, 2003). *For more details see Sections 1.2.6.2. and 1.4.2.*

### *1.2.5. Brain folding*

The normal sulcal and gyral fetal development pattern have been investigated by using different approaches such as neuropathological postmortem studies (Chi *et al.,* 1977; Dorovini-Zis and Dolman, 1977), ultrasound (Monteagudo and Timor-Tritsh, 1997; Toi *et al.,* 2004) and MRI (Abe *et al.,* 2004; Rutherford *et al.,* 2008). Anatomo-pathological studies seem to detect the beginning of cortical folding earlier than *in vivo* imaging techniques (Rouss *et al.,* 2001) and they describe foetal brains as lissencephalic up to week 18 of pregnancy (Chi *et al.,* 1977). The appearance of brain sulci and gyri is related to GA and this folding formation follows an invariable temporospatial schedule (Chi *et al.,* 1977; Rouss *et al.,* 2001; van der Knaap *et al.,* 1996). Primary fissures appear between the 18$^{th}$ and 24$^{th}$ weeks and lead to the demarcation of the frontal, parietal, occipital and temporal lobes. The cingular fissure occurs first, followed by the parieto-occipital fissure at 18 weeks and the Rolando (central) sulcus at 20 weeks. At the same time, operculization starts with the formation of the sylvian fossa. Operculization progresses between the 26th and 34th weeks with an invariable timetable and leads to the settlement of the sylvian (lateral) sulcus. Secondary sulci appear around the 24th week. Tertiary sulci appear between the 28th and 37th week and show large individual variability (Encha-Razavi and Sonigo 2003) (see Figure 9). The anatomopathological study by Chi *et al.* (1977) describes two trends in the sequence of sulcal development: firstly the mediolateral trend (sulcal development from the medial to the lateral part) and secondly the posterior-anterior trend (sulcal development from posterior to anterior regions). Regarding the folding formation assessed by MRI in preterm and term neonates, van der Knaap and colleagues 1996 reported that development of gyri and sulci was most advanced in the area of the central sulcus and the medial occipital area, and it ocurred latest in the frontobasal and frontopolar areas and the anterior part of the temporal lobe.

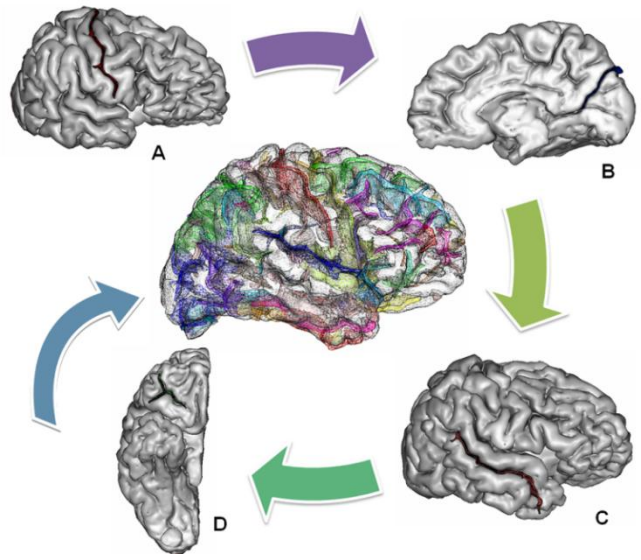



**Figure 9. Brain maturation of sulci and gyri.** Brain maturation of sulci and gyri assessed by early postnatal MRI in preterm and term newborn infants starts in the central area (**A**) and proceeds towards the parieto-occipital cortex (**B**) being the frontal cortex the last brain developed area (**D**). (Rouss et al. 2001) Brain images: Brain Visa 3.0.2 software. (**A**) central sulcus, (**B**) parieto-occipital sulcus, (**C**) superior temporal sulcus, (**D**) secondary orbitofrontal sulcus.

### *1.2.6. Normal brain maturation during childhood and through early adulthood*

Human brain maturation is a complex, lifelong process that can now be examined in detail using neuroimaging techniques, such as MRI and DTI. The first MRI studies of brain development were reported in the 1980s and focused on qualitative descriptions of GM and WM during the first two years of life. Quantitative MRI studies of brain structure in typically developing children and adolescents were first reported in the 1990s. These confirmed the earlier post-mortem findings that total brain volume was approximately 90% of adult size by age five (Lenroot and Giedd, 2006).

The earliest cross-sectional paediatric brain MRI studies of normal developmental changes showed that GM volumes generally declined after 6–7 years of age and continued to decrease during adolescence, whereas WM volumes increased linearly over time (Toga *et al.*, 2006). In one of the first studies to compile growth curves for the volumes of different lobes of the brain as subjects aged, Giedd *et al.* (1999) noted that there was a clear linear increase in WM up to age 20, whereas there were non-linear changes in cortical GM. The authors also demonstrated a preadolescent increase, with developmental curves peaking at ~12 years for the frontal and parietal lobe, and at ~16 years for the temporal lobe, after which GM loss occurs.

#### *1.2.6.1. Gray matter development*

Regarding GM maturation, the longitudinal study by Sowell *et al.*, 2004 measured changes in cortical thickness in a group of 45 normally developing children studied between 5 and 11 years of age. Changes in brain size were also assessed, showing local brain growth progressing at a rate of ~ 0.4 –1.5mm per year, most prominently in frontal and occipital regions. Estimated cortical thickness ranged from 1.5 mm in occipital regions to 5.5 mm in dorsomedial frontal cortex. GM thinning coupled with cortical expansion was highly significant in right frontal and bilateral parieto-occipital regions (See Figure 10 (A)). Moreover, in the left hemisphere, GM thickness was correlated with changing cognitive abilities. This interesting study was the first to trace the developmental changes in GM thickness, brain size, and structure–function relationships within the same individuals studied longitudinally during a time of rapid cognitive development.

This pattern of results is similar to that observed by Gogtay *et al.* (2004) in an MRI study that reported the dynamic anatomical sequence of human cortical GM development maturation in the pre- and post-pubertal period. Their results, while highlighting the remarkable

heterogeneity, showed that the cortical GM development appears to follow the functional maturation sequence, with the primary sensorimotor cortices maturing first along with frontal and occipital poles, and the remainder of the cortex developing in a parietal-to-frontal (back-to-front) direction. The superior temporal cortex, which contains association areas that integrate information from several sensory modalities, matured last (See Figure 10 (B)). Furthermore, phylogenetically older brain areas mature earlier than newer ones.

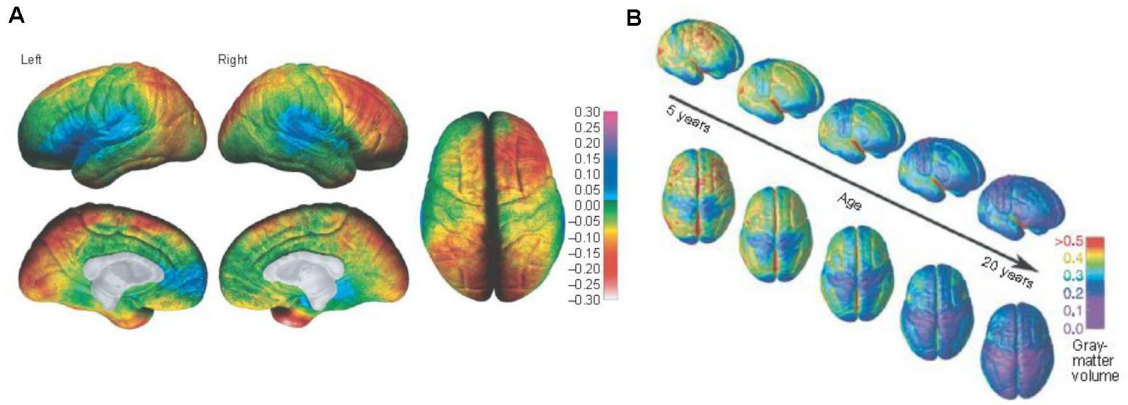



**Figure 10.** (**A**)**Annualized rate of change in cortical thickness.** This figure shows is the average rate of change in cortical thickness in millimetres according to the colour bar on the right. Maximum gray matter (GM) loss is shown in shades of red, and maximum GM gain is shown in shades of blue (Source: Sowell *et al.,* 2004). (**B**) Right lateral and top views of the dynamic sequence of GM maturation over the cortical surface between ages 4 and 21. The process of GM maturation (blue color) begins initially in the dorsal parietal cortices in the primary sensorimotor areas near the interhemispheric margin; it spreads rostrally over the frontal cortex, and caudally and laterally over the parietal, occipital, and finally the temporal cortex. The side bar shows a colour representation in units of GM volume (Source: Gogtay *et al.,* 2004).

As regards subcortical GM, caudate nucleus volumes, like the cortical GM structures, also follows an inverted U-shaped developmental trajectory (Lenroot and Giedd, 2006)

*1.2.6.2 White matter development*

DTI allows the study of WM maturation *in vivo* and in addition, DTI is unique in its ability to non-invasively visualize and quantify WM tracts in the human brain. Although it is superior to T1-weighted and T2-weighted imaging in detecting unmyelinated or premyelinated fibre tracts and in assessing the microstructural organization of the developing WM (Prayer and Prayer 2003; Dudink *et al.,* 2008), it is also limited by its dependence on the ability of the subject to remain still in the scanner and by its magnetic susceptibility to artefacts that can produce noisy and poor resolution images (Cascio *et al.,* 2007). DTI is sensitive to water diffusion characteristics: such as determination of directionality as well as the magnitude of water diffusion. The DTI information can be assessed using variuos parameters (such as

fractional anisotropy (FA) or mean diffusivity) and visualization techniques, usually based on anisotropy indexes (see Figure 11).

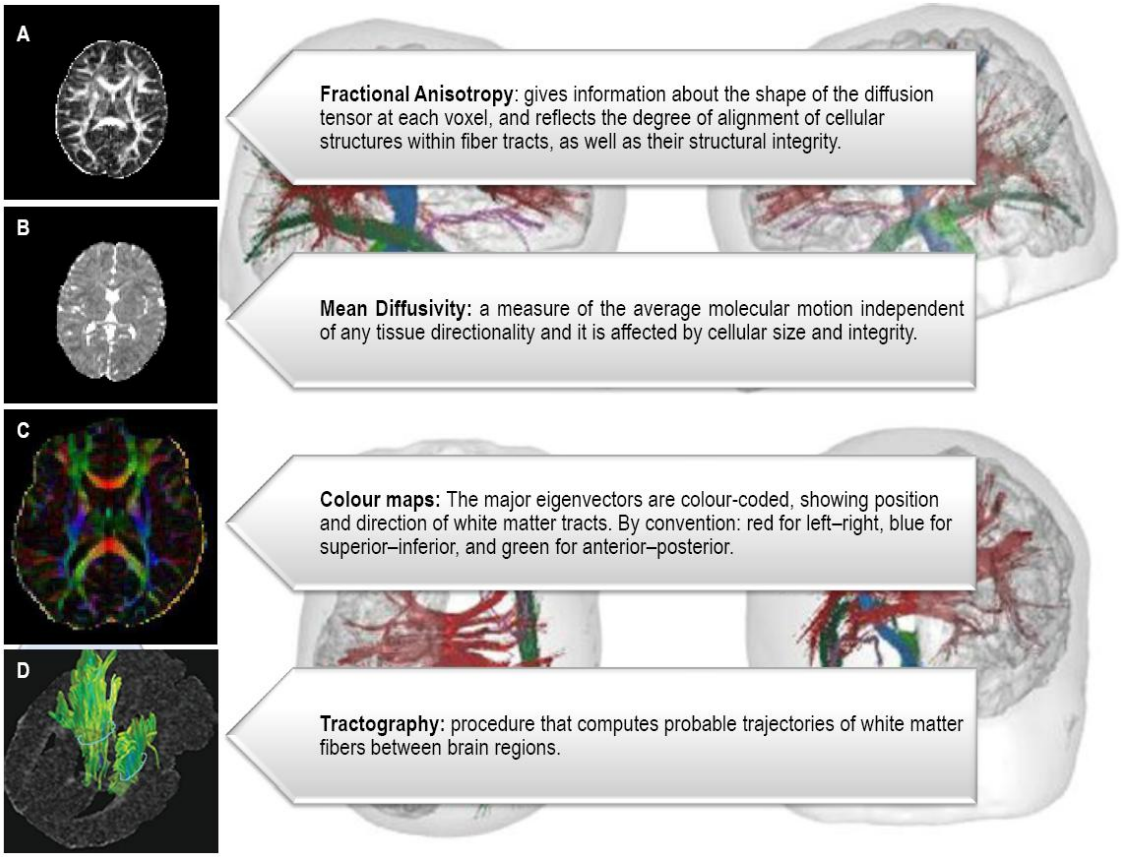



**Figure 11. Visualizing DTI data. A** and **B**; DTI parameters fractional anisotropy and mean diffusivity, respectively. **C** and **D**: two methods of visualizing three-dimensional white matter fiber pathways that offer a more complete threedimensional neuroanatomical picture than anisotropy or diffusion maps alone. The first one (**C**) uses color to illustrate anisotropy, with diffusion direction in three-dimensional space represented by hue and the magnitude of the anisotropy represented by the intensity of the color. The second one (**D**), known as tractography, computes probable trajectories of white matter fibers between brain regions. Source of images **D**: Yoo *et al.*, 2005; rear image: Huppi and Dubois, 2006.

DTI has been successfully used to describe WM development in paediatric samples. Changes in WM diffusion properties are consistent across studies, with anisotropy increasing and overall diffusion decreasing with age (Cascio *et al.*, 2007). The precise cause of the decrease of this diffusivity with increasing age is not known, although it has been shown to be influenced by both a decreasing water content and an increasing complexity of WM structures with increasing myelination (Huppi and Dubois, 2006). Changes in the magnitude and anisotropy of water diffusion follow stereotypical time courses during brain development which can be empirically described with multiexponential regression models, suggesting that quantitative scalar parameters derived from DTI may provide clinically useful developmental landmarks for brain maturity (Muhkerjee *et al.*, 2001). Regarding the maturation of brain tracts,

lower diffusion and higher anisotropy have been described in earlier maturing than later maturing tracts (Partridge *et al.,* 2004).

DTI has been applied to better understand neurodevelopment in several studies from neonates up to school age (Moseley, 2002 and Neil *et al.,* 2002). In adult studies (ages 20 years and above), general maturational trends of increasing mean diffusivity and decreasing FA were found (Bhagat and Beaulieu, 2004). As noted above, studies of neonates and children have found opposite tendencies of decreasing mean diffusivity and increasing anisotropy with age, with the exception of the cortex in preterm infants which shows decreases in anisotropy (McKinstry *et al.,* 2002) (*for more details see Section 1.4.2.*). A DTI study of 66 children up to 6 years of age also showed evidence of slower maturation of peripheral WM of the cerebral hemispheres compared with central WM tracts, continuing the trend first noted in preterm newborns (McGraw *et al.,* 2002). The study by Gao *et al.* (2009) in children younger than 2 years of age, revealed that FA alone may not depict the underlying biological-underpinnings of WM development, whereas directional diffusivities provide more insights into the development of WM. This study also concluded that the spatial development of WM spreads from the centre to the periphery and from the occipital to the frontal lobes.

Few investigations have 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 organization (Snook *et al.,* 2005). Another study by Schmithorst *et al.* (2002) reported a positive relationship of anisotropy and a negative correlation of diffusivity with age in WM, reflecting brain maturation. Some studies of WM maturation changes from childhood to young adulthood show an increase in the global WM volume (Reiss *et al.,* 1996 and Giedd *et al.,* 1999); in agreement with their findings, Lenroot and Giedd (2006) reported that in contrast to the inverted U shape of GM developmental curves, the amount of WM in the brain generally increases throughout childhood and adolescence. Recently, Tamnes *et al.* (2009) conducted a study to investigate brain development in adolescence using volumetric and cortical thickness measures by MRI and also DTI data. The results indicate that cortical thinning in adolescence cannot be explained by WM maturation in underlying regions as measured by volumetry or DTI. Moderate associations between cortical thickness and both volume and diffusion parameters in underlying WM regions were also found, although the relationships were not strong. The authors concluded that none of the measures are redundant and their combined will yield a more complete understanding of brain maturation.

Diffusion measures in relevant WM regions correlate with behavioural measures in healthy children and in clinical paediatric samples (Cascio *et al.*, 2007). In the coming years, with the development of 3D fibre tractography, it will be possible to follow the maturation of WM connectivity throughout infant development into adulthood and to study correlations between abnormalities on DTI and ultimate neurologic/cognitive outcome (Huppi and Dubois, 2006). Some current studies using DTI, provide normative databases of brain WM development from neonates to childhood (Hermoye *et al.*, 2006 and Saksena *et al.*, 2008).

## *1.3. Brain injury in preterm infants*

Adverse development in utero is now considered to contribute the presence of neurological disorders which appear after birth. The timing and severity of prenatal insults are critical in determining the outcome in terms of the severity of the damage and the regions of the brain affected. In animal models it has been demonstrated that relatively brief periods of hypoxemic compromise to the fetus can have significant effects on the foetal brain, for example death of susceptible neuronal populations (cerebellum, hippocampus, cortex) and cerebral WM damage. These effects appear to be more profound in mid than in late gestation (Rees and Inder, 2005).

### *1.3.1. White matter damage*

A range of factors that are uniquely present in the preterm infant (such as immature cerebral vasculature, selective vulnerability of oligodendroglial precursor cells or a prominent and highly vascular germinal matrix) lead to enhanced vulnerability of the cerebral WM to injury (Wyatt, 2007). Thus, preterm newborns are particularly vulnerable to cerebral WM damage (Volpe, 2003). Moreover, WM injury and abnormal maturation are thought to be major contributors to the neurodevelopmental disabilities observed in children and adolescents who were born preterm. Improved understanding of early WM damage as well as early detection of abnormal WM maturation is important in the design of preventive, protective, and rehabilitative strategies for the management of the preterm infant (Dudink *et al.*, 2008).

#### *1.3.1.1. Periventricular-intraventricular haemorrhage and infarction*

IVH is thought to begin with bleeding into the germinal matrix just below the lateral ventricles, and it is graded I-IV based on the haemorrhage extend as seen on ultrasound (Volpe, 2001a). According to Volpe (2001a), grade I haemorrhage refers to germinal matrix

haemorrhage with no or minimal IVH. Grade II and grade III refer to IVH involving 10% to 50% and over 50% of the ventricular area on a parasagittal ultrasound view, respectively. During the late second and early third trimesters, the subependymal germinal matrix supports the development of cortical neuronal and glial cell precursors, which migrate to the cortical layers. The germinal matrix is highly vascularized, with a rich capillary network and a relatively poor supportive matrix, so blood filling the lateral ventricles may dilate the ventricles. Severe IVH can lead to ventricular dilation and post-haemorrhagic hydrocephalus if there is an obstruction to the flow of cerebrospinal fluid, with increased intracranial pressure. The incidence of IVH ranges between 15% and 30% among preterm infants (Lemons *et al.,* 2001) and its incidence and severity increases with decreasing GA and BW (Vergani *et al.,* 2004; Kadri *et al.,* 2006). Factors that contribute to IVH include hypotension (Bada *et al.,* 1990), disturbances in coagulation (Whitelaw, 2001), fluctuating blood pressures, poor autoregulation of cerebral blood flow, hyperosmolarity, and injury to the vascular endothelium by oxygen free radicals (Volpe, 2001a). Infants with subependymal or germinal matrix haemorrhage or IVH without ventricular dilation have a good prognosis; but those with IVH with ventricular dilation or post-haemorrhagic hydrocephalus are at an increased risk of neurodevelopmental disability (de Vries and Groenendaal, 2002).

*1.3.1.2. Periventricular leukomalacia*

PVL refers to necrosis of WM adjacent to the external angles of the lateral ventricles and is regarded as the principal ischaemic lesion of the premature infant (Volpe, 2001a). PVL is related with two components: focal and diffuse (Banker and Larroche, 1962 and Volpe, 2009). The focal component consists of localized necrosis deep in periventricular (PV) WM with loss of cell elements. These necroses can be: macroscopic in size and evolving over several weeks to multiple cystic lesions, readily visualised by cranial ultrasonography and known as "cystic PVL", or microscopic in size and evolving into glial scars that are not seen by neuroimaging and known as "non-cystic PVL". This form of PVL accounts for the vast majority of cases (Volpe, 2009).The pathogenesis of PVL relates to, at least, three major interacting factors: vascular immaturity, impaired cerebrovascular autorregulation (which increases the risk for ischemic injury to cerebral WM) and the maturation-dependent vulnerability of the oligodendroglial precursor cell that represents the major cellular target in PVL (Volpe, 2001b). Recent neurobiological studies show that these cells are very vulnerable to attack by free radicals, known to be generated in abundance with ischaemia and inflammation (Khwaja and Volpe 2008). A meta-analysis found significant relationships between clinical chorioamnionitis, PVL, and cerebral palsy in preterm infants (Wu and Colford, 2000).

### *1.3.2. Gray matter damage*

Perinatal WM damage appears to be accompanied by cerebral-cortex and deep GM abnormalities, including excess apoptosis without replacement and the impairment of surviving neurons and resulting interference with synaptogenesis and connectivity. Recent advances in corticogenesis suggest that neurons migrate from the germinative zones through the WM to the cortex when the WM is most vulnerable and perhaps is being injured. Advances in developmental neuroscience also suggest that the excitotoxic and inflammatory processes that probably contribute to WM damage are also able to damage developing neurons. Together, these advances support the untested hypothesis that WM damage in the preterm newborn is accompanied by the death of neurons as they migrate through the dangerous minefield of WM and undergo injury (Leviton and Gressens, 2007).

Based on the work by Marin-Padilla (1999) with newborn brain using Golgi stains of autopsy or neurosurgical specimens of the cortical GM overlying destructive WM lesions, Inder *et al.*( 2005b) pointed out that; the reduction in cortical GM volumes in premature infants with cerebral WM injury could reflect blunted neuronal differentiation caused by destruction of ascending and descending axons (corticopetal, corticofugal, and corticocortical association fibers) in WM with resulting input deprivation and output isolation of the overlying cortical GM. As a consequence of this cortical GM isolation, GM differentiation may be impaired.

Recent observations in the premature infant suggest that the basis for the cognitive and related deficits may not relate directly to the WM injury *per se*. Qualitative studies of alteration in GM development have been undertaken in preterm newborns and have shown to have a relationship between WM injury and delayed GM gyral development (Inder *et al.,* 2003). In addition, an important role for the deep GM in preterm brain injury is suggested by its volume reduction in a dose-dependent manner with degree of prematurity at birth (Inder *et al.,* 2005a). In summary, the impairments in cerebral development in preterm infants include, in particular, highly significant reductions in cerebral cortical and deep nuclear GM volumes in comparison to volumes in term-born infants (Inder *et al.,* 2005a). *In Section 1.4.1. "Gray matter findings" structural brain imaging studies in children and adolescents born preterm are discussed.*

### *1.3.3. Brain plasticity at prematurity*

The human brain is functionally altered through experience, a phenomenon known as plasticity. Relevant experiences may be negative, such as brain injury; injuries occurring during the period of cell migration are particularly detrimental. Indeed, the developing brain

responds to injury in a different way to the adult brain and this response varies with its precise embryonic age. If the cortex is injured just after completion of neurogenesis and during the period of continuing cell migration, functional outcome is very poor. If the cortex is injured during the time of maximal dendritic and synaptic growth recovery is good, which is correlated by morphological changes in cortical pyramidal neurons. The compensatory changes in neural morphology that underlie functional recovery are similar to those that the brain uses normally during brain development and during the processes of learning and memory (Kolb *et al.*, 2000). In consequence, neural plasticity is not without limits (Kolb, 1995), and these limits will partially depend upon the child's intellectual temperament in conjunction with the timing and nature of the injury (Kolb, 1995 and Luciana, 2003). Thus, as Figure 12 illustrates, plasticity should be understood as a dynamic process that fluctuates across time.

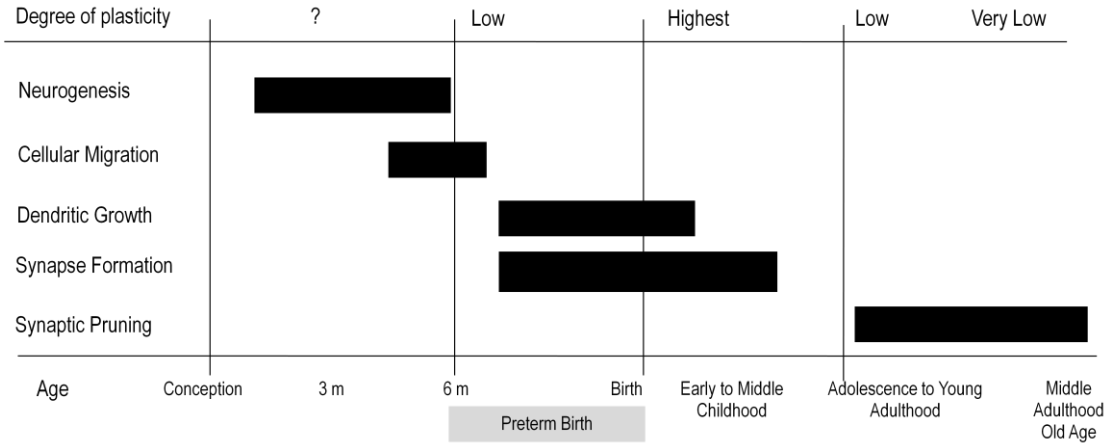



**Figure 12. Plasticity in relation to stages of neurodevelopment.** In the human, brain development proceeds in a sequence which begins with neurogenesis and ends with synaptic pruning, as described in Section 1.2. Following early brain damage, plasticity varies according to the point in the sequence in which the injury took place. Animal studies suggest that plasticity will be very low during the period of cell migration, corresponding to the second and third trimesters of pregnancy (second panel) and during adulthood (last panel) when synaptic networks have stabilized. Plasticity will be highest prior to synaptic stabilization during early and middle childhood (third panel). Adapted from Kolb, 1995 and Luciana, 2003.

As indicated above, the most common cerebral neuropathology observed in premature infants is WM injury which may subsequently have consequences on the overlying cerebral cortex, with alterations in GM development detected by advanced MRI techniques in expreterm infants. Interestingly the above-mentioned study by Marin-Padilla (1999) demonstrated subtle neuropathological abnormalities in the developing neocortex adjacent to perinatally acquired WM lesions which were thought to result from sensory deafferentation and/or axotomy. That study emphasizes the importance of the role played by progressive post-injury reorganization of the undamaged cortex in the underlying mechanisms of the ensuing neurological sequelae.

Both animal and human studies of developmental brain plasticity have indicated that the degree of sparing or recovery of function following damage to the central nervous system is dependent upon the age of the individual when the lesion is acquired. However, although age at the time of lesion has been extensively studied, it is only one of many variables that can influence the pattern and degree of brain plasticity, because brain plasticity depends on several factors such as the age at injury, size and localization of the lesion, or the maturational state of the injured areas (Chugani *et al.*, 1996).

Interestingly, outcome must be assessed longitudinally because apparent recovery in childhood may reverse as the brain matures. In this sense, this kind of long-term effects "sleeper effects", which are thought to reveal insult, recovery, and potential plasticity of the brain not identifiable until later ages, have been identified in preterms (Sostek, 1992).

Functional MRI (fMRI) may provide important insights into emerging data that suggest that recovery from injury can occur in the brains of children born prematurely. fMRI investigations of language and memory suggest the engagement of alternative compensatory neural systems in preterm children at school age and beyond (Gimenez *et al.*, 2005; Ment and Constable, 2007; Schafer *et al.*, 2009).

### *1.4. Structural brain imaging studies in children and adolescents born preterm*

MRI has proved to be a valuable tool for monitoring development and pathology in the preterm brain (Counsell, 2003a). Most of neuroimaging studies in the 1980s and 1990s in preterm samples were qualitative, with poorly controlled samples and, in some cases, combining different types of brain lesions. In summary, these studies indicate elevated rates of anatomical brain abnormalities (Ment *et al.*, 2000). Recent quantitative MRI reports using volumetric and voxel-based analyses have demonstrated specific regional and more subtle cerebral abnormalities in cortical and subcortical brain areas in preterms which cannot be detected by visual assessment.

Descriptive MRI studies performed in childhood and adolescence have revealed lesions of the parenchyma, thinning or atrophy of the CC, signs of ventricular dilatation and reduced WM and cortical volume (Hack and Taylor, 2000a). In the following sections, the main GM and WM findings in preterm populations are discussed.

### *1.4.1. Gray matter findings*

#### *1.4.1.1. Cortical development in preterm infants*

It seems that the human brain grows during development in a particular way, in which the surface area grows more than the volume. When babies are born prematurely this pattern of growth is disrupted, and the extent of growth disruption seems to predict whether there is delayed development two years later. The earlier the birth, the greater the disruption, and in addition boys more affected than girls (Kapellou *et al.,* 2006). Despite the developmental quantitative abnormalities Tzarouchi *et al.*, 2009 concluded that, in healthy preterm infants, GM development progresses in a region-specific manner coinciding with functional, phylogenetical and regional WM maturation.

Quantitative data on brain volumes indicates abnormal cortical development. Infants who survive prematurity appear to have reduced cortical surface area and less cortical GM compared to normal term-born infants, despite apparent preservation of total brain volume (Ajayi-Obe *et al.,* 2000 and Inder *et al.,* 2005a). Similarly, in late childhood and adolescence the cortical abnormalities are still present (Kesler *et al.,* 2004; Martinussen *et al.,* 2005; Gimenez *et al.,* 2006a; Nosarti *et al.,* 2008). Premature birth also affects cerebral gyrification (Gimenez *et al.,* 2006b and Kesler *et al.,* 2006) and is related to decreased cortical thickness (Martinussen *et al.,* 2005); being these impairments not reversible during childhood. To sum up, Table 4 shows that preterm birth is associated with decreased global volumes of cortical and cerebellar GM, and regional reductions are observed in areas involving all the cerebral lobes.

#### *1.4.1.2. Subcortical gray matter (basal ganglia, thalamus and hippocampus)*

As shown in Table 4, the volume of subcortical GM in preterms is also lower in preterms than in controls. The basal ganglia, the thalamus and the hippocampus are the most affected subcortical GM regions.

**Table 4.** Magnetic resonance imaging studies of gray matter abnormalities in preterm samples

**Cortical and cerebellar gray matter abnormalities**

- Inder et al., 1999 ■● (Adol, VPT) ↓ cortical
- Ajayi-Obe et al., 2000 ■● VBM (Inf,VPT) ↓ cortical surface and complexity
- Allin et al., 2001 ■ ○ (Adol, VPT) ↓ cerebellar volume
- Isaacs et al., 2001 ■● VBM (Adol,VPT) ↓ parietal lobe
- Nosarti et al., 2002 ■● (Adol, VPT) ↓ cortical
- Argyropoulou et al., 2003 ■ (Adol, PT) ↓ cerebellum area
- Inder et al., 2003 □ (Inf, VPT) gyral abnormalities
- Isaacs et al., 2003a ■● VBM (Adol,VPT) ↓ extrastriate cortex
- Peterson et al., 2003a ■● ( (Inf, EPT) ↓ sensoriomotor, parieto-occipital, inferior-occipital
- Isaacs et al., 2004 ■● VBM (Adol,VPT) parieto-occipital ↓
- Kesler et al., 2004 ■● (Chi, EPT) ↑ parietal and frontal
- Reiss et al., 2004 ■●(Chi, EPT) global ↓
- Inder et al., 2005b ■● (Inf,VPT) ↓ cortical and deep nuclear GM volume
- Martinussen et al., 2005 ■● (Adol, VPT) thinning parietal, occipital and temporal cortical surface
- Giménez et al., 2006b ■● (Adol, VPT) ↓ in the secondary sulci depth but not in the primary sulcus
- Kapellou et al., 2006 ■● (Inf, EPT) cortical surface related to cerebral volume
- Kesler et al., 2006 ■●(Chi, EPT) ↑ temporal lobe gyrification
- Mewes et al., 2006 ■● (Inf,VPT) ↑ cortical GM volume
- Shah et al., 2006 ■●(Chi, EPT) ↓ inferior occipital volume in PT with impaired oculomotor function
- Srinivasan et al., 2006 ■○ (Inf, VPT) no differences in cerebellar and vermal volumes
- Zacharia et al., 2006 ■● (Inf,VPT) ↓ cortical GM
- Thompson et al., 2007 ■● (Inf, PT) ↓parieto-occipital, sensorimotor, orbitofrontal
- Kesler et al., 2008 ■● VBM (Chi, EPT) ) ↓ prefrontal and temporal lobe in preterm males
- Nosarti et al., 2008 ■● VBM (Adol,VPT) ↓↑ frontal, ↓↑temporal, ↓occipital and ↓↑cerebellum
- Ment et al., 2009■●(Chi-Adol,EPT) lower GM reduction over time
- Tzarouchi et al., 2009 ■● (Inf,VPT) GM development progresses in a region-specific manner
-

**Subcortical gray matter: basal ganglia, thalamus and hippocampus**

Isaacs et al., 2000 ■●(Inf,VPT) ↓ hippocampus bilateral

- Gadian et al., 2000 ■● VBM (Adol, VPT) ↓ hippocampus bilateral
- Peterson et al., 2000 ■○ (Chi,EPT) ↓ bilateral basal ganglia ↓ hippocampus bilateral
- Sie et al., 2000 □ (Chi,PT) ↓ bilateral basal ganglia and thalamus
- Abernethy et al., 2002■● (Adol, VPT) ↓ bilateral caudate nuclei
- Nosarti et al., 2002 ■● (Adol, VPT) ↓ hippocampus bilateral
- Isaacs et al., 2003b □ (Adol,VPT) ↓ hippocampus bilateral
- Abernethy et al., 2004■○ (Chi, VPT) ↓ bilateral caudate nuclei
- Giménez et al., 2004■● VBM (Adol, VPT) ↓ left hippocampus and bilateral thalamus
- Isaacs et al., 2004 ■□●○ (Adol, VPT) ↓ hippocampus bilateral
- Nosarti et al., 2005■● (Inf, PT) ↓ caudate nuclei
- Ricci et al., 2006 □ (Adol,VPT) thalamic abnormalities
- Boardman et al., 2006 ■● (Inf, VPT) ↓ thalamic and lentiform volumes
- Srinivasan et al., 2007 ■○ (Inf, VPT) ↓ thalamic and lentiform volumes
- Kesler et al., 2008 ■●VBM (Chi, EPT) ↓ basal ganglia in preterm males
- Nosarti et al., 2008 ■● VBM (Adol,VPT) ↓ thalamus and caudate

Table shows Type of study: □ Qualitative ■ Quantitative, Type of technique used: ● Automatic-semiautomatic volumetry ○ Manual volumetry (ROIs), VBM: voxel-based morphometry, Characteristics of the sample (In: infants, Chi: children, Adol: adolescents / VPT: very preterm, EPT: extremely preterm, PT: preterm) and Main results: ↓ reduction ↑ increase gray matter.

*This table is exclusively based on investigation works in the last ten years, and does not include revisions. Source search: PubMed (www.pubmed.gov), language: English, last update; June 2009.*

### *1.4.2. White matter findings*

The developing brain is susceptible to injury from infective, ischaemic, and inflammatory insults. The majority of preterm infants show some evidence of brain damage on MRI in the early neonatal period (Maalouf *et al.,* 1999). As previously exposed, several studies suggest that brain injury in preterms predominantly involves WM (Stewart *et al.,* 1999; Huppi *et al.,* 2001; Counsell *et al.,* 2003b; Volpe, 2003; Huppi, 2004; Gimenez *et al.,* 2006a). Indeed, axonal brain connectivity develops mainly during the preterm period, which is highly vulnerable to cerebral WM damage (Follet *et al.,* 2000; Back *et al.,* 2001; Chamananvanakij *et al.,* 2002; McQuillen and Ferreiro, 2004).

Using qualitative and quantitative neuroimaging approaches, global cerebral WM abnormalities have been described in preterm-born infants (Huppi *et al.,* 2001; Inder *et al.,* 1999; Inder *et al.,* 2003; Miller *et al.,* 2005), children (Nagy *et al.,* 2003; Reiss *et al.,* 2004, Yung *et al.,* 2007) and adolescents (Stewart *et al.,* 1999; Gimenez *et al.,* 2006a, Nosarti *et al.,* 2008). Furthermore, Counsell *et al.* (2003b) and Gimenez *et al.* (2006a) demonstrated that there is diffuse WM loss involving several brain areas in addition to the classical PV WM injury seen in clinical MRI studies. Table 5 summarizes the main WM MRI findings from studies in preterm samples in the last ten years.

Children and adolescents born preterm have a thinner CC and a smaller cross-sectional area than controls; being the posterior parts particularly affected (*see also Table 5, corpus callosum section*). Some studies have performed a segmentation of the CC into different parts and have quantified the total CC and its subregions (Peterson *et al*., 2000; Nosarti *et al*,. 2004; Caldu *et al.,* 2006). Peterson *et al.* (2000), using volumetric analysis performed manually on MRI scans in a sample of 25 eight-year olds reported a significant reduction in CC size of as much as 35 %. Regarding the subregions, significant reductions were found in splenium, isthmus, midbody, anterior body and rostrum/genu. Nosarti *et al.* (2004) studying a sample of 66 preterm adolescents demonstrated a smaller size of total CC area (7.5%), mainly in the posterior (14.7%) and mid-posterior (11.6%) quarters. Preterm individuals who had experienced PV haemorrhages and ventricular dilation in the neonatal period showed the greatest decrease in CC. Caldu *et al.,* 2006 examined CC measurements of 25 adolescents born preterm and they showed an overall reduction owing mainly to thinning in the splenium, posterior midbody, and genu compared to matched controls. CC size significantly correlated with GA, Wechsler Performance Intelligence Quotient (PIQ), and memory performance. These results suggest that

cerebral growth during infancy does not compensate for CC reduction and that this reduction reflects neuropsychological deficits.

Neonatal cranial ultrasound of the preterm infant shows high reliability in the detection of cystic WM injury but has significant limitations in the demonstration of noncystic WM injury. This deficiency of neonatal cranial US is important, because noncystic WM injury is considerably more common than the cystic form (Inder *et al.*, 2003). Therefore, MRI shows the well-recognized pathologies seen on ultrasound even detecting more subtle abnormalities (Counsell *et al.*, 2003a; O'Shea *et al.*, 2005; Arthur, 2006; Leijser *et al.*, 2008). In the immature brain, T2-weighted fast spin echo sequences give the best contrast between different structures, because the increased water content of the neonatal brain is associated with a marked increase in T1 and T2 relaxation times in comparison to adults (O'Shea *et al.*, 2005). In addition, due to this high water content of the immature brain, fluid-attenuated inversion recovery (FLAIR) images are of limited use in the first year after birth, and it has recently been demonstrated that FLAIR images do not contribute to detection of hypoxic-ischaemic brain injury in near full-term neonates (van Wezel-Meijler *et al.*, 2009).

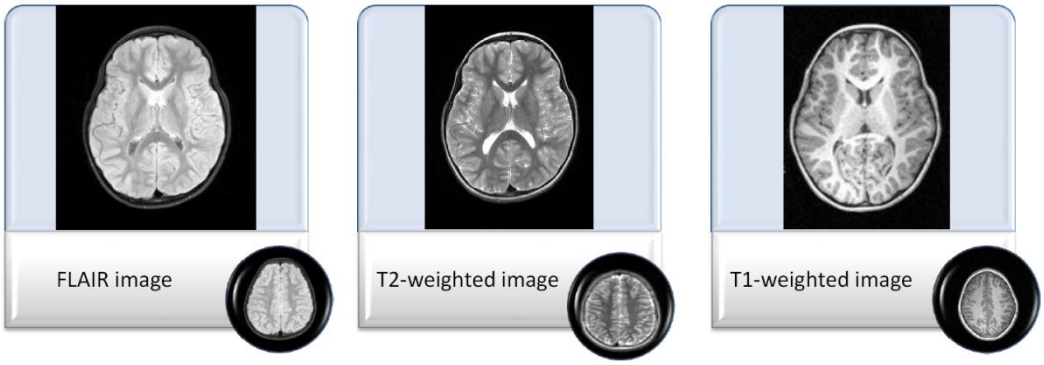



**Figure 13. Transversal FLAIR, T2 and T1 images adquired in a 3 T scanner.** Images of a child with antecendents of prematurity (GA: 29 w, BW: 1220 g) at 8 years of age.

Huppi *et al.* (2001) showed that WM development in preterms is different from control term born infants. WM changes in infants with no other lesions within the brain have also been shown on conventional imaging of the preterm brain at term, in which abnormal WM signal, known as diffuse and excessive high signal intensity has been identified in the majority of infants (Maloouf *et al.*, 1999). In addition, as noted below, other techniques, such as diffusion tensor imaging (DTI) have proved useful for detecting microscopic WM changes in preterm neonates and children (Huppi *et al.*, 2001; Miller *et al.*, 2002; Nagy *et al.*, 2003; Counsell *et al.*, 2006; Gimenez *et al.*, 2008a).

*1.4.2.1. Diffusion tensor imaging studies in preterms*

Changes in WM diffusion properties are consistent across studies, with anisotropy increasing and overall diffusion decreasing with age during the neurodevelopmental maduration (Cascio *et al.,* 2007). Sakuma *et al.* (1991) reported that WM anisotropy increases with age in a sample ranging from preterm and term infants to healthy adults. In preterms the patterns of development is similar to that in normal controls; that is anisotropy increases and overall diffusion decreases with GA (Huppi *et al.,* 1998 and Huppi *et al.,* 2001). However, anisotropy is lower and overall diffusion higher in preterm infants than in full-term infants (Counsell *et al.,* 2003b). Comparing DTI findings to predictions from a theoretical model, Mukherjee *et al.* (2002) demonstrated that these observations at major WM sites are consistent with decreased water content and increased myelination with age. DTI has also been successfully used in very premature infants to distinguish early patterns of laminar organization in the cerebrum (Maas *et al.,* 2004).

Moreover, DTI of premature newborns can detect differences in WM maturation in infants with and without WM injury (Miller *et al.,* 2002). Anjari *et al.,* 2007 noted that DTI with tract-based spatial statistics reveals local WM abnormalities in 26 VPT infants at term equivalent age with no evidence of focal lesions; specifically, the centrum semiovale, frontal WM and the genu of the CC showed significantly lower FA in the preterm group. In addition, preterm neonates showed greater anisotropy in early myelinating central axonal pathways such as the pyramidal tract at the level of the internal capsule, than in slower maturing peripheral WM of the cerebral hemispheres (Partridge *et al.,* 2004).

The relationships between neonatal visual performance and the microstructure of the optic radiation have been studied in preterm infants, showing that FA in the optic radiation increases with GA and correlates with scores of visual fixation (Berman *et al.,* 2009). In agreement with these results, Bassi *et al.* (2008) also described correlations between visual scores and FA measures for whole brain demonstrating a significant linear correlation between visual assessment scores and FA in the optic radiation.

Deipolyi and co-workers (2005) conducted a study comparing microstructural and macrostructural development of the cerebral cortex in premature newborns using DTI versus cortical gyration technique. Comparing primary sensorimotor cortex (specifically the precentral and postcentral gyri) with higher order association areas, such as the superior frontal gyrus and superior occipital gyrus, they reported regional anisotropy differences in the cortical plate in 37 premature newborns with a GA from 25 to 38 weeks. Thus, this study demonstrated that DTI

can be used to differentiate and segment histologically distinct layers present transiently during development of the foetal cerebrum, confirming that DTI offers a unique in vivo window into the process of human brain development.

Advances in DTI have made it easier to detect subtle WM abnormalities also in children and adolescents with antecedents of prematurity. The first long-term follow-up DTI study by Nagy *et al.* (2003) reported that preterm children have WM disturbances at 11 years in both the CC and the internal capsule, and that these are not repaired or compensated for before this age. Yung *et al.* (2007) concluded that both whole brain WM volume and FA as assessed by DTI were significantly lower in preterm children. Recent studies have reported a relationship between WM integrity and cognitive performance in children and adolescents who were born preterm (*for more details, see Section 1.6.*).

Als *et al.* (2004) used DTI to demonstrated developmental changes in premature neonates in response to a therapeutic intervention program. The authors found increased anisotropy in internal capsule in a group of 30 VPT that received the developmental care program (NIDCAP) showing evidence that early experience improves brain function and structure. In the same way, Gimenez *et al.* (2008a) found that a sample of 27 preterm infants exhibited higher FA values, which may suggest accelerated maturation, in the location of the sagittal stratum. The results of this study are more consistent with accelerated WM development, possibly as a result of increased sensorimotor stimulation in the extrauterine environment.

#### *1.4.2.2. Tractography studies in preterm subjects*

Yoo *et al.* (2005) were able to visualize *in vivo* WM fibre tracts of 6 preterms brains using tractographic analyses from diffusion tensor images. Their results suggest that major WM tracts of preterm infant brains, with ages ranging from 28 weeks to term (40 weeks old), can be successfully visualized despite the small brain volume and low anisotropy. Diffusion tensor tractography was also used by Berman *et al.* (2005) to gauge maturational changes separately in the pyramidal tract and in the somatosensory radiations of premature newborns. These authors reported that diffusion properties within sensory and motor tracts significant correlated with age and in addition, the motor tracts were found to have higher anisotropy and lower diffusivity than the sensory pathway. In agreement with this, Rose *et al.* (2007) demonstrated that neonatal microestructural development of the internal capsule on DTI correlates with severity of gait and motor deficits.

### *1.4.3. Ventricular size and volumes*

The ventricular system enlarges following cerebral WM atrophy or abnormal development. Thus, ventricular volume and size have been used as a surrogate assessment of the severity of WM damage (Hart *et al.*, 2008). Diffuse WM abnormalities and post–haemorrhagic ventricular dilation (defined as an axial diameter > 10 mm) are common findings in preterm populations. Recently, Maunu *et al.* (2009) concluded that the ventricular brain ratio, widths of the lateral ventricular horns, and head circumference are appropriate measures for the estimation of both total and regional brain tissue volumes, and consequently ventriculomegaly is strongly associated with brain lesions in preterm infants. In older subjects, the ventricles are dilated with increased volumes in childhood and adolescence following preterm birth. Using morphometric analyses in MRI scans of preterm children, Peterson *et al.* (2000) showed that cerebral spinal fluid (CSF) in the occipital and temporal horns of the cerebral ventricles was markedly increased in the preterms at 8 years of age. Later, using the same procedure, Peterson *et al.* (2003a), also found that in a preterm sample of 10 infants near birth the lateral ventricles volumes were increased, specifically in the midbody, occipital horn, and temporal horns, compared to term infants. In agreement with these results, Kesler *et al.* (2004) observed disproportionately enlarged lateral ventricular volumes in 9 year-old preterm subjects compared to controls. Significant differences between groups were found in the ventricular body and occipital horns. Using stereological techniques, in preterm adolescents, Nosarti *et al.* (2002) observed a 42% increase in the size of lateral ventricles in the preterm group compared to controls. For a summary, see also the results of Table 5, Section: *Periventricular and internal capsule WM lesions in MRI*.

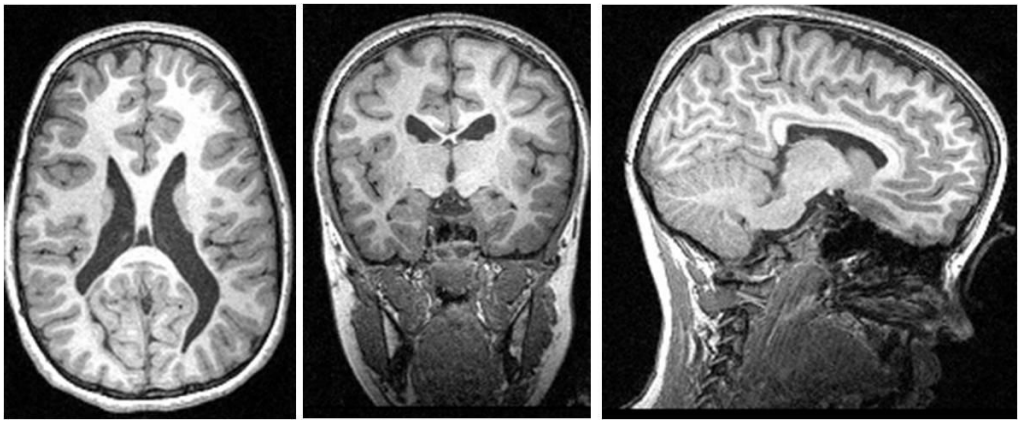


**Figure 14. Ventriculomegaly and thinner corpus callosum in a preterm child with history of periventicular leukomalacia at age 9.** Brain views: Axial, coronal and saggital, respectively. Images were acquired in a 3T scanner.

**Table 5.** Magnetic resonance imaging studies of white matter alterations in preterm samples

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|---|
| **Global, Cortical white matter abnormalities in MRI** |
| • Inder et al., 1999 ■● (Adol, VPT) ↓ total brain myelin volume |
| • Krageloh-Mann et al., 1999 □ (Chi,MPT) ↓ occipital WM reduction |
| • Panigrahy et al., 2001 ■● (Inf,VPT) ↓ WM volume |
| • Inder et al., 2003 □ (Inf, VPT) ↓ WM volume and abnormal signal intensities |
| • Peterson et al., 2003a ■●( (Inf, EPT) ↓ global WM ↓ parieto-occipital WM reductions |
| • Isaacs et al., 2003a ■● VBM (Adol,VPT) ↑ extraestriate cortex WM |
| • Isaacs et al., 2004 ■● VBM (Adol,VPT) ↑ frontal WM |
| • Kesler et al., 2004 ■● (Chi, EPT) ↑ parietal and frontal |
| • Reiss et al., 2004 ■●(Chi, EPT) global ↓ WM volume |
| • Inder et al., 2005 ■● (Inf,VPT) ↓ WM volume |
| • Miller et al., 2005 □(Inf, EPT) ) WM injury |
| • Dyet et al., 2006 □ (Inf, EPT) Diffuse WM abnormalities |
| • Gimenez et al., 2006a ■● VBM (Adol,VPT) ↓ WM volume and density in regions involving all lobes |
| • Mewes et al., 2006 ■● (Inf,VPT) ↓ WM volume |
| • Zacharia et al., 2006 ■● (Inf,VPT) ↓ myelinated and unmyelinated WM |
| • Thompson et al., 2007 ■● (Inf, PT) ↓parieto-occipital, sensorimotor, orbitofrontal |
| • Nosarti et al., 2008 ■● VBM (Adol,VPT) ↓ brainstem, internal capsule, temporal, major fasciculi ↑ temporal, frontal, parietal |
| • Ment et al., 2009 ■● (Chi-Adol,EPT) lessWM gain over time |
| **Periventricular and internal capsule white matter lesions in MRI** |
| • Cooke and Abernethy, 1999 ■□ (Adol, EPT) |
| • Krageloh-Mann et al., 1999 □ (Chi,MPT) |
| • Sie et al., 2000 □ (Chi,PT) |
| • Debillon et al., 2003 □ (Inf,PT) |
| • Inder et al., 2003 □(Inf,EPT) |
| • Peterson et al., 2003a □ (Inf,EPT) |
| • Abernethy et al., 2004 □(Chi, VPT) |
| • Isaacs et al., 2004 □(Adol, VPT) |
| • Dyet et al., 2006 □ (Inf, EPT) |
| • Pavlova et al., 2006 □○ (Adol, PT) |
| • Ricci et al., 2006□ (Inf, PT) |
| • Gimenez et al., 2006a ■● VBM (Adol,VPT) ↓ WM density and volume bilateral |
| • Thompson et al., 2007 ■● (Inf, PT) |
| • Nosarti et al., 2008 ■● VBM (Adol,VPT) ↓ WM volume |
| **Corpus callosum** |
| • Cooke and Abernethy, 1999 ■□ (Adol, EPT) ↓ volume and thinning |
| • Stewart et al., 1999 □ (Adol, VPT) thinning |
| • Peterson et al., 2000 ■○ (Chi,EPT) ↓ WM volume |
| • Santhouse et al., 2002 ⅋ □(Adol, VPT) thinning |
| • Argyropoulou et al., 2003 ■ (Adol, PT) ↓ area |
| • Inder et al., 2003 ■(Inf, VPT) thinning |
| • Isaacs et al., 2003b □ (Adol,VPT) ↓ genu and body parts |
| • Abernethy et al., 2004 □ (Chi, VPT)thinning |
| • Isaacs et al., 2004 □ (Adol, VPT) ↓ CC |
| • Nosarti et al., 2004 ■● (Adol, VPT) ↓ global and in the posterior and mid-posterior quarter |
| • Rademaker et al., 2004 ■(Chi, VPT) ↓ area |
| • Caldu et al., 2006■●○ (Adol,VPT) ↓ splenium, posterior midbody and genu |
| • Gimenez et al., 2006a ■● VBM (Adol,VPT) ↓ WM density and volume |
| • Ricci et al.,2006 □ (Inf, PT) thinning |
| • Allin et al., 2007 ■●○ (Adol, VPT) greater growth than controls |
| • Nosarti et al., 2008 ■● VBM (Adol,VPT) ↓ WM volume |

Table shows type of study: □ Qualitative ■ Quantitative, technique used ● Automatic-semiautomatic volumetry ○Manual volumetry (ROIs), ⅋ fMRI study, VBM: voxel-based morphometry, Characteristics of the sample (In: infants, Chi: children, Adol: adolescents / VPT: very preterm, EPT: extremely preterm, PT: preterm) and Main results: ↓ volume reduction ↑ increased white matter volume.

*This table is exclusively based on investigations in the last ten years and does not include revisions. Source search: PubMed (www.pubmed.gov), language: English, last update; June 2009.*

## *1.5. Cognitive and behavioural outcomes in preterm children and adolescents*

### *1.5.1. Early childhood outcomes*

Assessment of early childhood outcomes includes a measure of cognitive function and of the major neurosensory disorders including cerebral palsy, blindness and deafness. As the survival of less mature and lower BW infants increased in the 1990s, the rates of these neurodevelopmental impairments also increased; infants below 750 g and below 26 weeks of GA were the most affected affected (Hack, 2007). Since 2000, the rates of cerebral palsy have decreased among ELBW infants. A variety of perinatal and neonatal factors were responsible for the improved outcomes, including decreases in postnatal steroid therapy, severe cranial ultrasound abnormalities, and sepsis. However, cognitive outcomes, as measured with the Bayley Scales of Infant Development, have not changed (Wilson-Costello *et al.*, 2007).

Mortality and neurodevelopmental outcomes of preterm infants are due to the causes of preterm birth, immature organ systems not being up to the task of fully sustaining extrauterine life, adverse effects of obstetric and neonatal treatments as well as to genetic factors that we know little about (Allen, 2008).

### *1.5.2. School age and adolescence cognitive and behaviour outcomes*

At school age, cognitive and other functional abilities can be assessed more accurately than during early childhood. School age assessments include measures of Intelligence Quotient (IQ) and academic achievement including reading, mathematics, and spelling, and the neuropsychological measures of attention, executive function, memory, and fine and gross motor functions. Behaviour is also best assessed after 3 years of age through self-reports or parental / teacher questionnaires, although the variability in the constructs measured between tests makes it more difficult compare outcomes. As a summary, Table 6 shows assessments of behaviour and psychopathology commonly used in middle childhood. A global assessment of the child's functioning is important as an outcome measure in addition to the diagnoses of specific conditions such as cerebral palsy, mental retardation, and various learning disabilities (Hack, 2007).

As Table 7 shows, whilst VPT / VLBW children have group mean IQ scores within the normal range, they are significantly lower than their term peers (Bhutta *et al.*, 2002). Cognitive outcome is most compromised in those born at <33 weeks in whom IQ decreases by an average

of 1.5-2.5 points for each decreasing week of GA (Aylward, 2002 and Anderson *et al.,* 2008). Recent studies have not only confirmed that children born preterm have more cognitive impairments and academic difficulties than full-term controls, but they also suggest that these are more common than motor, visual or hearing impairments (Allen, 2008).

The main results on specific cognitive abilities also demonstrate that preterm /LBW children and adolescents show significant differences but normal mean values compared to full-term birth subjects in cognitive functions such; verbal and language skills (Korkman *et al.,* 1996; Wolke and Meyer, 1999; Isaacs *et al.,* 2000; Taylor *et al.,* 2000; Rushe *et al.,* 2001; Isaacs et al., 2003a; Taylor *et al.,* 2004; Caravale *et al.,* 2005; Wocadlo and Rieger, 2007; Luu et al., 2009), learning and memory (Olsen *et al.,* 1998; Pasman *et al.,* 1998; Isaacs *et al.,* 2000; Taylor *et al.,* 2000; Isaacs *et al.,* 2003b; Bohm et al., 2004; Gimenez *et al.,* 2004; Taylor *et al.,* 2004; Rose et al., 2005), perception and constructional functions (Korkman *et al.,* 1996; Olsen *et al.,* 1998; Pasman *et al.,* 1998; Taylor *et al.,* 2000; Torrioli et al., 2000; Briscoe and Gathercole, 2001; Foulder-Hughes *and* Cooke, 2003; Taylor *et al.,* 2004) and frontal - executive functions (Olsen *et al.,* 1998; Pasman *et al.,* 1998; Taylor *et al.,* 2000; Allin *et al.,* 2001; Böhm *et al.,* 2002; Taylor *et al.,* 2004; Gimenez *et al.,* 2006c; Saavalainen *et al.,* 2006; Frye *et al.,* 2009) (*Please, note that some of these studies are detailed in Table 7*). In summary, VPT children appear to have the poorest performance on tests of visuo-spatial skills and nonverbal reasoning and to have specific difficulties in the simultaneous processing of complex stimuli.

In addition, the VPT child is at increased risk for subclinical behavioural and emotional problems and can most often be described as inattentive, shy or withdrawn, and with poor social skills (*See Table 8*). A robust finding is the excess of attention problems in VPT/VLBW children. Above all, attention deficit/hyperactivity disorders are the most frequent abnormal psychiatric outcome, and although these disorders have been linked to the development of conduct disorders in the normal population, there is a notable lack of comorbid disruptive behaviour conditions in preterm children (Johnson *et al.,* 2007). The integrity of both WM and GM in specific regions, such as parenchyma or caudate nuclei, has been related with attention deficits in preterm samples (Indredavik *et al.,* 2004 and Nosarti *et al.,* 2005) (for more details see section 1.6.). There is also some evidence of increased risk for autistic spectrum disorders in VPT children but this issue requires further investigation (Limperopoulos *et al.,* 2008). Greater deficitson cognitive abilities have been noted in extremely preterm (EPT) / ELBW cohorts (*please, see EPT/ELBW studies in Tables 7 and 8*). The EPICure study (Wood *et al.,* 2000), which is the most comprehensive examination of early development in EPT children, indicated

high rates of intellectual impairment in those preterms. In summary, EPT children have high rates of developmental delay which increase with decreasing GA (Anderson *et al.*, 2008).

Moreover, there is a lot of variability in the methodology used in cognitive and behavioural studies of preterm samples, which complicates the comparison between them (Hack and Taylor, 2000). Consequently, variability in outcomes may be attributed to variations in study quality that reflect differences in population definitions, the application of comparative data and the selection of outcome measures (Johnson, 2007). The methodological problems inherent in many follow-up studies that often contribute to conflicting results fall into four broad areas: 1) conceptualization/ design issues, 2) subject populations, 3) procedural issues, and 4) measurement/ outcome (Aylward, 2002).

### *1.5.3. Cognitive changes over time*

There is no consensus about whether cognitive deficits in preterm children get worse, remain stable or improve over time. Longitudinal studies have typically failed to find evidence of "catch-up" growth over time, with some identifying a trend towards deteriorating performance in comparison to term peers (Johnson, 2007). Specifically, Ment *et al.* (2003) concluded that over time the majority of VLBW children had improvement in verbal and IQ test scores, and verbal scores only fell in children with early-onset IVH followed by significant central nervous system injury. Isaacs *et al.* (2004) reported that preterm children are at risk of declining IQ over time even if they have not suffered obvious neurological damage and that the decline is associated with specific neural regions (*see Table 7*).

To truly understand the long-term consequences of prematurity, it is necessary to follow these children throughout childhood and into adulthood. Early childhood outcomes are not particulary predictive of long-term consequences because many cognitive processes have yet to emerge and others are only in the early stages of development (Anderson *et al.*, 2008).

### *1.5.4. Gender differences*

As Table 8 shows, there is also controversy regarding the cognitive disadvantage for preterm boys compared to girls. Several studies, but not all, have demonstrated poorer outcomes for preterm boys compared to girls (Böhm *et al.*, 2002; Saigal *et al.*, 2003; Böhm *et al.*, 2004; Mikkola *et al.*, 2005; Hintz *et al.*, 2006). These sex differences are, as yet, unexplained, as they may occur irrespective of perinatal risk factors and demographic variables (Reiss *et al.*, 2004).

### *1.5.5. So, what influences neurodevelopmental outcomes in preterms?*

Within-group analyses for preterm children have shown a relationship between IQ and both GA and BW (Bhutta *et al.*, 2002; Larroque, 2004; Johnson *et al.*, 2007). Therefore, it seems to be a gradient of developmental sequelae in preterm children that is inversely related to decreasing BW and GA (Aylward, 2002).

In addition to BW and GA, other factors associated with cognitive outcomes include neuroimaging evidence of brain injury, neuromotor abnormalities on examination, male gender and some factors related to severity of neonatal illness or chronic lung disease (Allen, 2008).

As mentioned in Section 1.1.6. "*Neonatal complications following preterm birth*" preterm children are at increased risk for medical complications and such factors have been found to be related to poorer cognitive outcome (Johnson, 2007). Moreover it also appears that the impact of environmental factors reaches a ceiling limit at which point severe biological risk diminishes any potentially compensatory effect. It seems then, that biological factors may have more impact at the lower gestaional ages (Wolke, 1998).

However, a considerable proportion of these high-risk children will escape major impairments, and this variability in outcome is thought to be largely related to genetic (gender), perinatal (brain injury, bronchopulmonary dysplasia), and social–environmental factors (social risk, parenting) (Anderson, 2008).

Although direct links between genes and cognitive ability are difficult to establish, investigators are currently searching for intermediate phenotypes with plausible links to both genome and cognome (Leonard *et al.*, 2006). Regarding the genetic factors associated with cognitive development in preterms, an interesting paper by Harding *et al.* (2007), looked at the effect of COX2 genotype in 5.5-year old preterm children, and found lower cognitive scores with the C allele. This study reminds us that preterm birth and neurodevelopmental outcome of children born preterm are the result of multiple gene-environment interactions.

Hence, as Figure 15 illustrates, the child's cognitive status in adulthood will be determined by a host of variables, including genetic, sociodemographic, and neonatal risk factors, as well as interactions between them (Luciana, 2003; Allen, 2008).

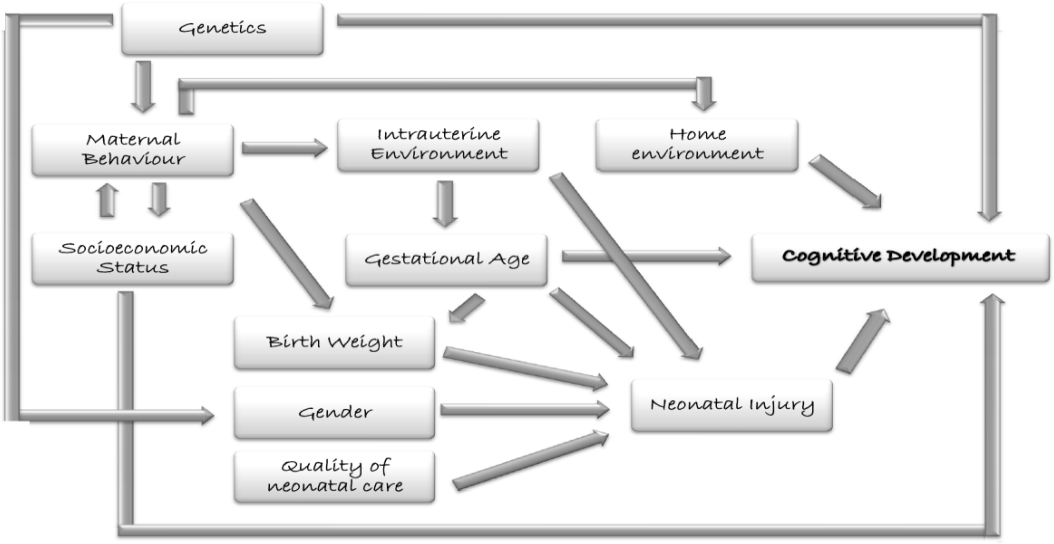


**Figure 15. The sources of influence on cognitive development in the preterm infant** (Modified from Luciana, 2003).

### *1.5.6. Preterms with low-risk for neurodevelopmental deficits*

As Aylward (2002) pointed out, cognitive and behavioural problems are among the most common adverse outcomes in preterm individuals and these "higher prevalence / lower severity" impairments are more evident at school age, even in subjects who are free of severe disability. The complex demands of the school's academic and social environment may illuminate emerging sequelae in middle childhood or exacerbate pre-existing dysfunctions (Aylward, 2005).

Although the majority of children born preterm do not develop major impairments, more preterm children than full-term children develop cerebral palsy and/or cognitive impairments, and the risk increases with decreasing GA. The additional risk of the more subtle impairments of attention, executive function, language, visual-perceptual abilities, and fine motor function that influence the ability to function at school and at home has become apparent. While most studies focus on the most immature infants, there is a growing recognition that infants born at 34–36 weeks gestation have higher mortality, morbidity, and cerebral palsy rates than full-term infants (Allen, 2008).

Therefore, even neonates thought to be at low risk of developmental difficulties, such as those born between 30-34 weeks of gestation with uncomplicated perinatal histories, normal cranial ultrasound scans and no obvious neurodevelopmetal deficits, may have subtle neuropsychological abnormalities later in life (Caravale *et al.*, 2005 and Hart *et al.*, 2008).

The incidence of major disabilities (moderate/severe mental retardation, neurosensory disorders, epilepsy, and cerebral palsy) has remained consistent, but high prevalence/low severity dysfunctions (learning disabilities, ADHD, borderline mental retardation, specific neuropsychological deficits and behavioural disorders) have increased in recent decades (Aylward, 2002). While the major disabilities are often identified during infancy, high prevalence/low severity dysfunctions become more obvious at school age. Furthermore, there are no good predictors of these more subtle problems that can be identified during infancy or preschool age (Hille *et al.*, 1994).

### *1.5.7. Predicted factors of future outcome in preterm infants*

Among preterm children, neurodevelopmental outcome has been related with GA (Hack and Taylor, 2000; Bhutta *et al.*, 2002; Larroque *et al.*, 2004) (the worst outcomes being recorded in those born most preterm) and the type of the intracranial lesion (Sie *et al.*, 2000; Vollmer *et al.*, 2003), highlighting the developmental vulnerability of the immature brain. In addition, regarding perinatal factors and later outcomes in preterms, longitudinal studies suggest that BW is another of the most reliable predictors of long term outcome. In a regional sample of VLBW children, Taylor *et al*. (1998) reported that BW alone is inadequate in accounting for neurodevelopmental impairment at early school age. In the study, a composite Neonatal Risk Index including both medical and neurologic complications was the best predictor of outcomes. Following the line of this study, McGrath *et al.* (2000) reported that neonatal medical status is an important indicator of neurocognitive and school performance outcomes in LBW infants. Subsequently, Taylor *et al.* (2004) demonstrated poorer outcomes for the <750 g group than for term-born controls on nearly all measures, with specific impairments in visual-motor skills, spatial memory, and executive function.

As pointed out in Section 1.1.2 "*Measures of size at birth*", infants born SGA or with IUGR are considered to be at risk for adverse neurocognitive development (Bos *et al.*, 2001 and van Wassenaer, 2005). However, recent investigations challenge this notion demonstrating no significant differences either in cortical formation (Abe *et al.*, 2004), cerebral metabolism, brain development or in neurodevelopmental outcome in SGA infants (Roelants-van Rijn *et al.*, 2004). Concerning IUGR, Leitner *et al.* (2000) conducted a prospective study to characterize the neurodevelopmental and cognitive difficulties specific to children with IUGR and to detect early clinical predictors of these difficulties. A significant difference in growth parameters, neurodevelopmental score and IQ was found between the children with IUGR and controls. In addition, the neuropsychological profile of children with IUGR at 9 years of age (difficulties in

executive functioning, inflexibility-creativity, and language) indicates that late-onset IUGR also compromises frontal network functioning (Geva *et al.,* 2006).

One tool that may assist early prognostic evaluations of the preterm infant is MRI during the neonatal period. In preterm infants, imaged at term, MRI may also be used to predict motor outcome in infants with focal lesions and possibly also in PVL (Rutherford, 2002) Woodward *et al.* (2006) found significant associations between the qualitative measures of cerebral WM and GM abnormalities on MRI at term equivalent age and the subsequent risks of adverse neurodevelopmental outcomes at two years of age among VPT infants. In this sense, moderately abnormal WM on cranial ustrasound was associated with variable outcome and, in addition, MRI slightly increased the predictive value of cranial ultrasound in sever WM changes (Leijser *et al.,* 2008). Therefore, measures of brain structure and function are by far the most predictive of neurodevelopmental outcomes (Allen, 2008). However, as discussed by Dammann and Leviton (2006), despite these promising reports, definitive predictive data that include sensitivity, specificity, and especially positive and negative predictive values for neurodevelopmental disabilities are needed before MRI or DTI become standard clinical practice.

Although the majority of surviving children will eventually lead fairly normal lives, major developmental and learning problems must be anticipated. Since it is not possible to predict how an individual child will later develop, ongoing assessment and support with proactive programs need to be provided from infancy and into the school years (Hack and Fanaroff, 2000).

**Table 6.** Commonly used assessments of behaviour and psychopathology in middle childhood

| **Assessment** | **Author and Publisher** | **Age range** | **Administration** | **Scales** | **Results** * |
|---|---|---|---|---|---|
| Achenbach System of Empirically Basses Assesment (ASEBA)<br>✓ Child Behaviour Checklist (CBCL)<br>✓ Teacher Report Form (TRF)<br>✓ Youth Self Report (YSR) | Achenbach and Rescorla (2001)<br>ASEBA Research Centre for Children, Youth and Families | CBCL, TRF: 1,5-18 y<br>YSR:11-18 y | Parent Report (CBCL)<br>Teacher Report (TRF)<br>Youth self-report (YSR) | Total Problem Behaviour<br>Internalising Scale<br>Externalising Scale<br>*Withdrawn*<br>*Somatic complains*<br>*Anxious/depressed*<br>*Delinquent behaviour*<br>*Aggressive behaviour*<br>*Social problems*<br>*Thought problems*<br>*Attention problems*<br>Social Competence Score<br>*Activities*<br>*Social competence*<br>*School competence* | Raw scores, T scores and percentiles with empirical cut-offs for identification of abnormal on each scale |
| Conner's Rating Scales-Revised (CRS-R) | Conners (1996) Harcourt Assesment | 3-17 y<br><br>12-17 y | Parent or Teacher report<br>Adolescent self-report | (Short Form)<br>Oppositional<br>Cognitive Problems/inattention<br>Hiperactivity<br>Attention deficit/Hiperactivity disorder<br>Index | Raw scores are converted to T scores and percentiles for each scale |
| Strengths and Difficulties Questionnaire (SDQ) | Goodman (1997)<br>www.sdqinfo.com | 3-16 y | Parent or Teacher report (4-16)<br>Self rport (11-16) | Total difficulties (Sum of 1st 4 Scales)<br>Emotional symptoms<br>Conduct problems<br>Hyperactivity/inattention<br>Peer relationship problems<br>Prosocial behaviour<br>Impact supplement | Continuous scores for each scale and empirical cut-offs for identification of borderline and abnormal scores |

* Higher scores represent more impaired function. Source: *Johnson, 2007*

**Table 7.** Cognitive findings in children and adolescents preterm studies

| **Study**<br>*Reference and title* | **Preterm simple**<br>N, age (GA or BW)<br>Cognitive function assessed (Questionnaire / Test) | **Summary of main findings** |
|---|---|---|
| **Cooke and Abernethy, 1999**<br>*Cranial magnetic resonance imaging and school performance in very low birth weight infants in adolescence* | N= 87, 12-13 y (mean 29 w)<br>Intelligence (WISC-III) | No significant differences in IQ or motor clumsiness, were observed between those children with MRI lesions and those with normal scans. |
| **Stewart et al., 1999**<br>*Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm* | N=105, 14-15 y (<33w)<br>Intelligence (WISC, VIQ)<br>Reading (Schonnel) | Low VIQ.<br>Reading age was lower in preterms than in controls. |
| **Stjernqvist and Svenningsen, 1999 ≠**<br>*Ten-year follow-up of children born before 29 gestational weeks: health, cognitive development, behaviour and school achievement* | N=65, 10 y (<29 w)<br>Intelligence (WISC-III)<br>Visual-Motor Integration (VMI) | Differences on IQ and Visual-Motor integration between preterms and controls corresponded to approximately one SD. |
| **Wolke and Meyer, 1999**<br>*Cognitive status,language attainment,and prereading skills of 6-year-old verypreterm children and their peers: the Bavarian Longitudinal Study* | N= 264, 6 y (<32 w)<br>Cognitive assessment (Kaufman Assessment Battery for Children, K-ABC)<br>Battery for language development (Heidelberger Sprachentwicklungstest,HSET) | Compared with term peers, VPT children scored significantly lower (approximately –1 SD) on the measures of cognitive and language skills and had major cognitive deficits (<–2 SD) 10 to 35 times more often than the controls. |
| **Hack and Fanaroff, 2000 ¥**<br>*Outcomes of children of extremely low birthweight and gestational age in the 1990s* | A review of the world literature among regional populations with BW< 800 g and GA <26 w | Major neonatal morbidity increases with decreasing GA and BW. When compared with children born prior to the 1990s, the rates of neurodevelopmental disability have, in general, remained unchanged. |
| **Isaacs et al., 2000**<br>*Hippocampal volume and everyday memory in children of very low birth weight* | N= 11, 13 y (≤ 30 w, VLBW mean 998g)<br>Intelligence (WISC-III)<br>Verbal and nonverbal recall (Children's Auditory-Verbal Learning Test, CAVLT)<br>Attainment measures ( Wechsler Objective Numerical Dimensions, WOND and Wechsler Objective Reading Dimensions, WORD)<br>Everyday memory (RBMT) | Significant differences between groups but normal mean values in the preterm group for VIQ and Freedom from distractibility.<br><br>The preterm group had a specific deficit in numeracy. |
| **Peterson et al., 2000**<br>*Regional brain volume abnormalities and long-term cognitive outcome in preterm infants* | N= 25, 8 y (<29 w)<br>Intelligence (WISC-III)<br>Developmental Test of Visual-Motor Integration | Low IQ, significant differences but normal mean values in the preterm group. |
| **Saigal et al., 2000 ●**<br>*School difficulties at adolescence in a regional cohort of children who were extremely low birth weight* | N= 150, 12-16 y (ELBW)<br>Cognitive ability (WISC-R and Wide Range Achievement Test-Revised) | Differences of 13 to 18 points in psychometric measures in ELBW teens compared with controls are both statistically significant and clinically relevant. |

| | | |
|---|---|---|
| **Taylor et al., 2000 ¥ ●**<br>*School-Age Consequences of Birth Weight Less Than 750 g: A Review and Update* | N= 133, 7 y (<750g and between 750 – 1499 g)<br>Cognitive assessment (K-ABC and Woodcock–Johnson Tests of Achievement–Revised) | Results suggest a gradient of sequelae, with poorer outcomes in less than 750 g BW children compared to both 750 g to 1,499 g BW children and term-born control son cognitive measures. |
| **Torrioli et al., 2000**<br>*Perceptual-motor, visual and cognitive ability in very low birthweight preschool children without neonatal ultrasound abnormalities* | N= 36, 5 y (VLBW with a mean of 31 w)<br>Intelligence (WPPSI)<br>Perceptual motor skills assessment (developmental test of visual-motor integration)<br>Movement assessment (Movement assessment battery for children-ABC)<br>Spatial attention (Bell test) | The mean full IQ scale was in the normal range. Lower scoring in perceptual motor skills associated with defect of accuracy in spatial attention and higher incidence of steropsis impairment. |
| **Tiedman, 2000●**<br>*Longitudinal follow-up of children born preterm: cognitive development at age 19* | N= 39, 4, 9 and 19 y (<35 w)<br>Cognitive assessment: The Griffiths' Mental Development Scale II (4 y); The Raven's Coloured Progressive Matrices and the Raven's Standard Progressive Matrices (9 and 19 y); WAIS (19 y) | At 4 years of age the cognitive outcome of the preterms fell within the normal range, although their performance was inferior to that of the full-terms. This difference between the groups was not found at 9 and 19 years of age. |
| **Wood et al., 2000**<br>*Neurologic and developmental disability after extremely preterm birth. EPICure Study Group* | N= 283, 30 months (≤ 25 w)<br>Developmental assessment (Bayley Scales of Infant Development) | This cohort had a mean Mental Development Index of 84, which is more than 1 SD below the normative mean and clearly reflects significant cognitive delay. |
| **Rushe et al., 2001**<br>*Neuropsychological outcome at adolescence of very preterm birth and its relation to brain structure* | N= 75, 14-15 y (<33 w)<br>Language (The FAS test)<br>Reading and spelling (The Schonnel Graded Reading Test, GWRT and the Schonnel Spelling Test)<br>Visuomotor (Trails A) and executive function (Trails B)<br>Verbal memory (Wechsler Memory Scale and RBMT )<br>Perceptual organization and visuospatial memory (The Rey–Osterrieth Complex Figure Test)<br>Attention(The digit span subtest of the WISC-R) | Compared to controls VPT adolescents had impairment only on a measure of word production. On measures of attention, memory, perceptual skill, and visuomotor and executive function, preterms performed in the normal range, whether or not they had evidence of MRI abnormality. |
| **Roth et al., 2001 ●**<br>*Neurodevelopmental status at 1 year predicts neuropsychiatric outcome at 14-15 years of age in very preterm infants.* | N= 89, 14-15 y (<33 w)<br>Intelligence (WISC-R)<br>The Premorbid Adjustment Scale | Neurodevelopmental assessment at 1 year is predictive of school performance and outcome in the adolescent period.<br>Results showed significant differences with altered mean values in the preterm group. |
| **Abernethy et al., 2002**<br>*Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight* | N= 87 , 15-16 y (<31 w and <1500 g)<br>Intelligence (WISC-III)<br>Motor disability (Movement ABC) | There was no significant difference in IQ or dyspraxia between children with qualitatively normal and abnormal scans. |
| **Böhm et al., 2002 ◘▲ ≠ (Stockholm Neonatal Project)**<br>*Developmental risks and protective factors for influencing cognitive outcome at 5 1/2 years of age in very-low-birthweight children* | N= 182, 5 y (VLBW mean 1043 g)<br>Cognitive ability (Wechsler Preschool and Primary Scale of Intelligence-Revised, WPPSI-R and a neuropsychological test battery, NEPSY) | Although the control group had significantly better results, the WPPSI–R results of the VLBW children fell well within the normal range. |

| | | |
|---|---|---|
| **Hansen et al., 2002 ●**<br>*Intelligence in preterm children at four years of age as a predictor of school function: a longitudinal controlled study* | N=333, 4 y (Very-low BW, Low BW, Normal BW)<br>McCarthy Scales of Children's Abilities<br>A telephone interview about school performance at 18 to 20 years | Birthweight was not a predictor for school performance. |
| **Rose et al., 2002 ●**<br>*Processing speed in the 1st year of life: a longitudinal study of preterm and full-term infants* | N= 39, 48 and 55 respectively with 5, 7 and 12 months (<1750 g) | In preterms, the deficits in processing speed are already present in the 1st year of life. |
| **Anderson et al., 2003 ▲**<br>**(Victorian Infant Collaborative Study)**<br>*Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s* | N= 298 , 8 y (ELBW <1000g, <28w)<br>Cognitive ability (WISC-III)<br>Educational progress (Wide Range Achievement Test and the Comprehensive Scales of Student Abilities) | The ELBW or VPT children scored significantly below controls on full-scale IQ and indices of verbal comprehension, perceptual organization, freedom from distractibility processing speed an on tests of reading. |
| **Foulder-Hughes et al., 2003 ▲ ≠**<br>*Motor, cognitive, and behavioural disorders in children born very preterm* | N=280, 7-8 y (<32w)<br>General intelligence (WISCIII) | Control children scored significantly better than the preterm group on all cognitive measures. |
| **Hopkins-Golightly and Raz, 2003 †**<br>*Influence of slight to moderate risk for birth hypoxia on acquisition of cognitive and language function in the preterm infant: a cross-sectional comparison with preterm-birth controls* | N= 26, 6 y (≤36)<br>Cognitive ability (WPPSI–R, WISC–III) | Significant differences between pretem groups in cognitive abilities (VIQ and PIQ) but within limits of normality. |
| **Isaacs et al., 2003b**<br>*Developmental amnesia and its relationship to degree of hippocampal atrophy* | N= 11, mean 14 y (<31 w)<br>Intelligence (WISC-III)<br>Verbal and nonverbal recall (Children's Auditory-Verbal Learning Test, CAVLT)<br>Attainment measures (WOND and WORD)<br>Memory (RBMT and Rey–Osterrieth Complex Figure) | Preterms showed lower scores than controls but their mean scores still fell within the average.<br>The preterm group was significantly impaired relative to the controls on only a few memory measures, i.e., route following and prospective memory.<br>No child in the preterm group presented with an amnesic profile. |
| **Luciana, 2003 ¥**<br>*Cognitive development in children born preterm: implications for theories of brain plasticity following early injury* | Children born preterm | Cognitive outcome in children born preterm |
| **Ment et al., 2003 ● ≠**<br>*Change in cognitive function over time in very low-birth-weight infants* | N= 296, 36, 54, 72, and 96 months of corrected age (BW 600 to 1250 g)<br>Neurodevelopmental assessment (WPPSI-R and Peabody Picture Vocabulary Test–Revised) | The majority of VLBW children had improvement in verbal and IQ test scores over time. |
| **Saigal et al., 2003 ● ◘**<br>*School-age outcomes in children who were extremely low birth weight from four international population-based cohorts* | N= 436 , 8-10 y (mean 28 w < 1000 g)<br>Intelligence (WISC-III, WISC-R, K-ABC) | The proportion of children who performed within the normal range (>85) were: IQ between 44% and 62%; reading between 46% and 81%; arithmetic between 31% and 76%; and spelling between 39% and 65%. |

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| **Anderson et al., 2004**<br>*Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s* | N= 298, 8 y (ELBW/VPT )<br>Neuropsychological assessment battery for executive function (Similarities, Digit Span, Block Design, Picture Arrangement, Tower of London, Rey Complexe Figure) | ELBW/VPT cohort exhibited significant executive dysfunction compared with their NBW peers in all areas assessed. The cognitive assessment revealed global impairment rather than deficits in specific executive domains. |
| **Böhm et al., 2004** ◙<br>*Impulse control, working memory and other executive functions in preterm children when starting school* | N= 307 (VLBW, <1500), 5 ½ y<br>Neuropsychological test battery (Nepsy 1990) | Related to executive functions girls surpassed boys on tests. Preterm children showed worst performance than controls in executive functions although their IQ was normal. |
| **Giménez et al., 2004**<br>*Hippocampal gray matter reduction associates with memory deficits in adolescents with history of prematurity* | N= 22, 13 y (25-35 w)<br>Rey Auditory Verbal Learning Test<br>Rey's Complex Figure | The groups significantly differed in learning , recognition and trend towards statistical significance in percentage of verbal memory loss. In contrast, the groups did not differ in visual memory. |
| **Grunau et al., 2004**◊<br>*Psychosocial and academic characteristics of extremely low birth weight (<800g) adolescents who are free of major impairment compared with term-born control subjects* | N= 53, 17 y ( ≤800 g)<br>Cognitive ability (WAIS-III)<br>Academic achievement (Wide Range Achievement Test, Third Edition) | ELBW group scored significantly lower than the control group on all 3 subtests: Vocabulary, Block Design, and the Digit-Symbol. |
| **Isaacs et al., 2004** ●<br>*Brain morphometry and IQ measurements in preterm children* | N= 82 , 7-15 y (<31 w)<br>Intelligence (WISC-R and WISC-III) | Decline of IQ over the time. |
| **O'Brien et al., 2004**<br>*The neurodevelopmental progress of infants less than 33 weeks into adolescence* | N= 151, 14-15 y ( ≤ 32 w)<br>Intelligence (WISC-R)<br>Visuomotor integration (Beery) | Between 8 and 15 years preterms showed a deterioration in neurodevelopmental outcome category, cognitive function, and extra educational support |
| **Reiss et al., 2004** ●<br>*Sex differences in cerebral volumes of 8-year-olds born preterm* | N= 65, 8 y (mean 28 w)<br>WPPSI-R (4.5 y) WISC-R (8 y) | The preterm group had lower mean Full Scale IQ scores than control children<br>Decline of IQ over time |
| **Schermann and Sedin, 2004**<br>*Cognitive function at 10 years of age in children who have required neonatal intensive care* | N= 226, 10 y (<36 w)<br>Cognitive assessment (K-ABC) | Preterm children from all the studied groups showed poorer performance than controls in the simultaneous processing scale. |
| **Taylor et al., 2004**<br>*Long-term neuropsychological outcomes of very low birth weight: associations with early risks for periventricular brain insults* | N= 48, 16 y (VLBW <750 -1499 g)<br>Intelligence (WISC-III, WAIS-III/short form) | Poorer outcomes for the <750 g group than for term-born controls on nearly all measures, with specific impairments in visual-motor skills, spatial memory, and executive function. |
| **Caravale et al., 2005** ◊<br>*Cognitive development in low risk preterm infants at 3–4 years of life* | N= 30, 3-4 y (GA between 30-34 w)<br>Cognitive level (Stanford-Binet intelligence scale)<br>Perceptual and motor abilities (Visual-motor integration test, Block construction, Visual-perceptual tasks)<br>Language abilities(Boston naming test, Word and phrase retrieval test, Peabody picture vocabulary test revised, Test of grammar comprehension)<br>Working memory ability (Memory for location) | Children born preterm achieved lower mean scores than controls on the Stanford-Binet intelligence scale, visual perception test, visual motor integration test, memory for location test, sustained attention test, and the picture vocabulary test. |
| **Hack et al., 2005** ▲<br>*Chronic conditions, functional limitations, and special health* | N= 219, 8 y (<1000g )<br>Cognitive assessment (K-ABC) | ELBW preterm children showed low IQ than normal BW term-control children. |

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| *care needs of school-aged children born with extremely low-birth-weight in the 1990s* | | |
| **Marlow et al., 2005 ▲ (EPICure Study)** *Neurologic and Developmental Disability at Six Years of Age after Extremely Preterm Birth* | N= 241, 6 y (<26 w) Cognitive assessment (K-ABC or Griffiths Scales for severely impaired) | Among EPT children, cognitive and neurologic impairment is common at school age. A comparison with their classroom peers indicates a level of impairment that is greater than is recognized with the use of standardized norms. |
| **Mikkola et al., 2005 ● ◙ ▲ ≠ (Finnish ELBW Cohort Study)** *Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997* | N= 172, 5 y (<1000 g) Cognitive assessment (WPPSI-R and a Developmental Neuropsychological Assessment NEPSY ) | The rate of cognitive impairment in the ELBW survivors was 9%. Attention, language, sensorimotor, visuospatial, and verbal memory values of NEPSY assessment were significantly poorer compared with normal population means. |
| **Rose et al., 2005 ●** *Recall memory in the first three years of life: a longitudinal study of preterm and term children* | N= 56 , 12, 24, and 36 months (BW <1750g) Recall memory was assessed using an elicited imitation task | Preterm children have deficits in recall memory that emerge by 12 months and persist into early childhood. |
| **Youngmei Peng et al., 2005** *Outcome of low birthweight in China: a 16-year longitudinal study* | N= 101, 5y (<37) Cognitive assessment (WPPSI) | Adolescents with BWs of 1200-2499 g, and particularly those who were SGA, lag behind peers in cognitive capacity, although within limits of normality. |
| **Casey et al., 2006 ●** *Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation* | N= 655, 8y (LBW preterms divided into 4 growths groups: normal growth, small for GA only, failure to thrive only, failure to thrive plus small for GA) WISC-III VMI Peabody Vocabulary Test-R | Children who both were SGA and had failure to thrive demonstrated the lowest cognitive and academic achievement scores. |
| **Hintz et al., 2006 ● ◙** *Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants.* | N= 2553, follow-up at 18-22 mo corrected age (<28 w) Neurodevelopmental measure (Bayley Mental, MDI) | Perinatal, neonatal and early childhood factors confer similar incremental risk or protection to boys and girls, but boys appear to have inherently greater baseline risk. |
| **Gimenez et al., 2006c** *Correlations of thalamic reductions with verbal fluency impairment in those born prematurely* | N=60 adolescents VPT Modified version of the Controlled Oral World Association Test Semantic fluency task Vocabulary scale of Wechsler Intelligence Scales | In preterms semantic fluency correlated with more thalamic nuclei than phonetic fluency. |
| **Bayless and Stevenson, 2007** *Executive functions in school-age children born very prematurely* | N= 81, 6-12 y (very pretems, <32 weeks) Children were assessed on Intelligent Quotient, Executive functions (inhibition, working memory and set shifting) and attention (sustained and selective). | Preterms showed mild executive function and executive attention difficulties. |
| **Davis et al., 2007** *Developmental coordination disorder at 8 years of age in a regional cohort of extremely-lowbirthweight or very preterm infants* | N= 20, 8y (<28 w , ELBW<1000g) WISC-III | ELBW/VPT children with developmental coordination disorder had worse cognitive function and academia test scores (up to 1SD below) than those without developmental coordination disorder. |
| **Johnson et al., 2007¥** *Cognitive and behavioural outcomes following very pretem birth* | VPT birth < 32 weeks. | VPT presented significant lower IQ scores as case-controlled studies showed. Problems were reported in non-verbal reasoning and simultaneous information processing. |

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| | | Regarding the behavioural problems, very pretem children showed highest scores in attentional and social problems.<br>Related to psychiatric disorders an increased risk for ADHD was reported. |
| **Limperopoulos et al., 2007♦**<br>*Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors?* | N= 86, 32 months (<32 w)<br>The Peabody Developmental Motor Scales<br>The Mullen Scales of Early Learning | Preterm infants with cerebellar hemorrhagic injury and supratentorial parenchymal injury were not at overall greater risk for neurodevelopmental disabilities, although neuromotor impairment was more severe. |
| **Narberhaus et al., 2007**<br>*Gestational age at preterm birth in relation to corpus callosum and general cognitive outcome in adolescents* | N= 117, 14 y (25-36 w)<br>Cognitive assessment (WISC-R and WAIS III depending on the age of the adolescent) | Those preterms with a GA ≤ 27 weeks showed a reduction in the anterior and posterior part of the CC, decrements in total WM and poor IQ performance. |
| **Saavalainen et al., 2007**<br>*Spatial span in very prematurely born adolescents*<br>*[abstract only]* | N= 66 (≤32 w), 16 y<br>Adolescents were assessed on Intelligent Quotient | Minor spatial working memory dificulties in preterm adolescents without major disabliliy and with normal cognitive capacity. |
| **Wocadlo and Rieger, 2007**<br>*Phonology, rapid naming and academic achievement in very preterm children at eight years of age* | N= 63, 8 y (<30 w)<br>Intellectual functioning (WISC-III)<br>Language assessment (Peabody Picture Vocabulary Test, The Expressive One Word Picture Vocabulary Test, The Comprehensive Test of Phonological Processing) | 38% of preterm simple showed low achievement in reading, spelling or mathematics.<br>Reading achievement was significantly correlated to phonological awareness, rapid naming and expressive vocabulary. |
| **Anderson and Doyle, 2008 ¥**<br>*Cognitive and educational deficits in children born extremely preterm* | EPT children born <26 w or BW <750 g | Development delay, cognitive impairments and learning disabilities. |
| **Gray et al., 2008**<br>*Behaviour and quality of life at school age of children who had bronchopulmonary dysplasia* | N= 66, 8y (26-33w)<br>WISC-III | Lower IQ, VIQ and PIQ in preterm children with bronchopulmonary dysplasia compared to controls. |
| **Larroque et al., 2008 ● ▲ (EPIPAGE Study)**<br>*Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study* | N= 1817, 5 y (22-32 w)<br>Cognitive assessment (K-ABC) | In children who are born VPT, cognitive and neuromotor impairments at 5 years of age increase with decreasing GA. |
| **Frye et al., 2009 ▲ ♦ †**<br>*Executive dysfunction in poor readers born prematurely at high risk* | N= 253, during the 3rd, 5th and 7th grades<br>Woodcock-Johnson Test of Achievement Word Attack subtest<br>Standford-Binet Intelligence Scale<br>Comprehensive Evaluation of Language Fundamentals<br>Executive tasks | High risk prematures with poor reading ability perform poorly on executive function tasks at childhood. |

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| **Luu et al., 2009 ♦**<br>*Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age* | N= 375, 12 y (BW 600-1250 g)<br>Intelligence (WISC-III)<br>Receptive listening vocabulary (The Peabody Picture Vocabulary Test-R)<br>Efficiency of phonological information retrieval from long-term memory (The rapid naming composite of the Comprehensive Test of Phonological Processing)<br>Developmental Test of Visual-Motor Integration (VMI)<br>Receptive and expressive language (The Clinical Evaluation of Language Fundamentals)<br>Reading skills (Test of Word Reading Efficiency and the Gray Silent Reading Test ) | Preterm children, especially those with severe brain injury born in the early 1990s, demonstrate significant neuropsychological deficits and increased needs for educational support services. |

Abbreviations
ELBW: extremely low birth weight, BW: birth weight, GA: gestational age, g: grams, IQ: intelligence quotient, K-ABC: Kaufman Assessment Battery for Children, PIQ: performance intelligence quotient, RBMT: Rivermead Behavioural Memory Test, SD: standard deviation, VIQ: verbal intelligence quotient, VLBW: very low birth weight w: weeks, VMI: Developmental Test of Visual-Motor Integration, VPT: very preterm, WAIS: Wechsler Adult Intelligence Scale, WPPSI: Wechsler Preschool and Primary Scale of Intelligence, WISC: for Children, WOND: Wechsler Objective Numerical Dimensions, WORD: Wechsler Objective Reading Dimensions, y: year/s.

Symbols
◊ Low-risk preterm sample
♦ Preterm sample with severe brain injury
† Perinatal complications
● Longitudinal study
¥ Review study
◙ Studies that demonstrated cognitive disadvantage for preterm boys compared to girls
◘ Studies that have not noted cognitive disadvantage for preterm boys compared to girls
▲ population-based studies of cohorts born in the 1990s
≠ Studies that have shown deficits of 5-10 points in mean PIQ scores compared to mean VIQ scores or deficits in perceptual and non-verbal abilities using other measures than Wechsler Scales.

*This table is exclusively based on investigation works in the last ten years including revisions. Source search: PubMed (www.pubmed.gov), language: English, last update; June 2009.*

**Table 8.** Behavioural and emotional studies in children and adolescents born preterm

| **Study** Reference and *Title* | **Preterm sample** N, age (GA or BW) Questionnaires | **Summary of main findings** |
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| ***Attention / Attention-hyperactivity*** | | |
| **Peterson et al., 2000** *Regional brain volume abnormalities and long-term cognitive outcome in preterm infants* | N= 25, 8 y (<29 w) CBCL and Psychiatric diagnoses | Separation anxiety disorder, ADHD, Simple phobia and Learning disability. |
| **Torrioli et al., 2000** *Perceptual-motor, visual and cognitive ability in very low birthweight preschool children without neonatal ultrasound abnormalities* | N= 36, 5 y (VLBW with a mean of 31 w) Parent symptom questionnaire of Conners | Emotional maturation and hyperactivity. |
| **Abernethy et al., 2002** *Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight* | N= 87 , 15-16 y (<31 w and <1500 g) Rutter A and B questionnaires with Connor's Hyperactivity Scale | There was no significant difference in attention deficit between children with qualitatively normal and abnormal scans. |
| **Foulder-Hughes et al., 2003** *Motor, cognitive, and behavioural disorders in children born very preterm* | N= 280, 7-8y (<32 w) Attention-deficit–hyperactivity disorder (CRS-Teachers) | Preterm children were more likely to have signs of inattention and impulsivity and have a diagnosis of ADHD. |
| **Indredavik et al., 2004** *Psychiatric symptoms and disorders in adolescents with low birth weight* | N= 56, 14 y (VLBW ≤ 1500 g) Schedule for affective disorders and schizophrenia for school aged children, ADHD rating scale IV, autism spectrum screening questionnaire, and children's global assessment scale | VLBW adolescents, have a high risk of developing psychiatric symptoms and disorders by the age of 14, especially ADHD, anxiety symptoms, and relational problems. |
| **Nosarti et al., 2005** *Hyperactivity in adolescents born very preterm is associated with decreased caudate volume* | N= 72, 15 y (<33 w) Behavioural assessment (Rutter Parents' Scale) | Preterm adolescents scored significantly higher than control subjects on the Rutter hyperactivity score, and boys scored higher than girls. |
| **Samara et al., 2008** *Pervasive behavior problems at 6 years of age in a total-population sample of children born at ≤ 25 weeks of gestation* | N= 200, mean 76 months (≤25 w) To assess components of ADHD (CBCL + DSM-IV+CIE-10) | Hyperactivity and conduct problems could be accounted by cognitive deficits, but attention, peer and emotional problems were not explained by poor cognitive functioning. |
| **Shum et al., 2008** *Attentional problems in children born very preterm or with extremely low birth weight at 7-9 years* | N= 45, 7-9y ( ≤27 w or ELBW ≤1000 g) Psychological tests of attention (Digits and Spatial Span Forward, Visual Attention from the NEPSY, Trail Making Test B, and Stroop Color andWord Test) | Children born VPT/ELBW were found to perform significantly more poorly than controls on a test that measures attention span or encoding. |
| ***Autism*** | | |
| **Limperopoulos et al., 2007♦** *Does cerebellar injury in premature infants contribute to the* | N= 86 (<32 w) CBCL | Significant differences on autism screeners and internalizing behavioural problems. |

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| *high prevalence of long-term cognitive, learning, and behavioral disability in survivors?* | A parent-report screening measure for autism spectrum Disorders (The Social Communication Questionnaire) | |
| **Limperopoulos et al., 2008**<br>*Positive Screening for Autism in Ex-preterm Infants: Prevalence and Risk factors* | N= 91preterm infants (1500 g, mean age 22 months)<br>Modified Checklist for Autism in Toddlers<br>The Vineland Adaptive Behaviour Scale<br>CBCL | High prevalence of autism spectrum features among survivors of EPT.<br>Abnormal scores correlated highly with internalizing behavioural problems on the CBCL and socialization and communication deficits. |
| ***Behavioural disorders*** | | |
| **Stewart et al., 1999**<br>*Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm* | N= 105, 14-15 y (<33w)<br>Rutter behavioural scale and the premorbid adjustment scale | Premorbid adjustment scores were impaired in cases with equivocal or abnormal magnetic resonance imaging. |
| **Stjernqvist and Svenningsen, 1999**<br>*Ten-year follow-up of children born before 29 gestational weeks: health, cognitive development, behaviour and school achievement* | N= 65, 10 y (<29 w)<br>CBCL | EPT children had more general behaviour problems than full-term children: Total problem score, internalization, externalization, social competence and attention problems. |
| **Peterson et al., 2000**<br>*Regional brain volume abnormalities and long-term cognitive outcome in preterm infants* | N= 25, 8 y (<29 w)<br>CBCL and Psychiatric diagnoses | Separation anxiety disorder, ADHD, Simple phobia and Learning disability. |
| **Torrioli et al., 2000**<br>*Perceptual-motor, visual and cognitive ability in very low birthweight preschool children without neonatal ultrasound abnormalities* | N= 36, 5 y (VLBW with a mean of 31 w)<br>Parent symptom questionnaire of Conners | Emotional maturation and hyperactivity. |
| **Anderson et al., 2003**<br>*Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s* | N= 298 , 8 y (ELBW <1000 g, <28 w)<br>The Behavior Assessment System for Children (BASC) | Attention difficulties, internalizing behaviour problems, and immature adaptive skills were more prevalent in the ELBW or VPT cohort. |
| **Foulder-Hughes et al., 2003**<br>*Motor, cognitive, and behavioural disorders in children born very preterm* | N= 280, 7-8 y (<32 w)<br>Fine and gross motor skills( MABC and COMPS)<br>Integration of visual and motor abilities (VMI) | Control children scored significantly better than the preterm group on all motor and behavioural measures. |
| **Stoelhorst et al., 2003**<br>*Behaviour at 2 years of age in very preterm infants (gestational age < 32 weeks)* | N= 206, 2 y (<32 w)<br>CBCL | The prevalence of behavioural problems at 2 y corrected age in this cohort of VPT infants was comparable with that in a general population sample. Children born small for GA or with neurological abnormalities at 2 y of age had higher syndrome scale scores, mainly for anxious/depressed and/or withdrawn behaviour. |
| **Anderson et al., 2004**<br>*Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s* | N= 298, 8 y (ELBW/VPT)<br>Behavior Rating Inventory of Executive Function | Preterm cohort scored higher across all behavioural parameters of executive function. |
| **Gray et al., 2004 ●**<br>*Prevalence, stability, and predictors of clinically significant behavior problems in low birth weight children at 3, 5, and 8* | N= 869, 3,5 and 8 y (<37 w, <2500 g)<br>CBCL | This sample had double the prevalence of behaviour problems expected in the general child population. These problems showed stability over time. |

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| *years of age* | | |
| **Grunau et al., 2004**◊<br>*Psychosocial and academic characteristics of extremely low birth weight (<800g) adolescents who are free of major impairment compared with term-born control subjects* | N= 53, 17 y ( ≤800 g)<br>CBCL for adolescents<br>Ability to focus and maintain attention was examined using the computerized Connors'CPT | ELBW teens showed significantly more problems above the clinical cut-off for total, internalizing, and externalizing problems. |
| **Indredavik et al., 2004**<br>*Psychiatric symptoms and disorders in adolescents with low birth weight* | N= 56, 14 y (VLBW ≤ 1500 g)<br>Schedule for affective disorders and schizophrenia for school aged children, ADHD rating scale IV, autism spectrum screening questionnaire, and children's global assessment scale | VLBW adolescents, have a high risk of developing psychiatric symptoms and disorders by the age of 14, especially ADHD, anxiety symptoms, and relational problems. |
| **Casey et al., 2006** ●<br>*Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation* | N= 655, 8 y (LBW preterms divided into 4 growths groups: normal growth, small for GA only, failure to thrive only, failure to thrive plus small for GA)<br>CBCL | No differences in behavioural status among the four growth groups. |
| **Delobel-Ayoub et al., 2006**<br>*Behavioral outcome at 3 years of age in very preterm infants: the EPIPAGE study* | N=1228, 3 y (VPT singletons, GA 22-32)<br>SDQ for parents | VPT children have a higher risk of behavioural problems at 3 years of age compared with term-born children. Health and neurodevelopmental status of the child were significantly associated with behavioural difficulties. |
| **Reijneveld et al., 2006**<br>*Behavioural and emotional problems in very preterm and very low birthweight infants at age 5 years* | N= 402, 5 y (<32 w, <1500 g)<br>CBCL | The prevalence rate of a CBCL total problems score in the clinical range was higher among VPT / VLBW children. |
| **Davis et al., 2007**<br>*Developmental coordination disorder at 8 years of age in a regional cohort of extremely-lowbirthweight or very preterm infants* | N= 20, 8 y (<28 w , ELBW<1000 g)<br>Behaviour Assessment System for Children (BASC) teachers and parents | ELBW children with developmental coordination disorder had more adaptive behaviour and externalizing problems, but not internalizing problems. |
| **Anderson and Doyle, 2008** ¥<br>*Cognitive and educational deficits in children born extremely preterm* | EPT born <26 w or BW <750 g | Findings are generally consistent and indicate that a large proportion of EPT children and their families will face major challenges, including significant development delay, cognitive impairments, learning disabilities, and behavioural and emotional problems. |
| **Gray et al., 2008** †<br>*Behaviour and quality of life at school age of children who had bronchopulmonary dysplasia.* | N= 66, 8 y (26-33 w)<br>CBCL<br>Questionnaires on anxiety and depression (The Delusions Symptoms States Inventory of Foulds and Bedford) | Significant differences between classroom controls and the preterm children were found for the total problem scores, internalising behaviours, social, attention and thought problems. |
| **Latva et al., 2008**<br>*How is maternal recollection of the birth experience related to the behavioural and emotional outcome of preterm infants?* | N= 28, 5-6 y (mean GA 33 w)<br>CBCL for parents | The impact of mother's birth experience seems to have long-lasting effects on the preterm child. |

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| **Samara et al., 2008**<br>*Pervasive behaviour problems at 6 years of age in a total-population sample of children born at ≤ 25 weeks of gestation* | N= 200, mean 76 months (≤25 w)<br>SDQ for parents and teachers | Pervasive behaviour problems are more frequent in children born at the limits of viability than previously reported for larger preterm populations. |
| **Delobel-Ayoub et al., 2009**<br>*Behavioral problems and cognitive performance at 5 years of age after very preterm birth: the EPIPAGE Study.* | N=1102 , 5 y, (22-32 w)<br>SDQ | Behavioural problems were strongly related to cognitive impairment, but VPT children were still at higher risk even after adjusting for cognitive performance. |
| **Luu et al., 2009 ♦**<br>*Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age* | N= 375 (BW 600-1250 g)<br>CBCL | Preterm children were 5 times more likely to have at least 1 behaviour problems than term controls. |
| **Whiteside-Mansell L et al., 2009 ●**<br>*Triple risk: do difficult temperament and family conflict increase the likelihood of behavioral maladjustment in children born low birth weight and preterm?* | N= 728 families, 8 y (LBW)<br>CBCL | LBW preterm children with a difficult temperament are more at risk for poor developmental outcomes, such as externalizing behaviour problems, when exposed to family conflict than children with a less difficult temperament. |
| ***Simple phobias*** | | |
| **Peterson et al., 2000**<br>*Regional brain volume abnormalities and long-term cognitive outcome in preterm infants* | N= 25, 8 y (<29 w)<br>CBCL and Psychiatric diagnoses | Separation anxiety disorder, ADHD, Simple phobia and Learning disability. |
| ***Sleep disorder*** | | |
| **Rosen et al., 2004**<br>*Increased behavioral morbidity in school-aged children with sleep-disordered breathing* | N= 829, 8-11y ( <37 w)<br>CBCL and the CRS-R for parents. | Preterm children with sleep-disordered breathing had higher prevalence of problem behaviours, with the strongest, most consistent associations for externalizing, hyperactive-type behaviours. |
| **Emancipator et al., 2006**<br>*Variation of cognition and achievement with sleep-disordered breathing in full-term and preterm children* | N= 835, 8-11 y (BW >999 - <2500 g)<br>Peabody Picture Vocabulary Test–Revised<br>Kaufman Assessment Battery for Children<br>CPT | Children with sleep disordered breathing had poorer scores on almost all tests of cognition and achievement. |

Abbreviations
ADHD: attention deficit/hyperactivity disorder, BW: birth weight, CBCL: Child Behaviour Checklist, CPT: Continuous Performance Task, CRS: Connor's Rating Scales, ELBW: extremely low birth weight, EPT: extremely preterm, GA: gestational age, g: grams, LBW: low birth weight, SDQ: Strengths and Difficulties Questionnaire, VLBW: very low birth weight, VPT: very preterm, w: weeks, y: year/s.

Symbols
◊ Low-risk preterm sample
♦ Preterm sample with severe brain injury
† Perinatal complications
● Longitudinal study
¥ Review study
*This table is exclusively based on investigation works in the last ten years including revisions. Source search: PubMed (www.pubmed.gov), language: English, last update; June 2009.*

## *1.6. Imaging studies relating cerebral structural integrity and cognitive outcome in preterm children and adolescents*

Several investigators have demonstrated a correlation between whole-brain GM volumes and intelligence measures in typically developing children, but the available data examining brain-behaviour relationships for prematurely born children are less robust. Ten years ago, the examination of the relationship between structural MRI abnormalities and concurrent neurobehavioural functioning of the preterm children had, in general, been disappointing, with little correlation found between children's intelligence and MRI findings (Hack and Taylor, 2000), although some studies have demonstrated a relationship between MRI abnormalities and motor function and behaviour (Olsen *et al.,* 1998; Cooke and Abernethy, 1999; Krageloh-Mann *et al.,* 1999; Stewart *et al.,* 1999). The study by Peterson *et al.* (2000) broadened our understanding of the relationship between morphologic disturbances in the brain development of preterm children and school-age cognitive function. These authors were the first to conclude that preterm birth is associated with regionally specific long-term reductions in brain volume (sensorimotor and midtemporal cortices) and that morphological abnormalities are, in turn, associated with poorer cognitive outcome. It is worth emphatizing, that this study strongly related MRI findings with cognitive outcomes, more than with demographic or perinatal risk factors.

Other studies have also related brain abnormalities with cognitive performance in preterm samples. In a whole brain study, Reiss *et al.* (2004) reported a positive correlation between cortical GM volume and IQ in preterm children at ~ 5 and 8 years of age. That study also found a gender effect; positive correlations between GM and cognitive outcome were observed in girls with preterm birth but not in boys. In a longitudinal study from childhood through adolescence, Isaacs *et al.* (2004) reported that regional GM and WM changes correlated with IQ in preterms. Voxel-based morphometry (VBM) analyses of the MRI scans revealed that absolute IQ scores were related to discrete regional areas in both the parietal and temporal lobes. The analyses also showed that frontal and temporal lobe regions were associated with the decline in Verbal IQ (VIQ), while occipital and temporal lobe regions (including the hippocampus) were associated with the decline in PIQ. The authors demonstrated a negative correlation between GM and VIQ and PIQ in areas involving the parietal and the temporal lobes, concretely the angular gyrus and the fusiform gyrus, respectively. Regarding WM results, correlation analyses demonstrated a significant positive correlation between the magnitude of VIQ decline and WM in a frontal lobe region underlying the medial/superior frontal gyri and a negative correlation in the temporal lobe, near the anterior transverse temporal sulcus and gyrus.

Using the same approach (VBM) Isaacs *et al.* (2001) and *et al.* (2003a) demonstrated relationships between cortical areas and calculation and visual-spatial skills. Specifically, in a sample of preterms born before 30 weeks of GA, the authors reported a correlation between GM reductions in the left parietal lobe, intraparietal sulcus, and calculation disability; and between GM decreases and WM increases and impaired performance on visuospatial processing. Language functions have also been related to cortical development. Kesler *et al.* (2006) found that preterm children at age 8 years showed a significantly increased bilateral temporal lobe gyrification index compared to term controls. In addition, left temporal gyrification index presented a significant negative correlation with left temporal lobe GM volume as well as reading recognition scores in the preterm group. Recently, with optimized VBM, Kesler *et al.* (2008) demonstrated extensive regions of decreased GM/WM volumes in preterm male subjects compared with term male subjects. However, the authors did not find any relationships between brain morphology and cognitive outcome or variables associated with preterm birth (ie, BW, GA).

Decreases in hippocampal volumes have been shown to be correlated with memory deficits in adolescents who were born prematurely (Isaacs *et al.*, 2000; Isaacs *et al.*, 2003a; Gimenez *et al.*, 2004). In this regard, Isaacs *et al.* (2000) reported that reduced hippocampal volumes in neurologically normal preterm children were associated with deficits in everyday memory and numeracy. Gimenez *et al.* (2004) quantitatively demonstrated the presence of volumetric abnormalities in the hippocampus. This hippocampal atrophy was related to different neuropsychological measures, such as verbal learning and long-term retention; visual memory was preserved. In addition, the results showed that the preterms had a posterior hippocampal predominance of GM reduction and that this specific area correlated with verbal memory impairment. Subsequently, Gimenez *et al.* (2005) designed an fMRI study to evaluate brain activity in a declarative memory task in adolescents who were born preterm and with hippocampal damage. Their 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. The authors suggested that this increased activation in the right hippocampus may reflect a contralateral function reorganization of the more impaired left hippocampus.

Previous studies have reported associations between the volumes of the caudate nuclei with learning difficulties and attention deficit in both term (Hynd *et al.*, 1990) and preterm children (Abernethy *et al.*, 2004; Nosarti *et al.*, 2005; Isaacs *et al.*, 2008). In a cohort of children born preterm, Abernethy *et al.* (2004) demonstrated that IQ correlated with caudate volume

bilaterally, although these authors did not find a selective relationship between caudate volume and verbal components of IQ. Recently, the study by Isaacs *et al.* (2008) demonstrated that VIQ was significantly related to left and right caudate volumes in preterm boys. Gimenez *et al.* (2006c) demonstrated that thalamic volumes correlated with verbal fluency in prematurely born children at adolescence.

The CC has been widely studied in preterm populations. A study by Nosarti *et al.* (2004) related CC area and its subregions with verbal skills. Specifically, the authors found that mid-sagittal CC size correlated with verbal fluency in males aged 14-15 years born preterm. Caldu *et al.* (2006) found that CC size significantly correlated with GA, PIQ and memory measures. The same research group explored the specific relationship between GA, the CC and IQ in a sample of preterm-born adolescents, showing specific significant correlations between CC subregions and GA (Narberhaus *et al.*, 2007). Similarily, Allin *et al.* (2007) reported that the CC grows dramatically in VPT adolescents, and that this growth is associated with neuropsychological outcome. The authors hypothesized that this may represent a delay of a normal maturational process in VPT individuals.

Reductions in cerebellar volumes have been described in preterms compared to term-born children (*see Section 1.4. and Table 4*), and some studies have directly associated this cerebellar reductions with poor scores on global cognitive measures (Allin *et al.*, 2001) verbal, performance and global IQ (Peterson *et al.*, 2000). Allin *et al.* (2005) reported that lateral cerebellar volume decrease was associated with reduced cerebral MW volume, and with reduced executive, visuospatial and language functions. The authors concluded that the decreased volume of the lateral lobes, rather than the vermis, is associated with neuropsychological dysfunction in VPT individuals. Recently, Parker et al., 2008 demonstrated that a reduction in cerebellar volume in VPT born adolescents was correlated with reduced mental wellbeing.

WM injuries, particularly parenchymal lesions and ventricular enlargements have been found to be strongly predictive of attention / hyperactivity disorders in LBW children (Indredavik *et al.*, 2004). In this regard, Nosarti *et al.* (2005) related externalizing behavioural and conduct problems observed in VPT boys with caudate volume reductions. In recent years, DTI investigations in preterm children have been conducted to study the correlates between WM integrity and cognitive and behavioural outcomes. In 2003, Nagy *et al.*, demonstrated that a group of 11-year-olds with attention deficit associated with preterm birth had lower anisotropy values in the posterior CC and internal capsule.

Young *et al.* (2007) aimed to evaluate the differences in whole brain WM volume and anisotropy between preterm and term children and to determine the relationships with cognitive outcome. Mean WM volume and FA were significantly lower in the preterm group and multiple regression analysis found both WM volume and FA to be independent variables that significantly affected full scale IQ after adjusting for BW, GA, and gender. Recently, the study by Counsell *et al.*, 2008, showed that specific neurodevelopmental impairments in infants born preterm are precisely related to microstructural abnormalities in particular regions of cerebral WM which are consistent between individuals. Constable *et al.*, 2008, reported that prematurely born children demonstrate WM microstructural differences at 12 years of age, relative to term control subjects, and also FA values in the left anterior uncinate correlated with VIQ and full scale IQ scores for preterm male subjects.

However, as Hart *et al.* (2008) point out in their review, the relationship between MRI appearances and developmental outcome remains unclear and needs further investigation.

# 2. APPROACH, OBJECTIVES AND HYPOTHESIS

# 2. Approach, Objectives and Hypothesis

## *2.1. Study I: Patterns of Cerebral White Matter Damage and Cognitive Impairment in Adolescents Born Very Preterm*

### *2.1.1. Objectives*

There is increasing evidence of the presence of WM damage in subjects with antecedents of premature birth, even in those classified as an apparently normal development. Although intellectual performance is within normal limits in premature children it has been highly reported to be significantly decreased in preterms compared to paired full-terms (Bhutta *et al.*, 2002). Therefore, the purpose of the first study was to investigate the relationship between cognitive performance and WM integrity in preterm adolescents. To our knowledge, no previous studies have used VBM to analyse possible WM structural correlates of cognitive processes (specifically, performance IQ (PIQ) and processing speed measures) in a preterm adolescent sample. Additionally, this is the first study to use single-case VBM analyses in a sample of VPT adolescents in order to assess patterns of WM abnormalities.

Thus, the goal of the present research was to investigate the neuroanatomical basis of a possible PIQ decrease in adolescents with antecedents of prematurity by using a VBM approach. Moreover, in the preterm group, we sought to characterize the patterns of WM abnormalities and their frequency using an individual VBM analysis approach.

In summary, the main aims of our study were:

I. Using a VBM approach, to examine and quantify the long term disturbances of WM in a large cohort of adolescents with a history of VPT birth with no evidences of WM damage according to clinical MRI visual inspection.

II. To determine the frequency of WM alterations in preterm adolescents.

III. To describe the patterns of WM abnormalities.

IV. To relate WM alterations with cognitive impairment.

### *2.1.2. Hypothesis*

- We hypothesize that preterm subjects will present WM abnormalities being these directly correlated with the PIQ performance, in the sense the greater the WM abnormalities, the higher the PIQ impairment.

## *2.2. Study II: Decreased Regional Brain Volume by Magnetic Resonance Imaging Associated with Cognitive Impairment in Low-risk Preterm Children*

### *2.2.1. Objectives*

While the neurodevelopmental and cognitive outcome of high-risk preterm samples is well known, little research has been conducted on preterms with a low risk of neurological deficit or developmental difficulties, such as those born between 30-34 weeks of GA, with uncomplicated perinatal histories, normal cranial ultrasound scans and no obvious neurodevelopmental deficits (Caravale *et al.,* 2005 and Hart *et al.,* 2008). There is a lack of MRI studies based on low-risk preterm samples, and only the infancy period has been studied (Mewes *et al.,* 2006; Zacharia *et al.,* 2006). Few studies have examined the long-term neurodevelopmental outcome of low-risk preterm children (Pietz *et al.,* 2004 ; Elgen *et al.,* 2005), and regarding neuropsychological abnormalities subtle deficits have been identified early in childhood in apparently normal ex-preterms (Caravale *et al.,* 2005).

To our knowledge no research has yet studied the brain volume characteristics of a low-risk preterm sample in childhood using an MRI approach (VBM technique) or has sought to relate these measures to cognitive performance. Therefore, MRI was used to investigate whether preterm children with low-risk for neurodevelopmental deficits show long-term changes in GM and WM volumes compared with full-terms and to relate these changes to cognitive outcome.

The aims of this study were:

I. To describe regional GM and WM brain volume changes associated with preterm birth.
II. To assess the cognitive outcome of low-risk preterm children.
III. To assess the behavioural outcome of low-risk preterm children.
IV. To relate regional brain volume changes with cognitive outcome.

### *2.2.2. Hypothesis*

- We hypothesize that low-risk premature children will demonstrate cognitive deficits and that these deficits will correlate with volume decreases of different GM and WM brain regions.
- In addition, and according to previous findings in preterms, we suggest that GA and BW will be related with both possible GM and WM abnormalities in low-risk preterm children.

# 3. METHODS

# 3. Methods

The present thesis consists of two studies examining cognitive functions and structural brain characteristics in children and adolescents who were born preterm. To do so, we studied two different samples and we used different cognitive and MRI approaches. The two studies were approved by the ethics committee of the University of Barcelona and all the subjects or their family gave written informed consent prior to participation in the study. A detailed description of the samples characteristics, methodological approaches; cognitive and/or behavioural tests and MRI methods are detailed within each study.

## *3.1. Study samples*

The adolescent sample involved in the first study formed part of a larger project on the long-term consequences of prematurity that was underway in the Neuropsychology Group (Department of Psychiatry and Clinical Psichobiology, Faculty of Medicine) at the University of Barcelona, Spain (*http://www.ub.edu/neuropsychology/html/portada.html*). Indeed, the Study I was an extension of the investigation by Gimenez *et al.* (2006a) and it comprised 44 adolescents ,with a mean age of fourteen years, born before 32 weeks of GA and 43 term-born adolescents matched to preterm subjects by age, sex, handedness and socio-cultural status (*see Chapter 4 Section 4.1.2.*).

In the second study, the preterm children sample was selected from the preterm population born at the Hospital Clinic (Barcelona-Spain) between 1996 and 1998. The study sample comprised twenty preterm children, with a mean age of 9 years, defined as low-risk for neurodevelopmental deficits group; born between 30-34 weeks GA, without neonatal major morbidity and absence of cerebral pathology in the neonatal period. A group of 22 matched term subjects constituted the control sample (*see Chapter 4, Section 4.2.2.*).

**Table 9.** Brief summary of subjects included in Studies I and II

| *Study number and type of the study* | *Neonatal characteristics of the preterm samples* | *MRI at current age* | *Characteristics of the study samples* |
|---|---|---|---|
| *Study I prospective,cross-sectional* | *GA ≤ 32 w*<br>*BW < 2500 gr*<br>*Perinatal complications (IVH, anoxia or foetal suffering)* | *Conventional T2-weighted images showed no evidence of WM injury in the preterm sample*<br>*MR 1.5 T* | *44 adolescents with antecedents of prematurity and 43 term-born matched by age (mean: 14 y ), gender, handeness and socio-cultural status*<br>*N = 87* |
| *Study II prospective,cross-sectional* | *GA: 30-34 w*<br>*BW< 2500 gr*<br>*Absence of major neonatal morbidity or cerebral pathology* | *Conventional T2-weighted images showed no evidence of WM injury in the preterm sample*<br>*MR 3 T* | *20 low-risk preterm children and 22 term-born children matched by age (mean: 9 y), gender, handeness and socio-cultural status*<br>*N=42* |

Abbreviations; BW: birth weight, GA: gestational age, IVH: intraventricular haemorrhage, MR: magnetic resonance

### *3.2. Cognitive and behavioural assessment*

A cognitive assessment was performed in both studies (*see Chapter 4 Sections 4.1.2. and 4.2.2.*). In the first study, the IQ was evaluated by the Wechsler Intelligence Scales in all the adolescents. Either the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1993) or the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1999) was used depending on the age of the subjects (Lezak et al., 2004).

Children who were recruited for the second study were evaluated using the Wechsler Intelligence Scale for Children- 4th Edition (WISC-IV) (Wechsler, 2007) in order to assess a range of cognitive abilities and to provide an estimate of general aptitude. Moreover, the children enrolled in the second study also underwent a behavioural assessment. The Child Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001) is one of the most widely used instruments for the broadband screening of children's behavioral and emotional symptoms. CBCL was used as a dimensional assessment of the general state of children based on the opinion of their parents. CBCL contains 113 items which are graded as 0 (not true), 1 (somewhat or sometimes true) or 2 (often true or very true). In this study we used the raw sum scores and computed eight syndrome scales, a total problem score obtained as the sum of these eight syndrome scales and two board-bank factors: internalizing, which consists of withdrawn behaviour, somatic complains and anxious/depressed scales, and externalizing, which consist of delinquent (rule-breaking) and aggressive behaviour scales.

### *3.3. Structural MRI approach: Voxel-based morphometry*

Image acquisitions for both studies were performed in the Centre de Diagnòstic per la Imatge (CDIC), Neuroradiology Section, Radiology Service, at the Hospital Clínic (Barcelona, Spain) according to the specific study protocol (for more details, *see Chapter 4 Sections 4.1.2. and 4.2.2.*).

To evaluate structural brain characterisitics for all subjects and differences between groups VBM approach was applied. In the first study VBM group comparisons and individual analyses of WM unmodulated images were carried out following a standard protocol described by Mechelli et al. (2005) using the SPM2 software (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm) running in Matlab 6.5 (MathWorks, Natick, MA). For the second study, we used the VBM-DARTEL method (Ashburner, 2007) which offers definite improvements for VBM studies in terms of localization and also increased sensitivity. Group comparisons of both GM and WM modulated images were obtained using SPM5 software running in Matlab 7.0.

To sum up, in the first study the analysis of unmodulated data tests for regional differences in concentration (density) of WM, whereas in the second study the modulated data can be taken to represent the regional differences in absolute GM and WM volume (see Figure 16).

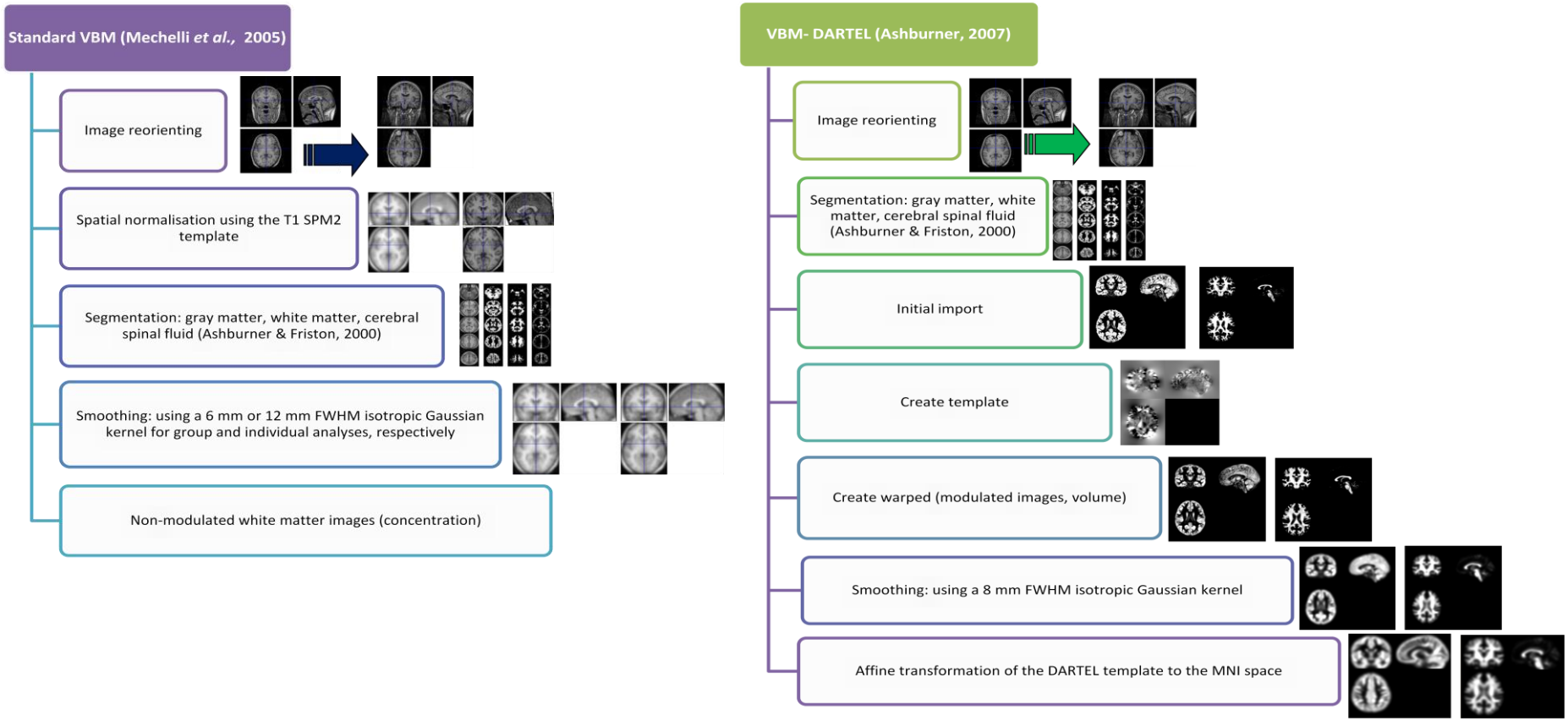


**Figure 16.** VBM protocols applied in studies I and II, respectively

Abbreviations: DARTEL: Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra, FWHM: full-width at half maximum, MNI: Montreal Neurological Institute, VBM: Voxel-based morphometry.

# 4. RESULTS

# 4. Results

## *4.1. Study I:*

## *Patterns of Cerebral White Matter Damage and Cognitive Impairment in Adolescents Born Very Preterm*

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**Abstract**

*There is increasing evidence about the presence of WM damage in subjects with a history of premature birth, even in those classified as good outcome because of an apparently normal development. Although intellectual performance is within normal limits in premature children it is significantly decreased compared to paired controls. The purpose of this study was to investigate the relationship between a lower PIQ and WM damage in preterm adolescents. The sample comprised 44 adolescents (mean age±SD: 14.4±1.6 years) born before 32 weeks of GA and 43 term-born adolescents (14.5±2.1 years). Individual VBM analyses demonstrated that 35/44 (80%) preterm subjects had WM abnormalities. The centrum semiovale and the posterior PV regions were the most frequently affected areas. Correlation analysis showed that in preterms the PIQ correlated with the whole-brain WM volume (r=0.32; P=0.036) but not with GM volume. Complementary analysis showed that low scores in the Digit Symbol subtest, a measure of processing speed, in the preterm group correlated with reductions in WM concentration. These results suggest that WM damage is highly common and that it persists until adolescence. Hence, diffuse WM loss may be responsible for PIQ and processing speed decrements in subjects with VPT birth.*

***Keywords:*** *Adolescent; MRI; Neurocognition; Preterm; White Matter*

### *4.1.1. Introduction*

Prematurity is associated with cerebral abnormalities. Moreover, preterm subjects born VPT and with VLBW are at high risk of brain injury in the perinatal period and, consequently, of later neurological, cognitive and behavioural impairments (Olsen *et al.,* 1998; Stjernqvist *et al.,* 1999; Hack *et al.,* 2002; Foulder-Hughes *et al.,* 2003; Taylor *et al.,* 2004). Several studies suggest that brain damage in preterms predominantly involves WM (Stewart *et al.,* 1999; Hüppi *et al.,* 2001; Counsell *et al.,* 2003; Hüppi, 2004; Giménez *et al.,* 2006), while others report PV WM damage to be the most common brain abnormality in preterm subjects (Volpe, 1997, 2001; Childs *et al.,* 2001; Miller *et al.,* 2002; Inder *et al.,* 2003). Furthermore, axonal brain connectivity is mainly developed during the preterm period, which is highly vulnerable to cerebral WM damage (Follet *et al.,* 2000; Back *et al.,* 2001; Chamananvanakij *et al.,* 2002; McQuillen and Ferreiro, 2004).

Global cerebral WM abnormalities have been described in preterm-born infants (Hüppi *et al.,* 2001; Inder *et al.,* 1999, 2003; Miller *et al.,* 2005), children (Nagy *et al.,* 2003; Reiss *et al.,* 2004, Yung *et al.,* 2007) and adolescents (e.g., Stewart *et al.,* 1999; Giménez *et al.,* 2006, Nosarti *et al.,* 2008) using qualitative and quantitative neuroimaging approaches. Furthermore, Counsell *et al.* (2003) and Giménez *et al.* (2006) concluded that there is diffuse WM loss involving several brain areas in addition to the classical PV WM injury seen in clinical MRI studies.

Advances in DTI have made it easier to detect subtle WM abnormalities in preterms. The first long-term follow-up DTI study from Nagy *et al.* (2003) reported that preterm children have WM disturbances at 11 years in both the CC and the internal capsule, and that these are not repaired or compensated for before this age. Recently, Yung *et al.* (2007) concluded that both whole brain WM volume and FA as assessed by DTI were significantly lower in preterm children.

VBM allows whole or regional brain analysis by comparing regional GM or WM volumes using standardized t-test models on a voxel-by-voxel basis (Ashburner and Friston, 2000, 2001). Although the statistical analysis usually used in VBM studies is group comparisons, the technique can also compare single subjects with an entire control group. This approach has been used to evaluate GM abnormalities in different types of epileptic patients (Woermann *et al.,* 1999a, 1999b) and to detect abnormalities in the amygdala in half the children with autism of a sample tested by Salmond *et al.* (2003).

Structural imaging of regional GM and WM volumes would provide unique information about the distribution of brain areas related to general intelligence (Haier *et al.,* 2004).The pilot study of Peterson *et al*. (2003a) showed that WM volumes in the sensoriomotor and midtemporal regions correlated strongly with measures of neurodevelopmental outcome in VPT infants. Later Isaacs *et al.* (2004) reported that preterm children are at risk of declining IQ over time even if they have not suffered obvious neurological damage and that the decline is associated with specific neural regions. In addition, preterm adolescents have been reported to perform worse than full-term controls on Wechsler Full Scale IQ (e.g., Isaacs *et al.,* 2003a; Taylor *et al.,* 2004; Allin *et al.,* 2006).

To our knowledge, no previous studies have used VBM to analyse possible WM structural correlates of cognitive processes (specifically, performance IQ (PIQ) and processing speed measures) in a preterm adolescent sample. Moreover, this is the first study to use single-case VBM analyses in a sample of VPT adolescents in order to assess patterns of WM abnormalities. The goal of the present research was thus to investigate the neuroanatomical basis of the PIQ decrease in adolescents with a history of prematurity by using a VBM approach to examine and quantify the long-term WM disturbances in a large cohort of adolescents with a history of VPT birth. We also investigated the correlation between PIQ and WM changes. Moreover, we sought to determine the frequency of WM structural abnormalities in the preterm group using an individual VBM analysis approach. Since PIQ depends on speed of processing and is affected by WM damage it was hypothesized that a greater WM volume or concentration would indicate more myelin and the subsequent facilitation of neural transmission; accordingly, WM brain abnormalities would be related with lower PIQ performance in preterm adolescents compared to full-terms.

### *4.1.2. Methods*

*Participants*

Subjects with antecedents of prematurity were first selected from the population born between1982 and 1994 at the Hospital Clinic, Barcelona, Spain. Inclusion criteria for this selection were: birthweight lower than 2500g, GA equal to or less than 32 weeks, and current age between 12 and 18 years. The Paediatric Division of this hospital registered 875 cases of prematurity. From this initial cohort, 275 cases were currently available at the data base. Ninety-three clinical histories were not accessible at the hospital archives (they were moved to other centers). Thirty cases did not fulfill inclusion criteria/clinical data were missing/or they died.

Eighty-eight cases were excluded either because of updated address or telephone number were not available. Fourteen cases declined to enroll (or parents refuse permission). Fifty subjects were included in the initial sample. Inclusion criteria for the present study were: current age between 12 and 18 years, and GA equal to or less than 32 weeks for the preterm group and equal to or more than 38 weeks for controls. Exclusion criteria for the whole sample were: history of focal traumatic brain injury, cerebral palsy or neurological diagnosis (including seizure and motor disorders) and the presence of global mental disabilities (full IQ scores equal to or less than 85). According with these criteria the final sample comprised 44 adolescents (20 boys and 24 girls; mean age=14.4±1.6 years) with a history of VPT birth (equal to or less than 32 weeks of GA, mean GA=29.9±1.8) and LBW (<2500g, mean gestational weight=1329±430) and 43 control adolescents. The control group was matched to preterm subjects by age (age mean=14.3±2.1), sex, handedness and socio-cultural status. Eight of the 44 preterm participants had low weight for their GA. Seven participants were left-handed. Conventional T2-weighted images showed no evidence of WM injury in the preterm sample according to the clinical evaluation of an expert neuroradiologist (NB). All the subjects followed normal schooling. Finally, the total sample comprised 87 adolescents with a mean age of 14 years.

The study was approved by the ethics committee of the University of Barcelona. All the subjects or their family gave written informed consent prior to participation in the study. This investigation forms part of a larger project on the long-term consequences of prematurity that is currently underway at the University of Barcelona; specifically, this study is an extension of the investigation by Giménez *et al.* (2006). Characteristics of the groups are summarized in Table 10.

**Table10.** Characteristics of the sample: demographic and clinical data

| | **Preterm group ( mean ± SD)** | **Control group (mean ± SD)** | ***Statistics* (*P* value)** |
|---|---|---|---|
| Age | 14.4 ± 1.6 | 14.3 ± 2.1 | $t$ = 0.21 (0.832) |
| Gender (M/F) | 20/24 | 18/25 | $X^2$ = 0.11 (0.735) |
| Gestational age (weeks) | 29.9± 1.8 | 39.5 ± 1.6 | $t$ =-26.23(<0.0001) |
| Weight at birth (g) | 1329 ± 430 | 3453 ± 435 | $t$ =-22.89(<0.0001) |

*Cognitive assessment*

Wechsler intelligence scales were used to obtain a measure of global intellectual functioning. Either the WISC-R (Wechsler, 1993) or the WAIS-III (Wechsler, 1999) was used, depending on the age of the subject.

*MRI acquisition and processing*

The MRI protocol was carried out with a GE Signa 1.5 T scanner (General Electric, Milwaukee, WI). A set of high-resolution inversion recovery T1-weighted images was acquired with an FSPGR 3D sequence (TR/TE= 12/5.2; TI 300 1 nex; FOV=24 x 24 cm; 256x256) The whole-brain data were acquired in an axial plane yielding contiguous slices 1.5 mm thick. Axial T2-weighted images were obtained from a fast-spin echo sequence (TR/TE = 4000/102; echo train; 10; matrix 256x256 thickness 5 mm, gap 1.5 mm).

The original MR images were registered in DICOM format and were saved in ANALYZE 7.5 format, compatible with the SPM2 software (*Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm*).

*Calculation of whole-brain native volumes*

The automated image processing was done using SPM2 software, running in Matlab 6.5 (MathWorks, Natick, MA). For the image preparation a single investigator (SS) performed the prior manual steps (line determination of the anterior-posterior commissures and image reorienting). Firstly, by means of the segmentation function of SPM2 software (using the default parameters) we segmented the original whole-brain files and obtained the native volumes of GM, WM and CSF for each subject. A specific value in $mm^3$ was obtained for each tissue. Intracranial volume (ICV) was calculated as the sum of the three values.

*General VBM procedure*

VBM was carried out following a standard protocol described by Mechelli *et al.* (2005) using the SPM2 steps, described below, without modifying the default parameters. Alter image preparation, we performed a spatial normalisation using the SPM2 T1 template in order to register the individual MRI images to the same template image. These spatially normalised

images were then segmented into GM, WM and CSF using the combined pixel intensity and the prior probabilistic knowledge approach for the spatial distribution of tissues (Ashburner and Friston, 2000). From then on we only focused on these normalised WM images, also called non-modulated images, which reflect WM concentration.

*Group VBM comparisons*

For group analyses the non-modulated WM images were smoothed using a 6 mm FWHM isotropic Gaussian kernel.

*Individual VBM analyses*

For individual analyses the non-modulated WM partition was then smoothed with a 12-mm FWHM isotropic Gaussian kernel to account for slight misalignments of homologous anatomical structures and to ensure statistical validity under parametric assumptions, according to the results discussed in Salmond *et al.* (2002). Each adolescent in the preterm group was compared with the entire control group, searching for abnormalities in WM concentration using a t-test comparison. The criteria applied on the comparison results was that only those results with false discovering rate (FDR)-corrected P values ($P < 0.05$) and with a minimum cluster size of 20 voxels were considered for the visual region pattern assessment. The visual inspection of the individual results was performed by two independent investigators (SS and CJ) who focused on different regions of interest: PV areas (PV anterior, PV body, PV posterior); regions located in the frontal lobes, distant from the PV regions (anterior); those located in the occipital regions (posterior), which were also distant from the PV regions; and the centrum semiovale. In all cases we detailed the laterality of the results (left, right or bilateral hemispheres).

*Statistical analysis*

*Cognitive data*

Group comparison of the results from the Wechsler tests was conducted by means of Student's t-test using the SPSS14.0 version.

*Whole-brain volumetric data*

The group comparisons of whole brain GM, WM, CSF and ICV native volume data were performed using SPSS14.0 version.

*Cognitive and whole-brain volumetric data*

Pearson correlation analyses between intellectual measures and volumetric data were also performed using SPSS14.0 version.

*Concentration data*

The processed WM images were analyzed using the SPM2 t-test models. We performed individual VBM analyses comparing each preterm adolescent with the entire control group in order to determine the frequency of WM damage in the preterm subjects and to describe patterns of WM injury (contrast: preterm subject < control group ).

To display the results we used a threshold at an uncorrected level (voxel P value of <0.001), and for statistical purposes we only report clusters that were significant at the corrected cluster P level ($P < 0.05$).

We also performed a "simple regression" (correlation) SPM2 analysis to evaluate the relationship between WM concentration changes and a neuropsychological processing speed measure for the preterm group.

### *4.1.3. Results*

*Cognitive results*

*Cognitive performance results*

Results from the Wechsler Intelligence Scales showed that the preterm group performed below controls on all global intelligence indexes, although verbal IQ showed only a trend toward significance (Verbal IQ: $t = -1.98$, $P = 0.051$; PIQ: $t = -2.31$, $P = 0.023$; Full IQ: $t = -2.56$, $P = 0.012$). As regards PIQ subtest results, the groups differed in their performance on the Digit Symbol Subtest, which is considered as a representative measure of mental processing speed. For more details, see Table 11.

**Table 11.** Cognitive performance

| **Neuropsychological measures** | **Preterm group ( mean ± SD)** | **Control group (mean ± SD)** | ***Statistics* (*P* value)** |
|---|---|---|---|
| **Intelligence global index** | | | |
| Verbal IQ | 111.5 ± 15.3 | 117.4 ± 10.7 | *t* = -1.98 (0.051) |
| Performance IQ | 99.1 ± 13.0 | 104.7 ± 9.9 | *t* = -2.31* (0.023) |
| Full IQ | 106.1± 13.9 | 112.8 ± 10.0 | *t* = -2.56* (0.012) |
| **Performance IQ subtest** | | | |
| Digit Symbol (Speed processing) | 9.77 ± 3.1 | 11.21 ± 2.7 | *t* = -2.30* (0.024) |

* $P < 0.05$.

*Cognitive performance correlations with native brain volumes*

For the whole-brain volumetric data, segmentation analyses revealed a reduced global WM volume in the preterm group ($t$ = -2.08, $P< 0.05$) compared with the full-term group (see Table 12).

**Table 12.** Volumetric data

| **Volumetric data ($mm^3$)** | **Preterm group ( mean ± SD)** | **Control group ( mean ± SD)** | ***Statistics* (*P* value)** |
|---|---|---|---|
| Cerebral spinal fluid | 325.979 ± 46.077 | 335.931 ± 41.283 | *t* = -1.06 (0.291) |
| Grey matter | 791.941 ± 80.175 | 810.831± 66.670 | *t* = -1.20 (0.235) |
| White matter | 377.825 ± 45.234 | 396.962± 40.383 | *t* = -2.08* (0.040) |
| Total intracranial volume | 1.495.744 ± 143.720 | 1.543.724± 126.417 | *t* = -1.65 (0.102) |

* $P < 0.05$.

Table 13 shows the correlations between IQs and whole-brain native volumes. In the preterm adolescent group there were several significant correlations between global intelligence indexes and GM, WM and total intracranial native volumes. Finally, after removing the effects of the ICV, only the PIQ remained significantly correlated with the whole WM volume ($r$ = 0.34, $P$ = 0.026) (see Figure 17). In contrast, in the control group the PIQ was only correlated positively with the whole brain GM volume ($r$ = 0.30, $P$ = 0.05), although this correlation lost its statistical significance after controlling for ICV.

**Table 13.** Correlations between intelligence quotients and native cerebral volumes

| Intelligence global index | Cerebral tissue | Correlation coefficients (*P* value) | | | |
|---|---|---|---|---|---|
| | | Preterms | Corrected by ICV | Controls | Corrected by ICV |
| Verbal IQ | GM | 0.33* (0.03) | 0.02 (0.89) | 0.18 (0.252) | |
| | WM | 0.33* (0.03) | 0.06 (0.718) | 0.01 (0.986) | |
| | ICV | 0.35* (0.02) | | 0.17 (0.276) | |
| Performance IQ | GM | 0.17 (0.262) | | 0.30* (0.050) | 0.19 (.233) |
| | WM | 0.32* (0.036) | 0.34* (0.026) | 0.12 (0.431) | |
| | ICV | 0.18 (0.252) | | 0.25 (0.106) | |
| Full IQ | GM | 0.33* (0.031) | 0.03 (0.859) | 0.27 (0.076) | |
| | WM | 0.41** (0.006) | 0.22 (0.151) | 0.07 (0.680) | |
| | ICV | 0.35* (0.021) | | 0.24 (0.114) | |

Abbreviations: GM: grey matter, ICV: intracranial volume, IQ: intelligence quotient, WM: white matter.

* $P < 0.05$.

** $P < 0.01$.

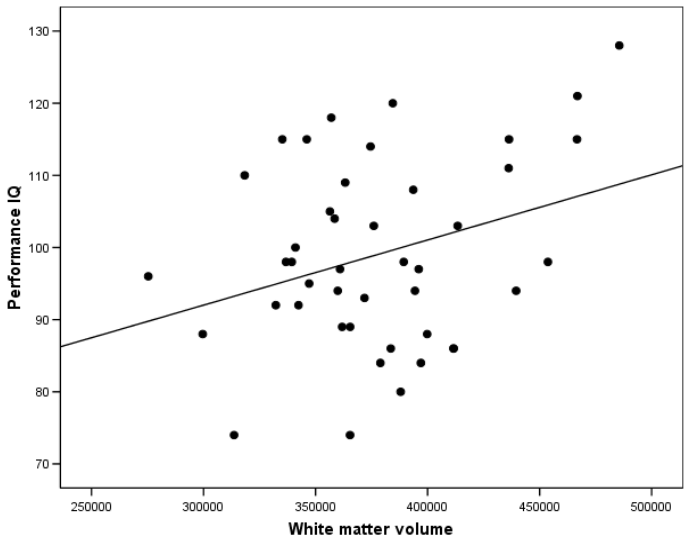


**Figure 17.** Correlation between whole-brain WM volume and PIQ in the preterm group.

*VBM results*

*Individual VBM analysis: patterns of WM abnormalities*

Individual VBM analysis demonstrated that 35 of the total sample of 44 preterm subjects (80%) had significant WM abnormalities when compared to the mean of the control group. We thus analysed the frequency of regional distribution of WM changes in the preterm group. As Table 14 illustrates, the most frequently affected region was the centrum semiovale, which showed bilateral WM alterations in 41% of preterm subjects. As regards the PV regions, 21% of preterms showed reduced WM concentration in both regions, i.e. the posterior PV areas and the PV bodies bilaterally. Moreover, 16% of the preterm group had a global loss in PV WM concentration. In summary, the posterior PV areas were more affected than the anterior ones.

**Table 14.** Percentages of preterms with a regional reduction in WM concentration.

| **White matter regions** | **Preterms white matter damage (%)** |
|---|---|
| Centrum semiovale | 40.9 |
| Periventricular posterior bilateral | 20.5 |
| Periventricular body bilateral | 20.5 |
| Total periventricular bilateral | 15.9 |
| Anterior left | 13.6 |
| Centrum semiovale left | 9.1 |
| Periventricular posterior left | 6.8 |
| Anterior bilateral | 6.8 |
| Anterior right | 6.8 |
| Periventricular body left | 6.8 |
| Centrum semiovale right | 4.5 |
| Periventricular anterior left | 4.5 |
| Periventricular posterior right | 4.5 |
| Periventricular body right | 4.5 |
| Posterior left | 2.3 |
| Periventricular anterior right | 2.3 |
| Posterior right | 0 |
| Posterior bilateral | 0 |
| Periventricular anterior bilateral | 0 |

*Preterm group VBM analysis: speed of mental processing and WM abnormalities*

When classifying the preterm subjects according to normal or abnormal scores (equal to or less than a scaled score of 7) on the Digit Symbol subtest we observed that compared to preterm subjects with normal scores (n=33) those with abnormal scores (n=11) had diffuse reductions in WM concentration in the right temporal and frontal sub-gyral WM, the left limbic area (anterior cingulate) and in the genu of CC (see Figure 18 and Table 15).

**Table 15.** Areas with WM concentration decrease in preterms with low Digit Symbol test scores

| **Anatomical region** | **Cluster size ($mm^3$)** | **Cluster-level** ***( P corrected)*** | **MNI coordinates** | | | ***t* statistic** |
|---|---|---|---|---|---|---|
| | | | **x** | **y** | **z** | |
| Temporal Lobe: Sub-Gyral (R) | 736 | 0.002 | 42 | -48 | -4 | 4.67 |
| Frontal Lobe: Sub-Gyral (R) | 496 | 0.020 | 28 | 14 | 30 | 4.52 |
| Sub-Lobar extra-nuclear (L) | 448 | 0.031 | -24 | -18 | 18 | 4.11 |
| Corpus Callosum, Genu (L) | 664 | 0.004 | -4 | 20 | 12 | 3.67 |
| Limbic lobe: anterior cingulate (L) | 448 | 0.031 | -14 | 46 | 8 | 3.80 |

MNI coordinates indicate: x increases from left (-) to right (+); y increases from posterior (-) to anterior (+); and z increases from inferior (-) to superior (+). Abbreviations: L: left hemisphere, R: right hemisphere.

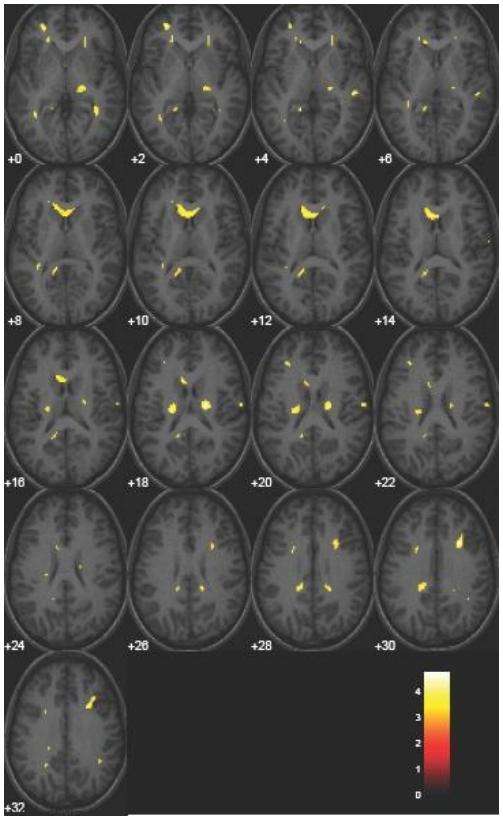


**Figure 18.** Axial sections of images illustrating WM reductions in the preterm sample with low scores on the Digit Symbol subtest compared to preterm subjects with normal scores on this test. Images are representative slices at the two-slice interval. Differences are mapped onto a brain from a control subject of our sample. The colour bar represents the *t* scores. Results are displayed at uncorrected voxel P value threshold of <0.001. Statistical parametric maps (SPMs) are represented according to neurological convention (left corresponding to the left hemisphere).

Additionally, we found a positive correlation between Digit Symbol performance and WM concentration in the right sub-gyral WM region of the temporal lobe (Montreal Neurological Institute (MNI) coordinates: 42, -46, -6; $r = 0.49$, $p<0.023$, cluster level corrected), which was also the most extensively affected area detected in the analysis described above.

### *4.1.4. Discussion*

This study provides evidence of the persistence of diffuse WM abnormalities in adolescents who were born VPT, and also reveals the high frequency of these WM abnormalities. Volumetric and MRI-related cognitive outcomes suggest that there are persistent impairments in speed of cognitive processing following early brain damage, despite the existence of developmental plasticity.

Our results showed that in preterm subjects without clinical evidence of WM impairment in the MRI assessment, the frequency of reductions in WM concentration was very high. Interestingly, these subjects are considered clinically to be a low-risk preterm sample. However, individual VBM analyses revealed significant reductions in 35 of 44 preterms (80%). These results suggest that WM reductions are common, even in those preterm subjects without motor impairment and who follow normal schooling. Our findings are consistent with those of other studies documenting the prevalence of WM damage. Stewart *et al.* (1999) reported that MRI at 14-15 years of age detected many more abnormalities in preterms than in full-term controls. WM lesions were noted in 36 of 40 children with abnormal MRI, confirming that brain damage in VPT infants predominantly occurs in WM. Counsell *et al.* (2003) claimed that diffuse WM injury with subsequently impaired WM development is extremely common in small premature infants. These authors suggested that WM susceptibility to injury may be attributed to the low blood flow to cerebral WM in preterm infants, and to the susceptibility of immature oligodendrocytes to injury from free radicals, certain cytokines and glutamate toxicity. Our results also agree with those reported in a study of low-risk preterm infants without magnetic resonance-visible brain injury which demonstrated a reduction in myelinated WM, thus suggesting an adverse influence of early birth on WM development (Mewes *et al.*, 2006). Recently, Constable *et al.* (2008) showed that compared with control subjects, prematurely born children with no neonatal ultrasound evidence of WM injury manifest changes in neural connectivity at 12 years of age. In agreement with these findings, our results suggest that WM changes occurring during pregnancy or the perinatal period persist until adolescence after a long period of cerebral changes.

Our individual analyses showed patterns of reduced WM, mainly in PV areas and the centrum semiovale, the latter being the most frequently affected region, followed by posterior PV areas. According to Taylor *et al.* (2006) the nature of cognitive outcomes may depend on damage to WM vs. GM, or on the extent to which insults are localized in PV brain regions; these authors pointed out that preterm children or those with VLBW can have both global and selective cognitive deficits.

The cognitive assessment showed significant differences between VPT and full-term adolescents. In agreement with previous reports (Peterson *et al.*, 2000; Cooke *et al.*, 2003), preterms obtained lower scores on all the IQ scales. Although their intellectual performance was within the normal range the preterm population experience learning disabilities more often than full-terms do (Olsen *et al.*, 1998), and they also require more extra educational provision (e.g., Botting et al., 1998; O'Brien *et al.*, 2004). As in other studies (O'Brien, 2004; Isaacs *et al.*, 2000, 2003a; Abernethy, 2004) we found lower scores on the PIQ scale than on the VIQ scale. Within PIQ the most affected subtest was Digit Symbol. The Digit Symbol subtest of Wechsler intelligence scales, in which subjects fill in the symbols as fast as they can, is commonly used to assess processing speed (Kail and Salthouse, 1994). Rose *et al.* (2002) found that the deficits shown by preterm infants in processing speed are already present during the first year of life. Rose and Feldman (1996) also reported that preterm children at 11 years were slower on selected aspects of processing speed but not on motor speed, and concluded that a deficit in processing speed could be a central mechanism underlying the several cognitive impairments reported in the preterm population. In contrast, a recent study by Saavalainen *et al.* (2007) found no differences in processing speed between preterm and full-term adolescents at age 16, as assessed by the Coding subtest of the WAIS-R and by the verbal automatisms of the Wechsler Memory Scale III.

As Colom *et al.* (2006) pointed out, a number of published reports address the neural basis of human intelligence by using several imaging methods. Gignac *et al.* (2003) used structural imaging to demonstrate a significant correlation between total brain volume (GM and WM) and intelligence. Moreover, these authors hypothesized that whole brain WM may be more correlated to intelligence than is whole brain GM. In our study, the analysis of correlations between whole brain native volumes (GM, WM and ICV) and IQ scales showed that in preterm adolescents there were several significant correlations between IQ scales and both GM and WM volumes; however, the most robust correlation was observed between the whole WM volume and the PIQ scale. Our results are consistent with those of Allin *et al.* (2001), who also reported

correlations between intelligence and whole brain volume in VPT adolescents. Recently, using a DTI approach, Yung *et al.* (2007) concluded that whole brain WM volume and FA were independent variables significantly affecting Full Scale IQ.

As regards the analysis of processing speed, we observed an interesting correlation between Digit Symbol performance and WM concentration in the right sub-gyral WM region of the temporal lobe. This region was also involved as one of the areas showing reduced WM concentration in the preterm group with abnormal Digit Symbol scores compared with preterms whose scores were normal. In this regard, the study by de Groot *et al.* (2000) with an adult sample found a relationship between PV but not subcortical WM lesions and cognitive function, the most affected tasks being those involving speed of cognitive processes. Moreover, studies of leukoaraiosis (Junqué *et al.*, 1990; Ylikoski *et al.*, 1993) support the relationship between PV WM lesions and processing speed, which may be due to the high density of pathways running through PV regions and interconnecting distant cortical structures (Desmond, 2002).

A number of aspects of the present study require further mention. As Ridway *et al.* (2008) pointed out in their comment paper, in performing a VBM study many methodological options are available, so according to their work and following their recommendations we have tried to report the core principles and the information that should be included when reporting a VBM study in order to improve the level of transparency and to permit the reader to assess the validity of our work and compare it to similar literature in the field. Additionally, it is important to notice that one limitation of our study is implicit in the VBM procedures. A critique of VBM is that it is sensitive to systematic shape differences attributable to misregistrations from the spatial normalization step. Moreover, this software was not initially designed to evaluate structural abnormalities and, although the algorithms in SPM are considered robust, imperfect registration may lead to inaccuracy (Bookstein, 2001). To minimize the problems arising from this procedure, we performed the entire normalisation subject by subject, ensuring that all subjects were well adapted to the T1 SPM template. Furthermore, we cannot avoid the fact that spatial normalization of pediatric brains is influenced by standard adult references.

Although smoothing is used to improve the validity of statistical inferences and to reduce inter-individual variation, it is important to use the appropriate size of the smoothing filter, because variations in smoothing can produce very different results (Jones *et al.*, 2005). Since non-normality in the error terms can be an issue in the individual use of VBM (Salmond *et al.*, 2002) we decided to use different sizes of smoothing kernel depending on the type of comparison: 12 mm or 6 mm kernels for individual vs. group or between-groups comparisons,

respectively. Although we focused on WM lesions and cognitive performance in preterm adolescents it is important to remember that cognition requires higher cortical functions (Dammann *et al.*, 2002). In this regard, a study by Inder *et al.* (1999) of preterm infants showed that WM damage is commonly accompanied by GM involvement; in fact, the pattern of cerebral alterations has been reported to be related to the degree of immaturity at birth and to concomitant WM injury (Inder *et al.*, 2005). Although we found WM abnormalities in preterm adolescents compared to controls these differences were apparently not relevant for daily living, since our subjects received normal schooling. Indeed, as Desmond (2002) noted, some studies have suggested that cognitive deficits are related to the total volume of the WM lesion, with a threshold that perhaps needs to be surpassed before clinically meaningful deficits are evident. As regards methods of cognitive assessment a limitation of our study is the lack of a widespread neuropsychological assessment, with an emphasis on executive functions and, in particular, measures of cognitive processing speed. Future prospective studies are thus required in order to investigate a possible cause-and-effect relationship between WM lesions and cognitive deficits in the preterm population. Finally, it should be noted that the pathological basis of WM abnormalities identified with VBM remains uncertain and awaits further investigation, including correlative neuropathological studies (Woermann *et al.*, 1999a).

In summary, although the nature of the relationship between diffuse WM injury and cognitive/behavioural deficits is complex and not entirely understood (Volpe, 2003) our results suggest that WM abnormalities are partially related with worse PIQ scores and slower speed of processing. Therefore, we conclude that diffuse WM loss in preterm children may be responsible for long-term cognitive outcome.

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## *4.2. Study II:*

### *Decreased Regional Brain Volume by Magnetic Resonance Imaging Associated with Cognitive Impairment in Low-risk Preterm Children*

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**Abstract**

*To investigate whether preterm children with low-risk for neurodevelopmental deficits show long-term changes in GM and WM volumes compared with full-terms, and to relate these changes to cognitive outcome. Magnetic resonance imaging was used to evaluate 20 preterm children (current mean age 9 years) defined as low-risk for neurodevelopmental deficits, born between 30-34 weeks GA, without major neonatal morbidity or cerebral pathology in the neonatal period, and 22 matched, term, control subjects. Volumetric images were analyzed by means of VBM to identify regional cerebral alterations. Subjects also underwent cognitive and behavioral/emotional assessments. Preterms showed global (P<0.033) and regional (P<0.001) GM volume reductions in several brain areas, including temporal and parietal lobes and concomitant WM volume reductions in the same areas, although only the left temporal regions achieved statistical significance (P<0.018). Although global intellectual performance was within normal limits in the premature group, it was significantly decreased compared to controls (P <0.001). Neither behavioral nor emotional problems were found in the low-risk preterm group. A significant positive relationship between BW and global GM volume, and also between the length at birth and global GM and WM volumes was found in preterms. In the whole sample we found a positive correlation between GM volume bilaterally in the middle temporal and in the postcentral gyri with IQ. Positive correlations were observed between GM and GA at birth in parietal and temporal cerebral regions (P<0.001) and with WM in parietal regions (P<0.002). Preterm birth has an important impact on the neurodevelopmental and cognitive outcome of children at 9 years of age, being a risk factor for decreased regional cortical GM and WM even in those preterms with low-risk for neurodevelopmental deficits.*

***Keywords:*** *children; magnetic resonance imaging; neurocognition; preterm; voxel-based morphometry*

### *4.2.1. Introduction*

Preterm birth is frequently associated with an increased risk of neurodevelopmental difficulties (Aylward, 2005) and of cognitive, behavioral and emotional problems during childhood (Bhutta *et al.,* 2002; Reijneveld *et al.,* 2006). Among preterm children, neurodevelopmental outcome has been related with GA (Hack and Taylor, 2000; Bhutta *et al.,* 2002; Larroque *et al.,* 2004) - the worst outcomes being recorded in those born most preterm- and the type of the intracranial lesion (Sie *et al.,* 2000; Vollmer *et al.,* 2003), highlighting the developmental vulnerability of the immature brain.

MRI has been widely used to detect brain damage subsequent to preterm birth (Hart *et al.,* 2008). Although in preterms the most common cerebral injury is PV WM damage (Volpe, 2003; Khwaja and Volpe, 2008), preterm birth is also associated with smaller volumes of cortical (Peterson *et al.,* 2000; Inder *et al.,* 2005) and subcortical GM (Boardman *et al.,* 2006; Srinivasan *et al.,* 2007). Furthermore, MRI has shown that regional brain volumes are affected by preterm birth, particularly GM volumes, which correlate with poorer cognitive outcome (Peterson *et al.,* 2003a; Kesler *et al.,* 2004; Isaacs *et al.,* 2004; Kesler *et al.,* 2008). The application of quantitative MRI techniques, such as VBM, to preterm samples offers the possibility of objectively measuring brain development and provides an accurate correlate for neurodevelopmental outcome (Counsell and Boardman, 2005).

While the neurodevelopmental and cognitive outcome of high-risk preterm samples is well known, little research has been conducted on preterms with a low risk of neurological deficit or developmental difficulties, such as those born between 30-34 weeks of GA, with uncomplicated perinatal histories, normal cranial ultrasound scans and no obvious neurodevelopmental deficits (Caravale *et al.,* 2005; Hart *et al.,* 2008). There is a lack of MRI studies based on low-risk preterm samples, and only the infancy period has been studied (Mewes *et al.,* 2006; Zacharia *et al.,* 2006). Few studies have examined the long-term neurodevelopmental outcome of low-risk preterm children (Pietz *et al.,* 2004; Elgen *et al.,* 2005), and regarding neuropsychological abnormalities subtle deficits have been identified early in childhood in apparently normal ex-preterms (Caravale *et al.,* 2005).

To our knowledge, no research has yet studied the brain volume characteristics of a low-risk preterm sample in childhood using an MRI approach or has sought to relate these measures to cognitive performance.

### *4.2.2. Methods*

The study was approved by the ethics committee of the University of Barcelona. Informed parental consent was obtained for each infant.

*Subjects*

The preterm group was selected from the preterm population born at the Hospital Clinic (Barcelona-Spain) between 1996 and 1998 attending the following inclusion/exclusion criteria. The inclusion criteria for the preterm group were; a current age between 8 to 10 years and fulfill the following criteria to be considered a preterm subject with a low-risk for neurodevelopmental deficits: 1) history of prematurity with GA between 30-34 weeks, 2) BW below 2500 g, 3) Apgar Score at fifth minute > 7, 4) absence of major neonatal morbidity: severe RDS, mechanical support, NEC, neonatal sepsis, bronchopulmonary dysplasia and 5) absence of cerebral pathology, such as intraventricular hemorrhage, ventriculomegaly, or WM injury assessed by cranial ultrasound in the neonatal period. Neonatal data of preterm subjects from the Archives of the Neonatology Service of the Hospital Clinic were recorded retrospectively. The GA was calculated according to the mother's last menstrual period. Exclusion criteria for whole sample were: history of focal traumatic brain injury, cerebral palsy or neurological impairment (including seizure and motor disorders), cerebral lesions visually detected by the current MRI, and the presence of global mental disabilities (full IQ equal to or less than 80).

After analyzing the database from the Neonatology Service 76 preterms met these criteria. From these subjects, updated addresses or telephone numbers were not available in 36 cases. Nineteen cases were not enrolled in the study as their parents declined to participate. Therefore, the initial sample comprised 44 children, 21 preterm children and 23 controls. Due to the abnormalities in the MRI findings described below, two subjects were excluded. Finally, our study sample included 20 preterms with a low-risk for neurodevelopmental deficits and 22 full-terms with no history of perinatal problems matched by age, gender and sociocultural status, who were mainly friends and classmates of the preterm children. All the subjects followed normal schooling and information about requiring extra educational provision was registered. Parental education was collected attending to the highest education of the parents: low, intermediate or high according to Weisglas-Kuperus *et al.*, 2008.

*Cognitive and Behavioral Assessment*

Children underwent a cognitive assessment using the WISC-IV (Wechsler, 2007). The WISC-IV comprises four indices: Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed; taken together these give a Full Scale IQ score.

The Child Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001) was used as a dimensional assessment of children's behavioral and emotional symptoms based on the opinion of their parents.

*MRI Data*

MRI was performed using a TIM TRIO 3T scanner (Siemens, Germany). A set of high-resolution 3-dimensional T1-weighted images was acquired with a MPRAGE sequence in sagittal orientation (TR/TE= 2300/2.98 ms; TI= 900 ms; 256x256 matrix, 1 mm isotropic voxel). T2-weighted images in axial orientation (TR/TE= 5533/88 ms; 122x122 matrix, flip angle 90º, slice thickness 2mm, gap= 0.6 mm) were acquired. No sedation was necessary and no children were excluded due to suboptimal images.

MRI scans were reviewed by a neuroradiologist (N.B.) blind to group membership. A control subject with a venous vascular malformation and a preterm with a giant arachnoid cyst were excluded. Conventional T2-weighted images showed no evidence of WM injury in the preterm sample.

**Image Analysis**

The image processing was done using SPM5 software (*Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm*), running in Matlab 7.0 (MathWorks, Natick, MA). We segmented the original whole-brain files and obtained the native volumes of GM, WM and CSF for each subject. A specific value in $mm^3$ was obtained for each tissue. ICV was calculated as the sum of the three values.

For the VBM group analysis, the GM and WM segments were further normalized to the population templates generated from all the images in each group using an implementation of a Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm (Ashburner, 2007). A separate 'modulation' step (Ashburner and Friston, 2000) was

used to ensure that the overall amount of each tissue class was not altered by the spatial normalization procedure. Modulation was performed by multiplying the warped tissue probability maps by the Jacobian determinant of the warp on a voxel-by-voxel basis, thus allowing voxel intensities in the segmented GM or WM map, together with the size of the voxels, to reflect regional volume and preserve total GM or WM volume from before the warp. Modulated images were smoothed using an 8-mm full-width at half maximum Gaussian kernel. Affine transformation of the DARTEL template to MNI space was applied.

*Statistical Analyses*

Group comparisons were conducted using Student's t-test for normally distributed quantitative variables, and when the variables did not fulfill the requirements for normality two non-parametric approaches were used; $X^2$ test of independence with categorical variables and two-tailed Mann-Whitney *U* test for quantitative ones. Pearson correlations were used to evaluate associations in neonatal, cognitive and MRI data. All statistical analyses were carried out using SPSS v. 14.0. (SPSS Inc, Chicago, IL). Bonferroni's correction for multiple comparisons was not applied because of the exploratory nature of the study and the low sample size (Rothman, 1990; Perneger, 1998). Effect size analyses were conducted (Hojat and Xu, 2004).

VBM-DARTEL analyses: t-test group comparisons were performed to evaluate the volume changes between groups, and "simple regression" (correlation) analyses were performed in the whole group to test for a possible relationship between whole-brain GM volume and both cognitive data and GA. Whole sample correlations between cerebral regions with GM reductions in preterms and IQ were performed. We analyzed these regions of interest (middle temporal gyrus and postcentral gyrus) contained in the Pickatlas toolbox software version 2.4. (Maldjian *et al.*, 2003).For statistical purposes, we used a threshold at the FDR-corrected ($P < .05$), and only clusters larger than 20 voxels were considered.

### *4.2.3. Results*

*Subjects*

Neonatal and demographic results are detailed in Table 16. In the preterms antenatal steroids were applied in 80% of newborns, the mean umbilical arterial pH was 7.29 ± 0.03 and the mean of length of stay in NICU was 7.94 ± 11.97 days. Three of the 20 preterms were small for their GA.

**Table 16.** Characteristics of the sample: neonatal and demographic data

| | **Preterm mean ± SD n= 20** | **Term mean ± SD n=22** | **Statistics (*P* value)** |
|---|---|---|---|
| Neonatal data | | | |
| Gender, M/F | 11/9 | 14/8 | $X^2$ = 0.32 (0.569) |
| Gestational age, wk | 32.5 ± 1.4 | 39.5 ± 1.0 | *t* = -18.80(<0.001) |
| Birth weight, g | 1754 ± 452 | 3392 ± 357 | *t* = -13.10 (<0.001) |
| Length, cm | 42.9 ± 4.1 | 50.7 ± 2.1 | *t* = -7.74 (<0.001) |
| Head circumference, cm[a] | 30.0 ± 2.3 | 35.2 ± 1.1 | *t* = -8.66 (<0.001) |
| Demographic data | | | |
| Age at scan, y | 9.3 ± 0.7 | 9.3 ± 0.6 | *t* = 0.14 (0.892) |
| Right-handed, n (%) | 18 (90) | 22 (100) | $X^2$ = 2.31 (0.129) |
| Extra education assistance, n (%) | 1 (5) | 1 (5) | $X^2$ = 0.00 (1.00) |
| Parental education, n (%) | | | |
| high | 12 (60) | 15 (68) | $X^2$ = 0.33 (0.564) |
| intermediate | 4 (20) | 4 (18) | $X^2$ = 0.00 (1.00) |
| low | 4 (20) | 3 (14) | $X^2$ = 0.14 (0.705) |

[a]N= 20 for preterm group and 18 for control group

*Cognitive Performance*

Although global intellectual performance was within normal limits in the premature group, it was significantly decreased compared to controls (Table 17).

For the whole sample, there were positive correlations between Full Scale IQ and neonatal data (GA: $r$ = 0.46; $P$ = 0.002; BW: $r$ = 0.55; $P$ = 0.001; length: $r$ = 0.49; $P$ = 0.001; head circumference: $r$ = 0.43; $P$ = 0.007).

**Table 17.** Cognitive performance: Intelligence Global Indices and their corresponding Subtests

| **Cognitive Measures WISC-IV** | **Preterm** **mean ± SD** | **Term** **mean ± SD** | ***Statistics*** **(*P* value)** | **Effect size[a]** **Cohen's *d*** |
|---|---|---|---|---|
| *Verbal Comprehension Index* | 107.3 ± 15.2 | 123.7± 19.0 | t = -3.09 (0.004) | 0.2 |
| Similarities | 18.4± 6.2 | 24.5± 9.0 | t = -2.55 (0.015) | 0.2 |
| Vocabulary | 33.0± 6.3 | 40.4± 8.2 | t = -3.25 (0.002) | 0.3 |
| Comprehension | 19.7± 5.4 | 25.2± 7.6 | t = -2.67 (0.011) | 0.2 |
| *Perceptual Reasoning Index* | 101.1± 13.6 | 115.6± 16.6 | t = -3.08 (0.004) | 0.2 |
| Block Design | 29.0 ± 9.8 | 37.7 ± 10.3 | t = -2.82 (0.007) | 0.2 |
| Picture Concepts | 15.5± 3.3 | 18.5± 2.9 | t = -3.18 (0.003) | 0.2 |
| Matrix Reasoning | 18.1± 6.1 | 22.0± 5.3 | t = -2.20 (0.033) | 0.2 |
| *Working Memory Index* | 107.6± 15.2 | 108.5± 16.2 | t = -0.19 (0.854) | |
| Digit Span | 14.4± 2.6 | 15.2± 2.4 | t = -1.07 (0.291) | 0.1 |
| Letter-Number Sequencing | 16.3± 3.3 | 16.6± 3.2 | t = -0.34 (0.736) | |
| Arithmetic | 18.3± 3.6 | 20.8± 3.9 | t = -2.14 (0.039) | 0.2 |
| *Processing Speed Index* | 107.3± 14.5 | 114.5± 8.8 | t = -1.98 (0.055) | 0.1 |
| Digit Symbol | 44.3± 7.6 | 44.6± 6.6 | t = -0.18 (0.861) | |
| Symbol Search | 21.4± 4.8 | 26.8± 3.9 | t = -4.02 (<0.001) | 0.3 |
| Animals | 63.0± 16.9 | 82.1± 20.9 | *t* = -3.25(<0.001) | 0.3 |
| *Full Scale IQ* | 105.8±13.8 | 121.9±15.3 | *t* = -3.57 (0.001) | 0.3 |

[a]0.2 is indicative of a small effect, 0.5 a medium and 0.8 a large effect size.

The CBCL results showed no significant differences between groups (Table 18).

**Table 18.**Child Behaviour Checklist scores between preterm and term children

| **CBCL Problem Scales** | **Preterm** **mean ± SD** **n= 20** | **Term** **mean ± SD** **n=21** | **Statistics (*P* value)** |
|---|---|---|---|
| Withdrawn | 2.35 ± 1.5 | 2.00 ± 1.6 | t = 0.727 (0.471) |
| Somatic complains | 1.80 ± 2.2 | 1.10 ± 2.0 | U = 162.0 (0.186) |
| Anxious/depressed | 4.60 ± 3.5 | 4.67 ± 2.9 | t = -0.067 (0.947) |
| Social problems | 1.75 ± 1.9 | 2.62 ± 2.5 | t = -1.258 (0.216) |
| Thought problems | 0.50 ± 0.8 | 0.67 ± 1.0 | U = 190.0 (0.553) |
| Attention problems | 4.75 ± 3.6 | 4.24 ± 3.6 | t = 0.455 (0.652) |
| Delinquent behaviour | 1.40 ± 1.2 | 1.19 ± 1.2 | t = 0.570 (0.572) |
| Aggressive behaviour | 7.95 ± 5.4 | 8.14 ± 4.9 | t = -0.120 (0.905) |
| Total problems | 25.40 ± 14.7 | 24.62 ± 14.6 | t = 0.171 (0.865) |
| Internalising problems | 8.95 ± 6.1 | 7.76 ± 4.7 | t = 0.698 (0.489) |
| Externalising problems | 9.35 ± 6.0 | 9.33 ± 5.6 | t = -0.009 (0.993) |

*Global Brain Volume Data*

The preterm group showed reduced global GM volume than controls (Table 19).

**Table 19.** Global brain volume data

| **Volumetric data ($cm^3$)** | **Preterm ( mean ± SD)** | **Term ( mean ± SD)** | ***Statistics* (*P* value)** |
|---|---|---|---|
| Cerebral spinal fluid | 400.306 ± 60.767 | 401.895 ± 55.896 | $t$ = -0.06 (0.953) |
| Gray matter | 821.684 ± 84.920 | 874.683 ± 70.431 | $t$ = -2.21 (0.033) |
| White matter | 419.228 ± 53.829 | 439.585 ± 46.897 | $t$ = -1.31 (0.198) |
| Total intracranial volume | 1,641.220 ± 172.625 | 1,718.568 ± 145.409 | $t$ = -1.58 (0.123) |

In whole sample, there were significant positive correlations between neonatal data and global brain volumes (Table 20). Regarding the preterms there was a significant positive relationship between the BW and GM volume ($r$ = 0.46; $P$ = .042) while the correlation of BW with WM showed a trend toward significance ($r$ = 0.43; $P$ = .056). There was also a positive correlation between the length measure and GM ($r$ = 0.47; $P$ = .036) and WM ($r$ = 0.47; $P$ = .036) volumes.

**Table 20.** Brain volume correlations with neonatal data for the whole sample (N = 42)

| | **Global Brain Volume** r statistic [a] (*P* value) | | |
|---|---|---|---|
| **Neonatal Data** | Gray Matter | White Matter | Total Intracranial |
| Gestational age | 0.33 (0.035) | 0.18 NS | 0.22 NS |
| Birth weight | 0.45 (0.003) | 0.37 (0.016) | 0.40 (0.008) |
| Length | 0.45 (0.003) | 0.39 (0.011) | 0.40 (0.009) |
| Head circumference[b] | 0.45 (0.004) | 0.40 (0.012) | 0.45 (0.005) |

Abbreviations: NS; indicates no significant.

[a] 0.1 is indicative of a small effect, 0.3 a medium and 0.5 a large effect size.

[b] N= 38.

*VBM-DARTEL Analyses*

In the 'term group > preterm group' comparison, preterms had significantly reduced GM volumes in several brain regions than full-terms. Decreased GM volumes were found bilaterally in the temporal lobe and in the left parietal lobe. Mean differences in WM volume between groups demonstrated WM decreases in the temporal and parietal regions that were concomitant with GM loss, although only left temporal regions achieved statistical significance (Table 21 and Figure 19).

**Table 21.** Decreased areas of gray and white matter volume in preterm children compared to controls

| Anatomical region (BA) | Cluster ($mm^3$) | Cluster-level (*P* corrected) | Local maxima MNI coordinates[a] | | | *t* statistic |
|---|---|---|---|---|---|---|
| | | | x | y | z | |
| **Gray matter results** | | | | | | |
| Parietal lobe | | | | | | |
| Postcentral gyrus (3) L | 51371 | <0.001 | -53 | -21 | 39 | 6.35 |
| Temporal lobe | | | | | | |
| Middle temporal gyrus (21) L | 15690 | <0.001 | -54 | -15 | -8 | 6.18 |
| Middle temporal gyrus (21) R | 49875 | <0.001 | 60 | -7 | -11 | 5.60 |
| **White matter results** | | | | | | |
| Parietal lobe | | | | | | |
| Postcentral gyrus (3) L | 1174 | NS | -51 | -21 | 23 | 4.90 |
| Temporal lobe | | | | | | |
| Middle temporal gyrus (21) L | 128 | 0.018 | -54 | -2 | -23 | 5.45 |
| Middle temporal gyrus (21) R | 2041 | NS | 54 | 9 | -41 | 5.06 |
| | 1181 | NS | 56 | -15 | -17 | 3.91 |

[a]MNI coordinates indicate: x increases from left (-) to right (+); y increases from posterior (-) to anterior (+); and z increases from inferior (-) to superior (+).

Abbreviations: BA: Brodmann area, L: left hemisphere; R: right hemisphere. NS indicates no significant.

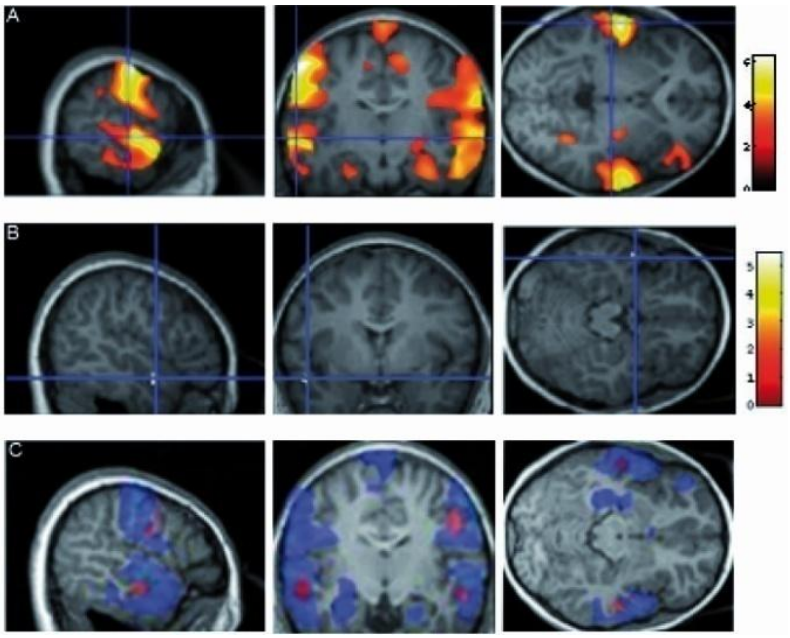


**Figure 19.** Statistical Parametric Maps illustrating GM (A) and WM (B) volume decreases between groups at FDR-corrected *P* value; C: GM (blue) FDR-corrected results and WM (red) results at an uncorrected voxel P<0.001. Differences are mapped on a T1 standard control brain. The color bar represents the *t* scores. Display orientation: A and B: neurological convention; C: radiological convention.

In whole sample, we observed positive correlations between GA at birth and GM and WM volumes (Table 22 and Figure 20).

**Table 22.**Whole sample correlations between cerebral tissues and gestational age

| **Anatomical region (BA)** | **Cluster ($mm^3$)** | **Cluster-level *( P* corrected*)*** | **Local maxima MNI coordinates[a]** | | | ***r* statistic** |
|---|---|---|---|---|---|---|
| | | | **x** | **y** | **z** | |
| **Grey matter correlations** | | | | | | |
| Parietal lobe | | | | | | |
| Postcentral gyrus (1,2,3) L | 73713 | <0.001 | -59 | -20 | 45 | 0.72 |
| Temporal lobe | | | | | | |
| Middle temporal gyrus (21) L | 20749 | 0.001 | -59 | -15 | -11 | 0.71 |
| Middle temporal gyrus (21) R | 56230 | <0.001 | 50 | 5 | -27 | 0.65 |
| **White matter correlations** | | | | | | |
| Parietal lobe | | | | | | |
| Postcentral gyrus (1,2,3) L | 870 | 0.002 | -51 | -20 | 27 | 0.61 |

[a] MNI coordinates indicate: x increases from left (-) to right (+); y increases from posterior (-) to anterior (+); and z increases from inferior (-) to superior (+). Abbreviations: BA: Brodmann area, L: left hemisphere; R: right hemisphere.

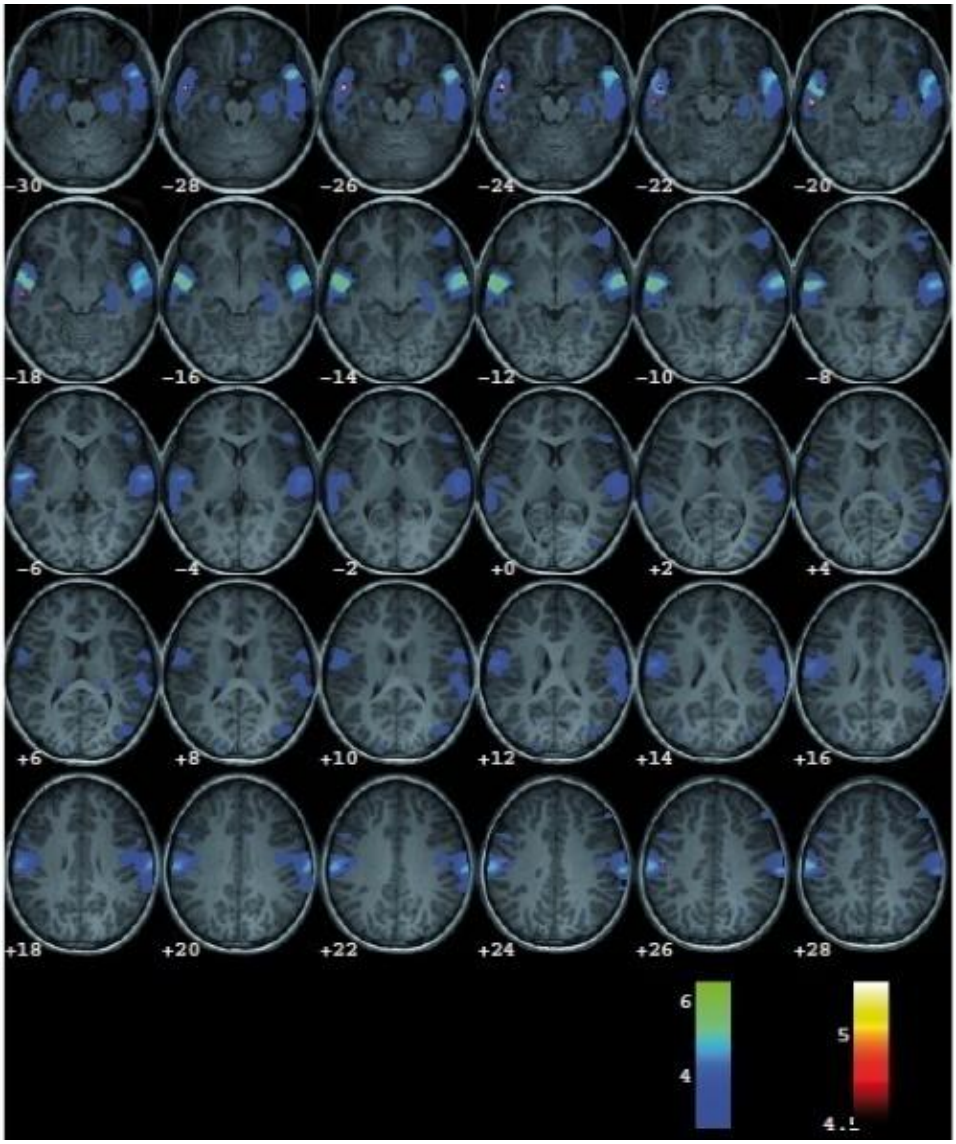


**Figure 20.** Axial slices showing the correlation between GA at birth and GM (hot colors) and WM (winter colors) volume decreases; the lower the GA, the lower the GM and WM integrity. Images are representative slices at a two-slice interval. Left is left in accordance with neurological convention. Results are superimposed on a T1 standard control brain.

Moreover, the temporal and parietal regions with GM reductions in preterms (middle temporal gyrus and postcentral parietal gyrus) showed positive correlations with IQ at voxel *P*-FDR corrected level (>0.03) (Figure 21).

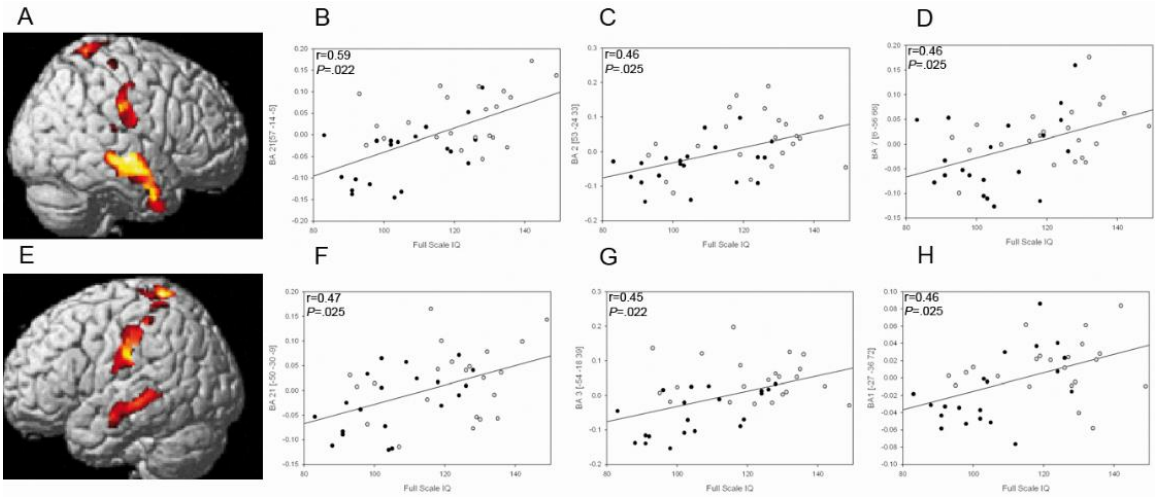


**Figure 21.** Correlations between GM volume involving the middle temporal (BA 21) and the postcentral parietal gyri (BA 1, 2, 3, 7), and Full Scale IQ in the whole sample. Statistical Parametric Maps displayed on a lateral brain view in neurological convention; A-D: right side, E-H: left side. Plots-points indicate real data (black: preterm, light-gray: term), the line indicates data adjusted to the theoretical model.

### *4.2.4. Discussion*

Our study used a VBM technique to investigate the regional distribution of GM and WM volume reductions and their relationship with cognitive outcome in a sample of preterm children with low-risk for neurodevelopmental deficits. We demonstrated that low-risk preterm children are characterized by the presence of regional cortical GM volume reductions unilaterally in the parietal lobe and bilaterally in the temporal lobe which correlated strongly with IQ. Preterms also showed WM volume reductions that were concomitant with the GM loss in the parietal and temporal regions.

In contrast to previous studies in high-risk preterm children which demonstrated decreases in total cerebral volumes (Peterson *et al.,* 2000; Isaacs *et al.,* 2000; Peterson *et al.,* 2003a; Reiss *et al.,* 2004), our preterms only had reduced the total GM volume. MRI studies reported abnormalities in several WM brain areas including all lobes, associative tracts and the CC in preterm children and adolescents (Giménez *et al.,* 2006; Allin *et al.,* 2007; Nosarti *et al.,* 2008). Contrary to these findings, the absence of major WM impairment in our preterms could be, in part, due to the strict inclusion/exclusion criteria applied. Our preterms showed a decreased GM volume in temporal and parietal regions, in accordance with volume reductions previously reported (Peterson *et al.,* 2000; Kesler *et al.,* 2004; Nosarti *et al.,* 2008). In contrast to previous studies (Kesler *et al.,* 2004; Nosarti *et al.,* 2008) we did not observe any region of increased GM volume in our preterms. However, it is necessary to consider differences between

these studies related to the inclusion of infants of different GA, the presence of significant neonatal morbidity, different ages of evaluation and the use of different MRI techniques. There is controversy as to the origin of brain GM volume reductions linked with prematurity (Hart *et al.,* 2008). Although there is evidence that GM reductions are a secondary effect of WM damage (Volpe, 2003), other studies have noted that even without signs of WM injury, prematurity is associated with decreased cortical GM volumes which are correlated with adverse neurodevelopmental outcome (Inder *et al.,* 2005). GM maturation in the intrauterine environment is genetically controlled and well protected but in preterm birth it is exposed to several environmental factors that may influence normal development (Peterson *et al.,* 2003b; Tzarouchi *et al.,* 2009). A recent study, reported that preterm birth continues to perturb the trajectory of cerebral development during late childhood (Ment *et al.,* 2009). The mean GA of our study sample was 33 weeks, and it is in the last trimester when GM appears to be more vulnerable (Krageloh-Mann, 2004) since this period is characterized by a dramatic growth in gyri, sulci, synapses and dendritic arborization (Kinney, 2006). Hence, following prematurity the normal increase in cortical surface area and complexity might be impeded even in the absence of major WM destruction (Ajayi-Obe *et al.,* 2000) findings provide support for these assumptions and suggest that prematurity itself might be a determining cause of altered GM.

Our results add new data to the divergent findings on low-risk preterm infants, with some authors having concluded that preterm infants at 40 weeks had similar brain tissue volumes compared to full-term infants (Zacharia *et al.,* 2006), while others have demonstrated a moderately decreased WM volume suggestive of an alteration in the course of myelination (Mewes *et al.,* 2006). Our study demonstrated that both, WM and specially GM volume abnormalities were mainly localized in the temporal lobe, particularly in the middle temporal gyrus. Volume reductions in the middle temporal gyrus were previously reported in preterms (Nosarti *et al.,* 2008). Cortical GM reaches a peak maximal volume in the temporal lobe around 16 years (Lenroot and Giedd 2006). Late development of these regions might make these structures more vulnerable to the influence of environmental factors during childhood. Therefore, we speculate that specific areas of lower GM volume found in our preterms could be related to primary cortical neuronal damage due to the fact that preterm labor occurs at a critical time in which brain architecture has yet to fully develop.

The abnormal brain structure findings noted on our study children indicate that, even in low-risk preterms, insults to the brain that occur at critical periods of development disrupt maturation. Kinney, 2006 postulated that the combined gray and WM damage in late preterms could be due to hypoxia-ischemia, infection, and/or as yet undefined factors in a vulnerable

period in the development of oligodendrocytes and neurons, and that the combined lesions in the susceptible WM and GM sites reflect interactions between oxidative-, nitrative-, glutamate-, and cytokine-toxicity. Nevertheless, conventional MRI is not very sensitive to identify subtle changes in WM (Vangberg *et al.,* 2006; Hart *et al.,* 2008). Using a non-corrected threshold, we saw WM changes underlying GM changes; our results may indicate the limitations of VBM analysis of T1-weightened images for detecting such WM decreases. Other techniques, as DTI have proved useful for detecting microscopic WM changes in preterm neonates and children (Huppi *et al.,* 2001; Miller *et al.,* 2002; Nagy *et al.,* 2003; Counsell *et al.,* 2006; Giménez *et al.,* 2008). Therefore, further analyses using DTI approach are necessary to clarify the integrity of WM in low-risk preterms.

In agreement with Nosarti *et al.,* 2008, our correlation results showed that GM and WM changes were linearly associated with length of gestation. Authors have noted a GA-related gradient in IQ for those born before 33 weeks (Johnson, 2007). A meta-analysis study concluded that preterm children are more likely to have low cognitive performance, and that their immaturity at birth is directly proportional to their mean cognitive scores (Bhutta *et al.,* 2002). These results are corroborated by our findings, given that we found a linear relationship between IQ and both BW and GA from 30 to 40 weeks.

Our preterms achieved intelligence scores within the normal range and this is consistent with the fact that adverse cognitive sequelae are a more frequent outcome among EPTs (Marlow *et al.,* 2005). In agreement with previous reports, our preterms obtained lower scores on scales related with verbal, non-verbal material and time-dependent tasks than control subjects (Peterson *et al.,* 2000; Aylward, 2002). In contrast, a follow-up study of low-risk preterm infants reported no differences in general, verbal and performance quotients at 7 years (Fredrizzi *et al.,* 1986). Although a greater need for extra educational provision has been reported in school-age VPT populations (Hille *et al.,* 1994; Botting *et al.,* 1998; Horwood *et al.,* 1998; O'Brien *et al.,* 2004) we have not found this tendency.

Correlations between intelligence and brain volume have been reported in preterm studies (Allin *et al.,* 2001; Soria-Pastor *et al.,* 2008). Peterson *et al.* (2003a) noted that volume reductions in the temporal and sensorimotor language regions correlated with intelligence scores in preterm children, and Martinussen *et al.* (2005) demonstrated a thinner cortex involving these regions in very low BW adolescents. Indeed, we also found positive correlations between volume reductions in GM involving the middle temporal and the postcentral parietal gyri and IQ. While we did not find brain regions associated with cognitive outcome in our preterm

group, Isaacs *et al.* (2004) reported that preterm children are at risk of declining intelligence scores over time even if they have not suffered obvious neurological damage. Since the number of subjects in the preterm group was small and this reduced the power of our analysis, the lack of any relationship between full cognitive scores and GM volumes may reflect insufficient power of our study rather than the absence of a true association.

Environmental factors, especially parental education, are the best predictors of later intelligence in preterm infants (Weisglas-Kuperus *et al.*, 2008). Moreover, the risk of impaired cognitive development increases with decreasing socioeconomic status (Sommerfelt *et al.*, 1995). The parental education of our sample was very high; hence the good outcome obtained might in part be attributed to these favorable socioeconomic characteristics (Saigal et al., 2006; Weisglas-Kuperus *et al.*, 2008). Our findings based on CBCL data demonstrated that our preterms showed neither emotional nor behavior problems. In agreement with our results Fredrizzi *et al.* (1986) reported no behavior problems in low-risk preterms, while Schothorst et al. (1996) concluded a higher prevalence of social problems.

Our study has two main limitations. Firstly, the relatively small sample may have meant that statistical differences could not be observed in some comparisons and this prevents us from generalizing our findings to a wider and more heterogeneous population of low-risk preterm children. Secondly, those implicit in the VBM procedures (Bookstein, 2001). However, the DARTEL method offers definite improvements for VBM studies in terms of localization and it also increased sensitivity which should decrease the impact of our sample size (Ashburner, 2007). It will therefore be important to continue to follow this cohort of low-risk preterms, in order to study to what extent the decreased brain volumes we found will compromise their neuropsychological and behavioral outcome in adolescent and adult life.

*Conclusion*

The current MRI study demonstrates that low-risk preterm children are mainly characterized by cortical GM damage which correlates with IQ performance. Preterm birth itself has a significant impact on GM and WM volume, the temporal lobe being the most affected region. Although low-risk preterm children show a cognitive outcome within the normal range, it remains significantly lower than full-term controls. No differences between the groups were found regarding behavioral or emotional problems. Further research is required to determine the effects of low-risk preterm birth on brain morphology and on subsequent cognitive and behavioral correlates.

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# 5. GENERAL DISCUSSION

## 5. General discussion

Preterm infants are at risk of adverse neurodevelopmental outcome and functional disabilities because of the increased vulnerability of the brain before and after premature birth. In addition, there is evidence that impaired development of the brain in preterms contributes to neurological, cognitive and behavioural abnormalities which manifest themselves during the individual's life span. As Luciana (2003) points out, preterm populations provide developmental neuroscientists and psychopathologists with a unique opportunity to observe the extent to which the developing brain can recover from early brain injury or, in the case of healthy preterm infants, from earlier than expected exposure to the extrauterine world.

The present thesis comprises two MRI studies that demonstrated patterns of GM and WM alterations and their cognitive correlates in children and adolescents who were born preterm. In the paragraphs that follow, a general discussion of the results of each study is presented.

To our knowledge, no previous studies had used VBM to investigate the possible WM structural correlates of cognitive processes (specifically, PIQ and processing speed measures) in adolescents with a history of prematurity. Moreover, this was the first study to use single-case VBM analyses in a sample of VPT adolescents in order to assess patterns of WM abnormalities. Our first study forms part of a large project on the long-term consequences of prematurity. More specifically, it is an extension of the research carried out by Gimenez *et al.* (2006a), whose results support the current concept that immaturity at birth is associated with extensive WM damage rather than with isolated PV involvement, as had classically been postulated (Counsell *et al.,* 2003; Huppi *et al.,* 2001; Inder *et al.,* 2005; Miller *et al.,* 2002). The authors demonstrated that VPT adolescents are characterized by reduced WM concentration and volume in several brain areas, including all lobes and several associative tracts. Moreover, WM integrity positively correlated with GA and BW in several brain areas: that is, the lower the GA and the BW, the lower the WM integrity.

Our first study provided evidence of the persistence of diffuse WM abnormalities in adolescents who were born VPT, and underlines their high frequency. The individual VBM analysis approach demonstrated that 80% of preterm subjects had WM abnormalities, the most frequently affected areas being the centrum semiovale and the posterior PV regions. These results suggest that WM reductions are common, even in those preterm subjects without motor impairment and who receive normal schooling. Volumetric and MRI-related cognitive outcomes

suggest that cognitive processing speed is persistenly impaired following early brain damage, despite the existence of developmental plasticity. Although the nature of the relationship between diffuse WM injury and cognitive/behavioural deficits is complex and not entirely understood, the results of our first study suggest that WM abnormalities are related with worse PIQ scores and slower processing speed. So, we can affirm that diffuse WM loss in preterm children plays an important role in long-term cognitive impairment.

As regards the cognitive results, although in general terms the cognitive performance of the preterm subjects was within the normal range, and although they received normal schooling, they scored lower on the PIQ scale than on the VIQ scale, being the processing speed measures the most affected.

We demonstrated that processing speed scores in the preterm group were correlated with reductions in WM concentration in regions involving temporal and frontal areas as well as the CC itself. In agreement with these results, previous findings of our research group regarding the long-term consequences of preterm birth showed significant correlations between general cognitive performance and CC damage; the lower the IQ scores, the thinner the CC in preterm born adolescents (Caldu et al., 2006 and Narberhaus et al., 2007).

However, despite the potential interest of our results regarding patterns of cerebral WM alterations in subjects with antecedents of prematurity, these findings must be considered with caution. Our sample is not representative of prematurity per se; because the majority of premature subjects in this study suffered perinatal complications such as IVH, anoxia or foetal suffering, the results cannot be generalized to the premature population as a whole. An in-depth study of premature subjects without these complications would be likely provide interesting information for the study of the neuroanatomical and neurofunctional brain bases of cognitive deficits in subjects with antecedents of prematurity.

Following on from these results, our second study focussed on the investigation of preterm children with a low risk either of neurological deficit or of developmental difficulties. While the neurodevelopmental and cognitive outcome of high-risk preterm samples is well known, little research has been conducted into low-risk preterms, such as those born between 30-34 weeks of GA, with uncomplicated perinatal histories, normal cranial ultrasound scans and no obvious neurodevelopmental deficits. To our knowledge, this is the first study to investigate the brain volume characteristics of a low-risk preterm sample in childhood using an MRI approach and the first attempt to relate these measures to cognitive performance.

This study demonstrated that low-risk preterm children are characterized by the presence of regional cortical GM volume reductions in the parietal and temporal lobes which correlate strongly with IQ. Moreover, preterm children also showed WM volume reductions that were concomitant with the GM loss in the parietal and temporal regions compared to full-terms. A study by Inder *et al.* (1999) of preterm infants showed that WM damage is commonly accompanied by GM involvement; in fact, the pattern of cerebral alterations has been reported to be related to the degree of immaturity at birth and to concomitant WM injury (Inder *et al.*, 2005). So, WM injury seems to have an influence on myelinization and dendritic connections and affects cortical and subcortical circuits as well as corticogenesis (Evrard *et al.*, 1992). New imaging techniques, such as DTI have been shown to provide non-invasive and quantitative means for evaluating preterm brain maturation and injury in vivo. DTI allows us to study brain connectivity and plasticity and has broadened our understanding of preterm WM maturation, WM injury and plasticity (Dudink *et al.*, 2008). Future studies using techniques such as DTI, are necessary in order to clarify the integrity of WM in low-risk subjects with a history of prematurity.

The results of our second study also emphasize that preterm birth itself has a significant impact on GM and WM volume, and that, the temporal lobe is the most affected region. Different neuroimaging approaches have shown that temporal cortex development was especially impacted by preterm birth. Studies on sulci and gyri development in preterm subjects demonstrate abnormalities in the temporal lobe associated with prematurity (Kesler *et al.*, 2006; Zubiaurre-Elorza *et al.*, 2009). Apart from the neuroanatomical studies, the evaluation of neurochemical characteristics of temporal lobe regions in preterms has also provided useful information regarding the vulnerability of this structure. Metabolic depletion patterns in the medial temporal lobe have been described in preterm adolescent groups (Isaacs et al., 2000; Gimenez *et al.*, 2008b), providing support for either neuronal dysfunction or neuronal loss in this cerebral region. In addition to volumetric and metabolic studies, fMRI investigations in preterm samples have also given evidence of functional impairment in cognitive domains associated with the temporal lobe. In this sense, Gimenez *et al.*, 2005 showed a greater activation of the hippocampus in a declarative memory task in adolescents with preterm birth and hippocampal damage compared to controls. Although the authors concluded that the study provides evidence of contralateral compensatory activation mechanisms, this reorganization does not seem to be sufficient to normalize neuropsychological outcomes in those adolescents who were born preterm.

In our correlation analyses, the relationships between brain volume and neonatal data showed that WM and GM integrity at childhood seems to be related to neonatal data such as GA and BW, corroborating the results of previous preterm studies (Larroque *et al.,* 2003; Gimenez *et al.,* 2006a; Nosarti *et al.,* 2008). Correlations between intelligence and brain volume have also been reported in subjects with antecedents of prematurity (Allin *et al.,* 2001; Isaacs *et al.,* 2004; Peterson *et al.,* 2003a; Martinussen *et al.,* 2005; Soria-Pastor *et al.,* 2008). In our study, positive correlations between full IQ and the temporal and parietal regions with GM reductions in preterms were observed in the whole sample. The lack of any relationship between full cognitive scores and GM volumes in the preterm group may reflect the insufficient power of our study rather than the absence of a true association.

Moreover, the second study provides information about the cognitive outcome in middle childhood for a preterm cohort born in the 1990s. Although low-risk preterm children show a cognitive outcome within the normal range, it remains significantly lower than full-term controls. The finding that low-risk preterm children achieved intelligence scores within the normal range is consistent with the fact that adverse cognitive sequelae are a more frequent outcome among EPTs (Marlow *et al.,* 2005). In agreement with previous reports, our preterm group obtained lower scores on scales related with verbal, non-verbal material and time-dependent tasks than control subjects. Therefore, as mentioned by Caravale *et al.* (2005), neuropsychological abnormalities can be detected early in childhood in apparently normal ex-preterm children and are consistent with a growing body of evidence that prematurity may be associated with long-term neuropsychological morbidity in childhood and adolescence. Regarding the behavioural and emotional assessment of our study, the CBCL results demonstrated that the preterm group showed neither emotional nor behavioural problems, in agreement with the results of other behavioural studies on low-risk preterm groups (Fredrizzi *et al.,* 1986). However, a long-term assessment is necessary to observe possible behavioural alterations that could emerge over time and to determine whether the findings on cognitive outcome indicate a developmental delay in brain maturation that will change over time or whether other problems will become evident in these children as the demands become increasingly challenging. In view of these findings, further research is required to determine the effects of low-risk preterm birth on brain morphology and on subsequent cognitive and behavioural correlates.

Additionally, we should mention a common limitation of our studies that is implicit in the VBM procedures. A criticism of VBM is that it is sensitive to systematic shape differences attributable to misregistrations from the spatial normalization step (Bookstein, 2001). To

minimize the problems arising from this procedure, in our first study we performed the entire normalization subject by subject, ensuring that all subjects were well adapted to the T1 SPM2 template, although we cannot avoid the problem that the spatial normalization of adolescents' brains is influenced by standard adult references. In study II, the use of the DARTEL method offers crucial improvements in terms of localization and sensitivity. On the other hand, MRI procedures have some limits in resolving distinctions between GM and WM which are relevant when assessing maturational changes. Recent algorithms for measuring cortical thickness (Thompson *et al.*, 2004) rely on the definition of a boundary between GM and WM. As GM becomes more myelinated, the border between gray and white changes, and can be displaced toward the pia. A factor in the cortical thinning seen in adolescence is not the absolute descrease of the cortical GM, but rather a change in the gray–white segmentation boundary because of increasing intracortical myelin with age, which may shift the gray–white junction further into the cortical mantle (Toga *et al.*, 2006).

In summary, the body of results derived from this thesis provides evidence that preterm birth is associated with brain abnormalities and cognitive impairment in middle childhood and adolescence. Future studies are required to assess the impact of cognitive and behavioural function in middle childhood on later outcomes in preterm samples with low risk of neurodevelopmental deficits. Research should be conducted in order to better understand the aetiology and neuropathological basis of sequelae, and the long term developmental implication of very premature birth as well as the type of care or intervention which could improve their development and future cognitive outcome.

# 6. CONCLUSIONS

# 6. Conclusions

The main conclusions of this thesis, derived from study I (I-III) and from study II (IV-VI), can be summarized as follows:

I. Adolescents with history of prematurity but without current clinical evidence of white matter lesions using MRI show a higher frequency of white matter concentration decreases than full-term born subjects. These results suggest that white matter decreases are more common than previously described by conventional MRI. Voxel-based morphometry is a sensitive technique for detecting such subtle abnormalities.

II. White matter changes occurring during pregnancy or perinatal period persist until adolescence after a long period of cerebral maturation. The individual analysis of white matter decrease patterns in adolescents with history of prematurity showed that the centrum semiovale is the most affected region followed by the periventricular posterior regions.

III. The Performance Intelligence Quotient is more affected than the Verbal Intelligence Quotient in preterm-born adolescents with perinatal complications. White matter abnormalities are related with worse Performance Intelligence Quotient scores and slower speed of processing. These results suggest that diffuse white matter decreases in preterm adolescents are related to long-term cognitive deficits.

IV. Preterm children with low-risk for neurodevelopmental deficits are characterized by global and regional gray matter volume reductions, mainly localized in the temporal lobe.

V. In low-risk preterm children white matter volume reductions were less extensive than gray matter reductions and were located in the same temporal regions. Therefore, these low-risk preterms are mainly affected by cortical gray matter abnormalities with associated but subtle white matter alterations that did not affect the classical periventricular regions seen in preterms with perinatal complications. Moreover, gray and white matter volume reductions in childhood in subjects who were born preterm are related to neonatal variables such as gestational age and birth weight.

VI. The cognitive performance of preterm children with a low risk for neurodevelopmental deficits is characterized by deficits in verbal comprehension and perceptual reasoning. Furthermore, low-risk preterms showed neither emotional nor behavioural problems.

Studies described in this thesis provide evidence that preterm birth with and without perinatal complications is related to different neuroanatomical damage and neuropsychological profiles: preterms with perinatal complications presented white matter reductions associated with processing speed deficits, and low-risk preterms presented mainly cortical gray matter reductions and cognitive deficits in verbal comprehension and perceptual reasoning.

# 7. SUMMARY OF THE THESIS

# RESUM DE LA TESI

# 7. Summary of the Thesis Resum de la Tesis

***Patrons d'afectació de la substància grisa i blanca cerebral en subjectes prematurs mitjançant imatges per ressonància magnètica***

## Introducció

L'Organització Mundial de la Salut en associació amb la Federació Internacional de Ginecologia i Obstetrícia van definir el naixement prematur com aquell part que succeeix abans que s'hagin completat les 37 setmanes de gestació (OMS, 1977). El naixement prematur segueix sent una de les majors causes de morbiditat i mortalitat infantil a nivell mundial, encara que els importants avenços en neonatologia i cures perinatals han augmentat l'índex de supervivència dels recent nascuts prematurs. En l'actualitat, la taxa de prematuritat a Espanya se situa al voltant del 8-9 % segons dades del *Instituto Nacional de Estadística de España* (www.ine.es), i un 85% dels nounats que neixen amb més immaduresa (pes <1500 g) sobreviuen (*Sociedad Española de Neonatología*: www.se-neonatal.es). L'etiologia del part prematur està associada a múltiples factors complexes, i alguns d'ells, encara poc entesos. Sembla ser, però, que tant factors biològics, psicològics com socials estan relacionats amb el fenomen de la prematuritat (Bherman i Butler, 2007).

Donada la immaduresa orgànica amb la que neixen els nadons prematurs, les complicacions neonatals associades al naixement prematur són múltiples i poden afectar a un ampli conjunt d'òrgans i sistemes, entre ells el sistema nerviós central. A més a més, una sèrie de factors que estan específicament presents en el part prematur, tals com: la immaduresa del sistema vascular cerebral, la vulnerabilitat dels preoligodendròcits o l'elevada vascularització de la matriu germinal) augmenten la vulnerabilitat al dany de la substància blanca cerebral (Volpe, 2003 i Wyatt, 2007).

Les seqüeles neurocognitives i neurocondutuals associades a la prematuritat constitueixen actualment un dels principals temes d'interès pediàtric. Les imatges per ressonància magnètica (IRM) han esdevingut una potent eina per a l'estudi de les lesions cerebrals associades a la prematuritat, encara que els correlats entre les troballes de IRM i els indicatius de neurodesenvolupament han estat poc estudiats.

La RM ha demostrat ser una tècnica important per a l'avaluació de les anomalies i el desenvolupament cerebral en infants prematurs (Counsell, 2003a). La majoria d'estudis en prematurs durant els anys '80 i '90 eren qualitatius, amb mostres poc controlades i que en alguns casos combinaven diferents tipus de lesions cerebrals. En resum, però, aquests estudis van ser indicatius de les elevades taxes d'anomalies cerebrals associades al naixement prematur (Ment *et al.,* 2000). Recentment, estudis quantitatius amb IRM mitjançant tècniques volumètriques basades en el vòxel han demostrat especificitats regionals i anomalies més subtils tant en regions cerebrals corticals com subcorticals, les quals no podien ser detectades per inspecció neuroradiològica visual. Així doncs, els estudis descriptius amb IRM, tant en nens com adolescents prematurs, han revelat reduccions volumètriques tant de la substància blanca com de la substància grisa així com també signes de dilatació ventricular i (Hack i Taylor 2000).

Els estudis neuropsicològics tant de rendiment cognitiu general (quocient d'intel·ligència (QI)) com de funcions cognitives específiques (funcions constructives, verbals, aprenentatge, memòria i funcions executives frontals) en nens i adolescents que han nascut prematurs presenten un rendiment significativament més baix comparat amb el dels subjectes nascuts a terme. És important destacar, però, que en termes generals les puntuacions dels QI dels prematurs es troben dintre dels límits de la normalitat (Bhutta *et al.,* 2002). Tanmateix, el rendiment cognitiu està més afectat en els prematurs que neixen amb menys de 33 setmanes de gestació, en els que el QI queda reduït en mitjana entre 1.5-2.5 punts per cada setmana de gestació de menys (Aylward, 2002; Anderson *et al.,* 2008). Específicament, els nens que van néixer molt prematurs, presenten pitjors execucions en tests que avaluen les habilitats visuo-espacials, el raonament no verbal i també tenen dificultats específiques en el processament simultani d'estímuls complexes. A més a més, aquests nens prematurs també presenten un major risc de presentar problemes tant conductuals com emocionals subclínics, sent freqüentment descrits com a nens desatents, tímids o retrets, i amb pobres habilitats socials (Johnson, 2007 i Allen, 2008). Així doncs els nens i adolescents nascuts prematurs tenen un alt risc de presentar dèficits cognitius i presentar un rendiment escolar baix (Rose *et al.,* 1996: Olsen *et al.,* 1998; Roth *et al.,* 2001; Aylward, 2002; Bhutta *et al.,* 2002; Anderson *et al.,* 2003; Anderson *et al.,* 2008).

## Objectius de la tesi

L'interès general d'aquest projecte de tesi doctoral es centra en l'estudi de les bases neuroanatòmiques (patrons d'alteració de la substància grisa i blanca cerebral) relacionades amb el rendiment cognitiu que presenten els nens i adolescents que han nascut prematurs. Amb aquest propòsit s'han fet servir tècniques de volumetria cerebral basades en imatges obtingudes amb RM així com avaluacions cognitives i de conducta a dues mostres de nens i adolescents amb antecedents de prematuritat.

La prematuritat s'ha associat a danys estructurals cerebrals, així com també a dèficits en el rendiment cognitiu general i en funcions cognitives específiques. Concretament, tal i com es detalla en la introducció d'aquesta tesi, els estudis recents posen de manifest la presència d'alteracions a la substància blanca en els subjectes que van néixer prematurs, fins i tot en aquells que presenten un desenvolupament aparentment normal. El propòsit del primer estudi va ser investigar les relacions entre el rendiment cognitiu i la integritat de la substància blanca cerebral (la concentració) en una mostra d'adolescents que van néixer prematurs. Segons el nostre coneixement, cap altre estudi previ havia utilitzat la tècnica de la morfometria basada en el vòxel (VBM, de l'anglès voxel-based morphometry) per analitzar els possibles correlats entre la substància blanca cerebral i els processos cognitius, específicament aquells relacionats amb el QI manipulatiu i les mesures de velocitat de processament, en una mostra d'adolescents amb antecedents de part prematur. A més a més, aquest va ser el primer estudi en usar un anàlisi de comparacions individuals amb la VBM per tal d'avaluar i establir els diferents patrons d'afectació de la substància blanca per a cada prematur. L'objectiu del primer estudi va ser doncs, investigar les bases neuroanatòmiques del QI manipulatiu en una mostra d'adolescents amb part prematur mitjançant la VBM, així com examinar i quantificar els efectes del dany de la substància blanca associats a la prematuritat.

En síntesis els objectius del primer estudi d'aquesta tesi doctoral es podrien concretar en aquests punts:

I. Examinar i quantificar, mitjançant un estudi estructural mitjançant l'anàlisi vòxel a vòxel del cervell (VBM), la densitat de la substància blanca cerebral en una cohort d'adolescents amb antecedents de part prematur, sense evidències radiològiques clíniques de dany en la substància blanca.

II. Determinar la freqüència d'alteracions de la substància blanca en els prematurs adolescents.

III. Descriure els patrons d'afectació de la substància blanca.

IV. Analitzar els possibles correlats cerebrals estructurals dels dèficits cognitius (relacionats amb el QI manipulatiu i la velocitat de processament).

La hipòtesi de treball del primer estudi va ser: "Nosaltres hipotetitzem que els subjectes prematurs presentaran anomalies de la substància blanca, i que aquestes correlacionaran directa i positivament amb el rendiment del QI manipulatiu, en el sentit següent: a més afectació de la substància blanca més dèficit del QI manipulatiu".

Mentre que el desenvolupament neurològic i cognitiu dels prematurs d'alt risc ha estat ben estudiat, pràcticament no hi ha estudis en referència a la població de prematurs amb baix risc de desenvolupar dèficits neurològics o cognitius (Hart *et al.,* 2008). Els prematurs amb baix risc per dèficits del desenvolupament es defineixen com els prematurs nascuts entre les setmanes 30-34, sense evidències de complicacions neonatals associades, amb proves d'ultrasons cranials normals i sense dèficits obvis del desenvolupament motor, cognitiu i social. Fins a la realització del nostre segon treball, cap estudi havia investigat les característiques volumètriques d'una mostra de nens prematurs de baix risc mitjançant IRM (amb la tècnica de la VBM) i havia intentat relacionar aquestes mesures amb l'execució cognitiva.

En síntesis, els objectius del segon estudi d'aquesta tesi doctoral van ser:

I. Descriure les alteracions de volum de la substància grisa i blanca cerebral associades al naixement prematur.
II. Avaluar el rendiment cognitiu dels nens prematurs de baix risc en comparació amb els nens nascuts a terme.
III. Avaluar les característiques tant conductuals com afectives dels nens prematurs de baix risc.
IV. Estudiar els correlats neuronatòmics del perfil cognitiu dels nens prematurs de baix risc.

La hipòtesi del segon estudi va ser: "Nosaltres hipotetitzem que els prematurs de baix risc mostraran dèficits cognitius, i aquests dèficits correlacionaran amb alteracions de la substància blanca i grisa en diferents regions cerebrals".

## Metodologia

La present tesis consisteix en dos estudis que examinen les bases neuroanatòmiques relacionades amb els dèficits cognitius de nens i adolescents que han nascut prematurs. Per això, s'han estudiat dues mostres de subjectes independents i s'han fet servir diferents aproximacions d'anàlisi de volumetria/concentració de teixit cerebral, com també diferents avaluacions del rendiment cognitiu i de les característiques conductuals de les mostres estudiades.

Ambdós estudis van ser aprovats pel Comitè Ètic de la Universitat de Barcelona (UB) i totes les famílies van signar el consentiment informat prèviament a la seva participació. Cada estudi conté una descripció detallada de les característiques de les mostres, de la metodologia d'anàlisis d'imatge per RM i de les avaluacions cognitives i conductuals emprades.

La mostra del primer estudi, forma part d'una cohort d'adolescents amb part prematur estudiada en un ampli projecte del Grup de Neuropsicologia de la UB. Específicament, es tracta d'una extensió de la investigació duta a terme per Giménez et al., 2006. La mostra final estava formada per 44 adolescents (amb una mitjana de 14 anys d'edat) nascuts abans de les 32 setmanes de gestació i de 43 adolescents nascuts a terme, aparellats per edat, gènere, dominància manual i estatus sociocultural.

La mostra del segon estudi, va ser seleccionada de la població de prematurs nascuts a l'Hospital Clínic de Barcelona entre els anys 1996 i 1998. Finalment, vint nens prematurs de baix risc (amb una mitjana de 9 anys d'edat), nascuts entre les setmanes 30-34 de gestació, sense morbiditat neonatal aguda i amb absència de patologia cerebral en el període neonatal van formar el grup d'estudi. El grup control de la mostra comprenia vint-i-dos nens aparellats amb la mostra de prematurs per diferents variables demogràfiques tals com l'edat, el gènere i l'educació paterna.

Per a l'avaluació cognitiva es van usar les escales Wechsler d'intel·ligència; WISC-R (1993) i WAIS-III (1999) segons l'edat dels adolescents del primer estudi, i WISC-IV (2007) per als nens del segon estudi. A més a més, als nens del segon estudi també se'ls va administrar una avaluació conductual mitjançant el qüestionari Child Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001), un dels instruments més àmpliament usats per a l'*screening* de problemes conductuals i emocionals.

Les IRM dels dos estudis es van adquirir en el Centre de Diagnòstic per la Imatge (CDIC), de l'Hospital Clínic de Barcelona. La tècnica de neuroimatge emprada per a avaluar les diferències cerebrals (de volum o densitat) tant de substància blanca com de substància grisa entre grups va ser la VBM (Ashburner and Friston, 2000, 2001) en ambdós estudis; els protocols usats van ser els descrits per Mechelli et al. (2005) en el primer estudi, i Ashburner (2007) en el segon. El processament automàtic de les dades es va realitzar mitjançant els softwares SPM2 i SPM5 (*Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, University College London, UK*, http://www.fil.ion.ucl.ac.uk/spm) amb Matlab 6.5 i Matlab 7.0 (MathWorks, Natick, MA), respectivament. Les anàlisis estadísitques restants, es van dur a terme emprant el programa SPSS v. 14.0. (SPSS Inc, Chicago, IL).

## Resultats

### Estudi I: *Patrons d'afectació de la substància blanca cerebral i deteriorament cognitiu en adolescents que van néixer prematurs*

Els resultats del primer estudi demostren una elevada freqüència d'alteracions de la substància blanca cerebral en una cohort d'adolescents amb història de part prematur, inapreciables segons una avaluació neuroradiològica de les imatges de RM. Concretament, les anàlisis individuals, mitjançant la VBM, van demostrar que 35 dels 44 adolescents prematurs (un 80% de la mostra) mostraven reduccions de la densitat de la substància blanca en comparació amb els adolescents nascuts a terme. El centre semioval i les àrees periventriculars posteriors van ser les regions freqüentment més afectades en la mostra de prematurs. Les anàlisis de correlacions van demostrar l'existència d'una relació positiva entre el QI manipulatiu i el volum total de la substància blanca cerebral ($r = 0.32$; $P = 0.036$) en el grup de prematurs, és a dir, menys volum de la substància blanca pitjor rendiment en el QI manipulatiu. Tanmateix, les anàlisis complementàries en el grup d'adolescents amb part prematur, van demostrar que els adolescents amb pitjors puntuacions en el subtest de claus, subtest que és indicatiu de velocitat de processament, mostraven reduccions de concentració de la substància en diferents regions cerebrals temporals i frontals així com també en els grans fascicles com el cos callós.

Els resultats del primer estudi van suggerir que les disfuncions en la substància blanca son altament freqüents en subjectes amb antecedents de part prematur, i que aquestes disfuncions persisteixen fins a l'adolescència. Per tant, les alteracions difuses de la substància

blanca tenen un efecte important en el rendiment cognitiu dels prematurs, sobretot en tasques d'organització perceptiva i de velocitat de processament.

**Estudi II:** ***Reduccions regionals de volum cerebral per IRM associades al rendiment cognitiu en nens prematurs de baix risc***

Els nens prematurs de baix risc van mostrar reduccions de volum de substància grisa cerebral tant a nivell global (*P<0.033*) com regional *(P<0.001),* incloent regions bilaterals del lòbul temporal (girus temporal medial, Brodmann area (BA) 21) i regions parietals esquerres (girus postcentral, BA 3). També, van presentar decrements de volum referents a la substància blanca adjacents a les regions d'afectació de la substància grisa, encara que només les regions temporals esquerres van assolir la significació estadística (*P<0.018*).
Malgrat que el rendiment cognitiu del grup de nens prematurs de baix risc estava dintre dels límits de la normalitat, aquest era significativament inferior al rendiment cognitiu dels nens nascuts a terme (P < 0.001). En comparació amb els nascuts a terme, els nens prematurs no van mostrar problemes conductuals ni afectius.

Tanmateix, en el grup de prematurs, van ser descrites associacions positives significatives entre el pes al néixer i el volum total de substància grisa cerebral, així com entre la talla al néixer i el volum total de substància grisa i blanca cerebral. En referència a tota la mostra, es van trobar correlacions positives entre les regions on hi havia les reduccions volumètriques significatives de substància blanca i grisa en el grup de prematurs (girus temporal medial i girus postcentral) i el QI total.
Finalment, també es van observar correlacions positives entre l'edat gestacional i regions parieto-temporals (P <0.001) pel que fa al volum de substància grisa i amb àrees parietals (P <0.002) pel que fa la substància blanca, en el següent sentit: a més edat gestacional més volum cerebral en les àrees indicades.

Per tant, el part prematur *per se* sembla tenir un impacte important en el desenvolupament i morfologia cerebral així com en el rendiment cognitiu. El part prematur, doncs, està associat amb reduccions volumètriques tant de la substància blanca, com sobretot de la substància grisa inclús en aquells prematurs amb baix risc de desenvolupar dèficits del neurodesenvolupament.

## Discussió

Els recent nascuts prematurs tenen un elevat risc de desenvolupar dèficits cognitius i alteracions conductuals, degut tant a lesions cerebrals subjacents com a un escàs desenvolupament cerebral fruit en molts casos de la vulnerabilitat cerebral existent tant abans com després del naixement prematur (Luciana, 2003; Peterson, 2003b).

Aquesta tesi es composa de dos estudis que han demostrat l'existència de dany cerebral tant de la substància grisa com de la substància blanca a través de tècniques de neuroimatge per RM així com els correlats cognitius d'aquests dèficits en nens i adolescents amb antecedents de prematuritat.

Segons el nostre coneixement, cap estudi previ havia usat la tècnica de la VBM per a investigar els correlats entre la substància blanca cerebral i els processos cognitius relacionats amb tasques d'intel·ligència manipulativa i de velocitat de processament. Tanmateix, aquest va ser el primer estudi en usar anàlisis de VBM individuals en una mostra d'adolescents amb antecedents de part molt prematur per tal d'establir patrons d'afectació de la substància blanca cerebral.

Aquest estudi forma part d'un projecte d'investigació més ampli sobre l'estudi de les conseqüències neuroanatòmiques i neuropsicològiques associades al naixement prematur, essent concretament una extensió de la investigació duta a terme per Giménez et al., (2006).
Els resultats derivats de l'esmenta't estudi van donar suport al concepte de que la immaduresa al naixement està associada amb una alteració difusa de la substància blanca cerebral. L'estudi previ, va demostrar que els adolescents nascuts prematurs estan caracteritzats per la presència de reduccions de volum i densitat de la substància blanca en nombroses regions cerebrals incloent tots els lòbuls i molts tractes d'associació. També, es va demostrar, que la integritat de la substància blanca està positivament relacionada amb l'edat gestacional i el pes al néixer en vàries regions cerebrals.

El nostre primer estudi va proporcionar evidència a favor de l'existència d'alteracions difuses de la substància blanca cerebral en adolescents que van néixer prematurs, revelant una molt elevada freqüència (80%) d'aquestes anomalies de la substància blanca en la mostra de prematurs estudiats. Tanmateix, l'anàlisi de patrons individuals va mostrar que les regions més freqüentment afectades van ser en primer lloc el centre semioval seguit de les regions periventriculars posteriors. Aquests resultats suggereixen doncs, que les reduccions de

substància blanca en adolescents que van néixer prematurs son comunes, fins i tot en aquells sense alteracions motores i que segueixen una escolaritat normal.

Els nostres resultats són consistents amb altres investigacions que documenten la prevalença de les alteracions en la substància blanca (Stewart *et al.*, 1999). Tanmateix, Counsell *et al.* (2003) van puntualitzar que el dany difús en substància blanca és extremadament comú en els nounats prematurs, i molt més freqüent del que estava establert fins el moment. Aquests autors van suggerir que aquesta susceptibilitat al dany de la substància blanca podia ser deguda a la combinació de diversos factors tals com un baix flux sanguini cerebral i la susceptibilitat dels precursors dels oligodendròcits a la toxicitat dels radicals lliures de certes citoquines i del glutamat. Els nostres resultats també estan en consonància amb els descrits en estudis recents amb tècniques de tensor per difusió que troben que els adolescents prematurs als 12 anys sense evidències de dany cerebral a l'etapa neonatal manifesten disfuncions en la connectivitat neuronal (Constable *et al.*, 2008).

Les anàlisis complementaries en el grup d'adolescents amb part prematur, van demostrar que els adolescents amb pitjors execucions en proves de velocitat de processament de la informació, mostraven reduccions de concentració de substància blanca en diferents regions cerebrals temporals i frontals així com també en fascicles com el cos callós. Alguns estudis previs del nostre grup d'investigació, centrats en les conseqüències neuropsicològiques a llarg termini en adolescents prematurs, van descriure correlacions significatives entre el baix rendiment cognitiu i la disminució del volum del cos callós. Així mateix, funcions cognitives específiques es relacionaven amb regions diferencials d'aquesta estructura (Caldú *et al.*, 2006; Narberhaus *et al.*, 2007).

Però, malgrat el potencial interès dels resultats esmentats del nostre primer estudi aquests han de ser considerats amb prudència. Aquesta mostra no és representativa de la prematuritat per se; donat que la majoria dels adolescents nascuts prematurs havien sofert complicacions perinatals associades tals com hemorràgies intraventriculars, anòxies o sofriment fetal, i per tant, els resultats no poden ser generalitzats a la població de prematurs en el seu conjunt. Aquest fet, ens va portar a la següent investigació duta a terme amb subjectes prematurs sense complicacions perinatals associades. Aquesta selecció de la mostra és de gran interès per a l'estudi de les disfuncions neuroanatòmiques i neurofuncionals associades a la permaturetat *per se*.

Conseqüentment, vam focalitzar l'objectiu del nostre segon treball en l'estudi de les característiques de volumetria cerebral i de rendiment cognitiu de nens prematurs amb baix risc de dèficits neurològics o problemes en el desenvolupament; com aquells amb una prematuritat moderada (nascuts entre les setmanes 30-34), amb històries perinatals poc complicades, ultrasons cranials normals i sense dèficits obvis del neurodesenvolupament. També, es va dur a terme una avaluació conductual i de l'esfera afectiva d'aquests nens prematurs.

Els resultats del segon estudi, van demostrar per primer cop, que els nens prematurs de baix risc es caracteritzen per la presència tant global com regional de decrements volumètrics de substància grisa cerebral tant al lòbul parietal, com sobretot, en regions temporals. A més a més, per al total de la mostra, aquestes disminucions volumètriques mostren correlacions positives i significatives amb el QI total. Els nens prematurs de baix risc també presenten reduccions de volum de la substància blanca en regions temporals adjacents a les reduccions corticals de substància grisa. En aquest sentit, Inder *et al.* (1999) en un estudi amb nounats prematurs, va demostrar que el dany en substància blanca acostuma a estar acompanyat de dany en la substància grisa cerebral. Per tant, el dany en la substància blanca cerebral podria ser indicatiu d'alteracions en processos com la mielinització, l'arborització dendrítica i la coritcogènesis (Evrard *et al.,* 1992; Rutherford *et al.,* 1999).

El recent desenvolupament de les tècniques de neuroimatge cerebral, com les tècniques d'imatge per tensor de difusió, han mostrat la seva eficàcia en l'avaluació del desenvolupament i del dany cerebral en prematurs (Dudink *et al.,* 2008). Per tant, calen estudis futurs amb tècniques d'imatge per tensor de difusió per tal d'estudiar la integritat de la microestructura de la substància blanca en nens prematurs de baix risc.

Els resultants del segon estudi, posen de manifest la vulnerabilitat de la regió temporal en nens amb antecedents de prematuritat. Diferents tècniques de neuroimatge han demostrat que les regions temporals son especialment vulnerables al part prematur. Els estudis recents sobre el desenvolupament de solcs i girs cerebrals en subjectes prematurs, han demostrat alteracions en el lòbul temporal associades a la prematuritat (Kesler *et al.,* 2006; Zubiaurre-Elorza *et al.,* 2009). A part dels estudis neuroanatòmics, hi ha investigacions centrades en l'estudi de les caracterísitques neuroquímiques del lòbul temporal en prematurs, que han trobat alteracions en concentracions d'alguns metabòlits cerebrals (Isaacs *et al.,* 2000; Gimenez *et al.,* 2008b); donant suport tant a les disfuncions neurals com a la pèrdua de neurones en aquesta regió. També, estudis amb RM funcional i neuropsicologia en mostres de prematurs, han donat suport a les disfuncions temporals (Giménez *et al.,* 2005).

Les relacions establertes entre la volumetria cerebral i les dades neonatològiques mostren que tant la integritat de la substància blanca com de la substància grisa a l'etapa infantil estan relacionades amb variables neonatològiques tals com l'edat gestacional o el pes al néixer, fet que està a favor d'altres resultats en mostres de nens i adolescents prematurs (Larroque et al., 2003; Gimenez et al., 2006a; Nosarti et al., 2008). Correlacions entre índexs d'intel·ligència i volumetria cerebral també han estat estudiades en subjectes amb història de part prematur (Allin *et al.*, 2001; Isaacs et al., 2004; Peterson et al., 2003a; Martinussen et al., 2005; Soria-Pastor *et al.*, 2008), però no amb mostres de prematurs de baix risc.

En relació amb estudis previs, els prematurs de baix risc mostraven un pitjor rendiment cognitiu en les escales relacionades amb tasques no verbals i dependents del temps. Per tant, tal i com va destacar Caravale *et al.* (2005), els dèficits neuropicològics poden ser detectats a la infància inclús en nens prematurs amb un desenvolupament aparentment normal. En quant a les dades conductuals i afectives del nostre segon estudi, els resultats del qüestionari CBCL van demostrar una manca de problemes afectius i de conducta en el grup de nens prematurs de baix risc. Malgrat tot, és necessària una avaluació continuada per tal d'observar les modificacions de conducta al llarg del temps i poder determinar si els dèficits cognitius son indicatius d'un retard en el desenvolupament cerebral.

Per tant, son necessaris estudis futurs que avaluin els efectes de la prematuritat *per se* en el desenvolupament i la morfologia cerebral, així com també en els subseqüents correlats cognitius.

## Conclusions

Les conclusions d'aquesta tesi derivades de l'estudi I (I-III) i de l'estudi II (IV-VI) son:

I. Els adolescents amb antecedents de prematuritat, sense evidències d'alteracions en la substància blanca segons una inspecció visual neuroradiològica de les imatges de RM, presenten amb una freqüència elevada reduccions de concentració de substància blanca en comparació amb els adolescents nascuts a terme, usant la tècnica de neuroimatge voxel-based morphometry.

II. Els resultats dels anàlisis de patrons d'alteració de la substància blanca cerebral en prematurs adolescents mostren que el centre semioval i les regions periventriculars posteriors son les àrees més freqüentment afectades. Aquests resultats suggereixen que

aquestes alteracions en substància blanca son altament comunes en subjectes amb antecedents de part prematur, i que persisteixen fins a l'adolescència, després d'un llarg període de maduració cerebral.

III. Els adolescents amb història de part prematur presenten una afectació major en el Quocient d'Intel·ligència Manipulatiu que en el Quocient d'Intel·ligència Verbal. Tanmateix, l'afectació difusa de la substància blanca cerebral té un efecte important en el rendiment cognitiu dels prematurs, sobretot en tasques d'organització perceptiva i de velocitat de processament.

IV. Els nens prematurs amb baix risc de desenvolupar dèficits del neurodesenvolupament presenten unes reduccions volumètriques de substància grisa cerebral tant globals com regionals localitzades principalment al lòbul temporal.

V. Els nens prematurs de baix risc presenten decrements de volum de la substància blanca adjacents a les regions d'afectació de la substància grisa, encara que a només a les regions temporals esquerres van assolir la significació estadística. Amb aquests resultats, queda palès que els nens prematurs de baix risc mostren una afectació principalment en la substància grisa cortical, amb reduccions associades, però no tant manifestes, de substància blanca. La integritat de les substàncies grisa i blanca cerebral en la infància estan relacionades amb variables neonatològiques tals com l'edat de gestació i el pes al néixer.

VI. El rendiment cognitiu dels nens prematurs de baix risc està caracteritzat per dèficits en la comprensió verbal i en el raonament perceptiu. Tanmateix, els nens prematurs de baix risc no mostren problemes de conducta o afectius en comparació amb els nens nascuts a terme.

Els estudis descrits en aquesta tesis aporten evidència que el naixement prematur, amb o sense complicacions perinatals associades, està relacionat amb diferents afectacions neuroanatòmiques i cognitives. En resum, els adolescents prematurs amb complicacions perinatals presenten reduccions de volum de la substància blanca relacionades amb dèficits de velocitat de processament, mentre que els nens prematurs de baix risc presenten principalment una reducció de la substància grisa cortical i dèficits en la comprensió verbal i el raonament perceptiu.

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# Patterns of cerebral white matter damage and cognitive impairment in adolescents born very preterm

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White matter

ABSTRACT

There is increasing evidence about the presence of white matter damage in subjects with a history of premature birth, even in those classified as good outcome because of an apparently normal development. Although intellectual performance is within normal limits in premature children it is significantly decreased compared to paired controls. The purpose of this study was to investigate the relationship between a lower performance intelligence quotient and white matter damage in preterm adolescents. The sample comprised 44 adolescents (mean age ± S.D.: 14.4 ± 1.6 years) born before 32 weeks of gestational age and 43 term-born adolescents (14.5 ± 2.1 years). Individual voxel-based morphometry analyses demonstrated that 35/44 (80%) preterm subjects had white matter abnormalities. The centrum semiovale and the posterior periventricular regions were the most frequently affected areas. Correlation analysis showed that in preterms the performance intelligence quotient correlated with the whole-brain white matter volume ($r = 0.32$; $P = 0.036$) but not with grey matter volume. Complementary analysis showed that low scores in the Digit Symbol subtest, a measure of processing speed, in the preterm group correlated with reductions in white matter concentration. These results suggest that white matter damage is highly common and that it persists until adolescence. Hence, diffuse white matter loss may be responsible for performance intelligence quotient and processing speed decrements in subjects with very preterm birth.


## 1. Introduction

Prematurity is associated with cerebral abnormalities. Moreover, preterm subjects born very preterm (VPT) and with very low birth weight are at high risk of brain injury in the perinatal period and, consequently, of later neurological, cognitive and behavioural impairments (e.g., Olsen et al., 1998; Stjernqvist and Svenningsen, 1999; Hack et al., 2002; Foulder-Hughes and Cooke, 2003; Taylor et al., 2004). Several studies suggest that brain damage in preterms predominantly involves white matter (WM) (e.g., Stewart et al., 1999; Hüppi et al., 2001; Counsell et al., 2003; Hüppi, 2004; Gimenez et al., 2006), while others report periventricular (PV) WM damage to be the most common brain abnormality in preterm subjects (Volpe, 1997, 2001; Childs et al., 2001; Miller et al., 2002; Inder et al., 2003). Furthermore, axonal brain connectivity is mainly developed during the preterm period, which is highly vulnerable to cerebral WM damage (e.g., Follett et al., 2000; Back et al., 2001; Chamnanvanakij et al., 2002; McQuillen and Ferriero, 2004).

Global cerebral WM abnormalities have been described in preterm-born infants (e.g., Hüppi et al., 2001; Inder et al., 1999, 2003; Miller et al., 2005), children (e.g., Nagy et al., 2003; Reiss et al., 2004; Yung et al., 2007) and adolescents (e.g., Stewart et al., 1999; Gimenez et al., 2006; Nosarti et al., 2008) using qualitative and quantitative neuroimaging approaches. Furthermore, Counsell

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*Abbreviations:* CSF, cerebral spinal fluid; DTI, diffusion tensor imaging; FA, fractional anisotropy; GA, gestational age; GM, grey matter; ICV, intracranial volume; IQ, intelligence quotient; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; PIQ, performance intelligence quotient; PV, periventricular; TIQ, total intelligence quotient; VBM, voxel-based morphometry; VIQ, verbal intelligence quotient; VPT, very preterm; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children; WM, white matter.

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et al. (2003) and Gimenez et al. (2006) concluded that there is diffuse WM loss involving several brain areas in addition to the classical PV WM injury seen in clinical magnetic resonance imaging (MRI) studies.

Advances in diffusion tensor imaging (DTI) have made it easier to detect subtle WM abnormalities in preterms. The first long-term follow-up DTI study from Nagy et al. (2003) reported that preterm children have WM disturbances at 11 years in both the corpus callosum and the internal capsule, and that these are not repaired or compensated for before this age. Recently, Yung et al. (2007) concluded that both whole-brain WM volume and fractional anisotropy (FA) as assessed by DTI were significantly lower in preterm children.

Voxel-based morphometry (VBM) allows whole or regional brain analysis by comparing regional grey matter (GM) or WM volumes using standardized t-test models on a voxel-by-voxel basis (Ashburner and Friston, 2000, 2001). Although the statistical analysis usually used in VBM studies is group comparisons, the technique can also compare single subjects with an entire control group. This approach has been used to evaluate GM abnormalities in different types of epileptic patients (Woermann et al., 1999a,b) and to detect abnormalities in the amygdala in half the children with autism of a sample tested by Salmond et al. (2003).

Structural imaging of regional GM and WM volumes would provide unique information about the distribution of brain areas related to general intelligence (Haier et al., 2004). The pilot study of Peterson et al. (2003) showed that WM volumes in the sensorimotor and midtemporal regions correlated strongly with measures of neurodevelopmental outcome in very preterm infants. Later Isaacs et al. (2004) reported that preterm children are at risk of declining Intelligence Quotient (IQ) over time even if they have not suffered obvious neurological damage and that the decline is associated with specific neural regions. In addition, preterm adolescents have been reported to perform worse than full-term controls on Wechsler Full Scale IQ (e.g., Isaacs et al., 2003; Taylor et al., 2004; Allin et al., 2006).

To our knowledge, no previous studies have used VBM to analyse possible WM structural correlates of cognitive processes (specifically, performance IQ (PIQ) and processing speed measures) in a preterm adolescent sample. Moreover, this is the first study to use single-case VBM analyses in a sample of VPT adolescents in order to assess patterns of WM abnormalities. The goal of the present research was thus to investigate the neuroanatomical basis of the PIQ decrease in adolescents with a history of prematurity by using a VBM approach to examine and quantify the long-term WM disturbances in a large cohort of adolescents with a history of VPT birth. We also investigated the correlation between PIQ and WM changes. Moreover, we sought to determine the frequency of WM structural abnormalities in the preterm group using an individual VBM analysis approach. Since PIQ depends on speed of processing and is affected by WM damage it was hypothesized that a greater WM volume or concentration would indicate more myelin and the subsequent facilitation of neural transmission; accordingly, WM brain abnormalities would be related with lower PIQ performance in preterm adolescents compared to full-terms.

## 2. Methods

### 2.1. Participants

Subjects with antecedents of prematurity were first selected from the population born between 1982 and 1994 at the Hospital Clinic, Barcelona, Spain. Inclusion criteria for this selection were: birthweight lower than 2500 g, GA equal to or less than 32 weeks, and current age between 12 and 18 years. The Paediatric Division of this hospital registered 875 cases of prematurity. From this initial cohort, 275 cases were currently available at the data base. Ninety-three clinical histories were not accessible at the hospital archives (they were moved to other centers). Thirty cases did not fulfill inclusion criteria/clinical data were missing/or they died. Eighty-eight cases were excluded either because of updated address or telephone number were not available. Fourteen cases declined to enroll (or parents refuse permission). Fifty subjects were included in the initial sample. Inclusion criteria for the present study were: current age between 12 and 18 years, and GA equal to or less than 32 weeks for the preterm group and equal to or more than 38 weeks for controls. Exclusion criteria for the whole sample were: history of focal traumatic brain injury, cerebral palsy or neurological diagnosis (including seizure and motor disorders) and the presence of global mental disabilities (full IQ scores equal to or less than 85). According with these criteria the final sample comprised 44 adolescents (20 boys and 24 girls; mean age = 14.4 ± 1.6 years) with a history of VPT birth (equal to or less than 32 weeks of GA, mean GA = 29.9 ± 1.8) and low birth weight (<2500 g, mean gestational weight = 1329 ± 430) and 43 control adolescents. The control group was matched to preterm subjects by age (age mean = 14.3 ± 2.1), sex, handedness and socio-cultural status. Eight of the 44 preterm participants had low weight for their (GA). Seven participants were left-handed. Conventional T2-weighted images showed no evidence of WM injury in the preterm sample according to the clinical evaluation of an expert neuroradiologist (NB). All the subjects followed normal schooling. Finally, the total sample comprised 87 adolescents with a mean age of 14 years. The study was approved by the ethics committee of the University of Barcelona. All the subjects or their family gave written informed consent prior to participation in the study. This investigation forms part of a larger project on the long-term consequences of prematurity that is currently underway at the University of Barcelona; specifically, this study is an extension of the investigation by Gimenez et al. (2006). Characteristics of the groups are summarized in Table 1.

### 2.2. Cognitive assessment

Wechsler Intelligence Scales were used to obtain a measure of global intellectual functioning. Either the Wechsler Intelligence Scale for Children (WISC-R) or the Wechsler Adult Intelligence Scale (WAIS-III) was used, depending on the age of the subject.

### 2.3. MRI acquisition and processing

The MRI protocol was carried out with a GE Signa 1.5 T scanner (General Electric, Milwaukee, WI). A set of high-resolution inversion recovery T1-weighted images was acquired with an FSPGR 3D sequence (TR/TE = 12/5.2; TI 300 1 nex; FOV = 24 cm × 24 cm; 256 × 256) The whole-brain data were acquired in an axial plane yielding contiguous slices 1.5 mm thick. Axial T2-weighted images were obtained from a fast-spin echo sequence (TR/TE = 4000/102; echo train; 10; matrix 256 × 256 thickness 5 mm, gap 1.5 mm).

The original MR images were registered in DICOM format and were saved in ANALYZE 7.5 format, compatible with the SPM2 software (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm).

### 2.4. Calculation of whole-brain native volumes

The automated image processing was done using SPM2 software, running in Matlab 6.5 (MathWorks, Natick, MA). For the image preparation a single investigator (SS) performed the prior manual steps (line determination of the anterior-posterior commissures and image reorienting). Firstly, by means of the segmentation function of SPM2 software (using the default parameters) we segmented the original whole-brain files and obtained the native volumes of GM, WM and CSF for each subject. A specific value in $mm^3$ was obtained for each tissue. Intracranial volume (ICV) was calculated as the sum of the three values.

**Table 1**
Characteristics of the sample: demographic and clinical data

| | Preterm group (mean ± S.D.) | Control group (mean ± S.D.) | Statistics (*P* value) |
|---|---|---|---|
| Age | 14.4 ± 1.6 | 14.3 ± 2.1 | $t = 0.21$ (0.832) |
| Gender (M/F) | 20/24 | 18/25 | $X^2 = 0.11$ (0.735) |
| Gestational age (weeks) | 29.9 ± 1.8 | 39.5 ± 1.6 | $t = -26.23$ (<0.0001) |
| Weight at birth (g) | 1329 ± 430 | 3453 ± 435 | $t = -22.89$ (<0.0001) |

### 2.5. General VBM procedure

VBM was carried out following a standard protocol described by Mechelli et al. (2005) using the SPM2 steps, described below, without modifying the default parameters. After image preparation, we performed a spatial normalisation using the SPM2 T1 template in order to register the individual MRI images to the same template image. These spatially normalised images were then segmented into GM, WM and CSF using the combined pixel intensity and the prior probabilistic knowledge approach for the spatial distribution of tissues (Ashburner and Friston, 2000). From then on we only focused on these normalised WM images, also called non-modulated images, which reflect WM concentration.

#### 2.5.1. Group VBM comparisons

For group analyses the non-modulated WM images were smoothed using a 6 mm FWHM isotropic Gaussian kernel.

#### 2.5.2. Individual VBM analyses

For individual analyses the non-modulated WM partition was then smoothed with a 12-mm FWHM isotropic Gaussian kernel to account for slight misalignments of homologous anatomical structures and to ensure statistical validity under parametric assumptions, according to the results discussed in Salmond et al. (2002). Each adolescent in the preterm group was compared with the entire control group, searching for abnormalities in WM concentration using a $t$-test comparison. The criteria applied on the comparison results was that only those results with FDR-corrected $P$ values ($P < 0.05$) and with a minimum cluster size of 20 voxels were considered for the visual region pattern assessment. The visual inspection of the individual results was performed by two independent investigators (SS and CJ) who focused on different regions of interest: PV areas (PV anterior, PV body, PV posterior); regions located in the frontal lobes, distant from the PV regions (anterior); those located in the occipital regions (posterior), which were also distant from the PV regions; and the centrum semiovale. In all cases we detailed the laterality of the results (left, right or bilateral hemispheres).

### 2.6. Statistical analysis

#### 2.6.1. Cognitive data

Group comparison of the results from the Wechsler tests was conducted by means of Student's $t$-test. Using the SPSS 14.0 version.

#### 2.6.2. Whole-brain volumetric data

The group comparisons of whole-brain GM, WM, CSF and ICV native volume data were performed using SPSS 14.0 version.

#### 2.6.3. Cognitive and whole-brain volumetric data

Pearson correlation analyses between intellectual measures and volumetric data were also performed using SPSS 14.0 version.

#### 2.6.4. Concentration data

The processed WM images were analysed using the SPM2 $t$-test models. We performed individual VBM analyses comparing each preterm adolescent with the entire control group in order to determine the frequency of WM damage in the preterm subjects and to describe patterns of WM injury (contrast: preterm subject < control group).

To display the results we used a threshold at an uncorrected level (voxel $P$ value of <0.001), and for statistical purposes we only report clusters that were significant at the corrected cluster $P$ level ($P < 0.05$).

We also performed a "simple regression" (correlation) SPM2 analysis to evaluate the relationship between WM concentration changes and a neuropsychological processing speed measure for the preterm group.

## 3. Results

### 3.1. Cognitive results

#### 3.1.1. Cognitive performance results

Results from the Wechsler Intelligence Scales showed that the preterm group performed below controls on all global intelligence indexes, although verbal IQ showed only a trend toward significance (Verbal IQ: $t = -1.98$, $P = 0.051$; PIQ: $t = -2.31$, $P = 0.023$; Full IQ: $t = -2.56$, $P = 0.012$). As regards PIQ subtest results the groups differed in their performance on the Digit Symbol subtest, which is considered as a representative measure of mental processing speed. For more details, see Table 2.

#### 3.1.2. Cognitive performance correlations with native brain volumes

For the whole-brain volumetric data, segmentation analyses revealed a reduced global WM volume in the preterm group ($t = -2.08$, $P < 0.05$) compared with the full-term group (see Table 3).

Table 4 shows the correlations between intelligence quotients and whole-brain native volumes. In the preterm adolescent group there were several significant correlations between global intelligence indexes and GM, WM and total intracranial native volumes. Finally, after removing the effects of the ICV, only the PIQ remained significantly correlated with the whole WM volume ($r = 0.34$, $P = 0.026$) (see Fig. 1). In contrast, in the control group the PIQ was only correlated positively with the whole-brain GM volume ($r = 0.30$, $P = 0.05$), although this correlation lost its statistical significance after controlling for ICV.

### 3.2. VBM results

#### 3.2.1. Individual VBM analysis: patterns of WM abnormalities

Individual VBM analysis demonstrated that 35 of the total sample of 44 preterm subjects (80%) had significant WM abnormalities when compared to the mean of the control group. We thus analysed the frequency of regional distribution of WM changes in the preterm group. As Table 5 illustrates, the most frequently affected region was the centrum semiovale,

**Table 2**
Cognitive performance

| Neuropsychological measures | Preterm group (mean ± S.D.) | Control group (mean ± S.D.) | Statistics ($P$ value) |
|---|---|---|---|
| Intelligence global index | | | |
| Verbal IQ | 111.5 ± 15.3 | 117.4 ± 10.7 | $t = -1.98$ (0.051) |
| Performance IQ | 99.1 ± 13.0 | 104.7 ± 9.9 | $t = -2.31^{*}$ (0.023) |
| Full IQ | 106.1 ± 13.9 | 112.8 ± 10.0 | $t = -2.56^{*}$ (0.012) |
| Performance IQ subtest | | | |
| Digit Symbol (speed processing) | 9.77 ± 3.1 | 11.21 ± 2.7 | $t = -2.30^{*}$ (0.024) |

$^{*}$ $P < 0.05$.

**Table 3**
Volumetric data

| Volumetric data ($mm^3$) | Preterm group (mean ± S.D.) | Control group (mean ± S.D.) | Statistics ($P$ value) |
|---|---|---|---|
| Cerebral spinal fluid | 325.979 ± 46.077 | 335.931 ± 41.283 | $t = -1.06$ (0.291) |
| Grey matter | 791.941 ± 80.175 | 810.831 ± 66.670 | $t = -1.20$ (0.235) |
| White matter | 377.825 ± 45.234 | 396.962 ± 40.383 | $t = -2.08^{*}$ (0.040) |
| Total intracranial volume | 1495.744 ± 143.720 | 1543.724 ± 126.417 | $t = -1.65$ (0.102) |

$^{*}$ $P < 0.05$.

**Table 4**
Correlations between intelligence quotients and native cerebral volumes

| Intelligence global index | Cerebral tissue | Correlation coefficients (*P* value) | | | |
|---|---|---|---|---|---|
| | | Preterm | Corrected by ICV | Controls | Corrected by ICV |
| Verbal IQ | GM | 0.33* (0.03) | 0.02 (0.89) | 0.18 (0.252) | – |
| | WM | 0.33* (0.03) | 0.06 (0.718) | 0.01 (0.986) | – |
| | ICV | 0.35* (0.02) | – | 0.17 (0.276) | – |
| Performance IQ | GM | 0.17 (0.262) | – | 0.30* (0.050) | 0.19 (0.233) |
| | WM | 0.32* (0.036) | 0.34* (0.026) | 0.12 (0.431) | – |
| | ICV | 0.18 (0.252) | – | 0.25 (0.106) | – |
| Full IQ | GM | 0.33* (0.031) | 0.03 (0.859) | 0.27 (0.076) | – |
| | WM | 0.41** (0.006) | 0.22 (0.151) | 0.07 (0.680) | – |
| | ICV | 0.35* (0.021) | – | 0.24 (0.114) | – |

*Abbreviations*—GM: grey matter; ICV: intracranial volume; IQ: intelligence quotient; WM: white matter.
* $P < 0.05$.
** $P < 0.01$.

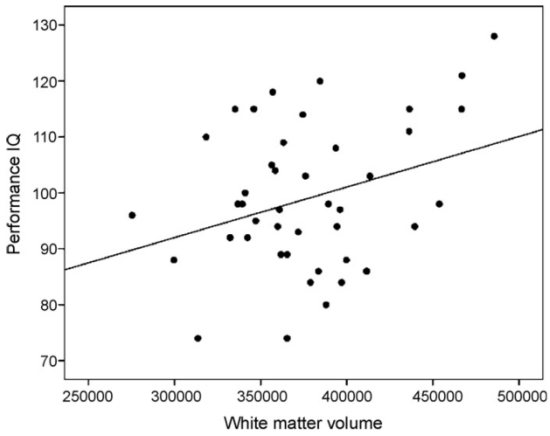


**Fig. 1.** Correlation between whole-brain WM volume and PIQ in the preterm group.

**Table 5**
Percentages of preterms with a regional reduction in WM concentration

| White matter regions | Preterms with white matter damage (%) |
|---|---|
| Centrum semiovale | 40.9 |
| Periventricular posterior bilateral | 20.5 |
| Periventricular body bilateral | 20.5 |
| Total periventricular bilateral | 15.9 |
| Anterior left | 13.6 |
| Centrum semiovale left | 9.1 |
| Periventricular posterior left | 6.8 |
| Anterior bilateral | 6.8 |
| Anterior right | 6.8 |
| Periventricular body left | 6.8 |
| Centrum semiovale right | 4.5 |
| Periventricular anterior left | 4.5 |
| Periventricular posterior right | 4.5 |
| Periventricular body right | 4.5 |
| Posterior left | 2.3 |
| Periventricular anterior right | 2.3 |
| Posterior right | 0 |
| Posterior bilateral | 0 |
| Periventricular anterior bilateral | 0 |

which showed bilateral WM alterations in 41% of preterm subjects. As regards the PV regions, 21% of preterms showed reduced WM concentration in both regions, i.e., the posterior PV areas and the PV bodies bilaterally. Moreover, 16% of the preterm group had a global loss in PV WM concentration. In summary, the posterior PV areas were more affected than the anterior ones.

### *3.2.2. Preterm group VBM analysis: speed of mental processing and WM abnormalities*

When classifying the preterm subjects according to normal or abnormal scores (equal to or less than a scaled score of 7) on the Digit Symbol subtest we observed that compared to preterm subjects with normal scores ($n = 33$) those with abnormal scores ($n = 11$) had diffuse reductions in WM concentration in the right temporal and frontal sub-gyral WM, the left limbic area (anterior cingulate) and in the genu of corpus callosum (see Fig. 2 and Table 6).

Additionally, we found a positive correlation between Digit Symbol performance and WM concentration in the right sub-gyral WM region of the temporal lobe (Montreal Neurological Institute (MNI) coordinates: 42, −46, −6; $r = 0.49$, $P < 0.023$, cluster level corrected), which was also the most extensively affected area detected in the analysis described above.

**Table 6**
Areas with WM concentration decrease in preterms with low Digit Symbol test scores

| Anatomical region | Cluster size ($mm^3$) | Cluster-level (*P* corrected) | MNI coordinates | | | *t* statistic |
|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | |
| Temporal lobe: sub-gyral (R) | 736 | 0.002 | 42 | −48 | −4 | 4.67 |
| Frontal lobe: sub-gyral (R) | 496 | 0.020 | 28 | 14 | 30 | 4.52 |
| Sub-lobar extra-nuclear (L) | 448 | 0.031 | −24 | −18 | 18 | 4.11 |
| Corpus callosum, genu (L) | 664 | 0.004 | −4 | 20 | 12 | 3.67 |
| Limbic lobe: anterior cingulate (L) | 448 | 0.031 | −14 | 46 | 8 | 3.80 |

MNI coordinates indicate: *x* increases from left (−) to right (+); *y* increases from posterior (−) to anterior (+); and *z* increases from inferior (−) to superior (+). *Abbreviations*—L: left hemisphere, R: right hemisphere.

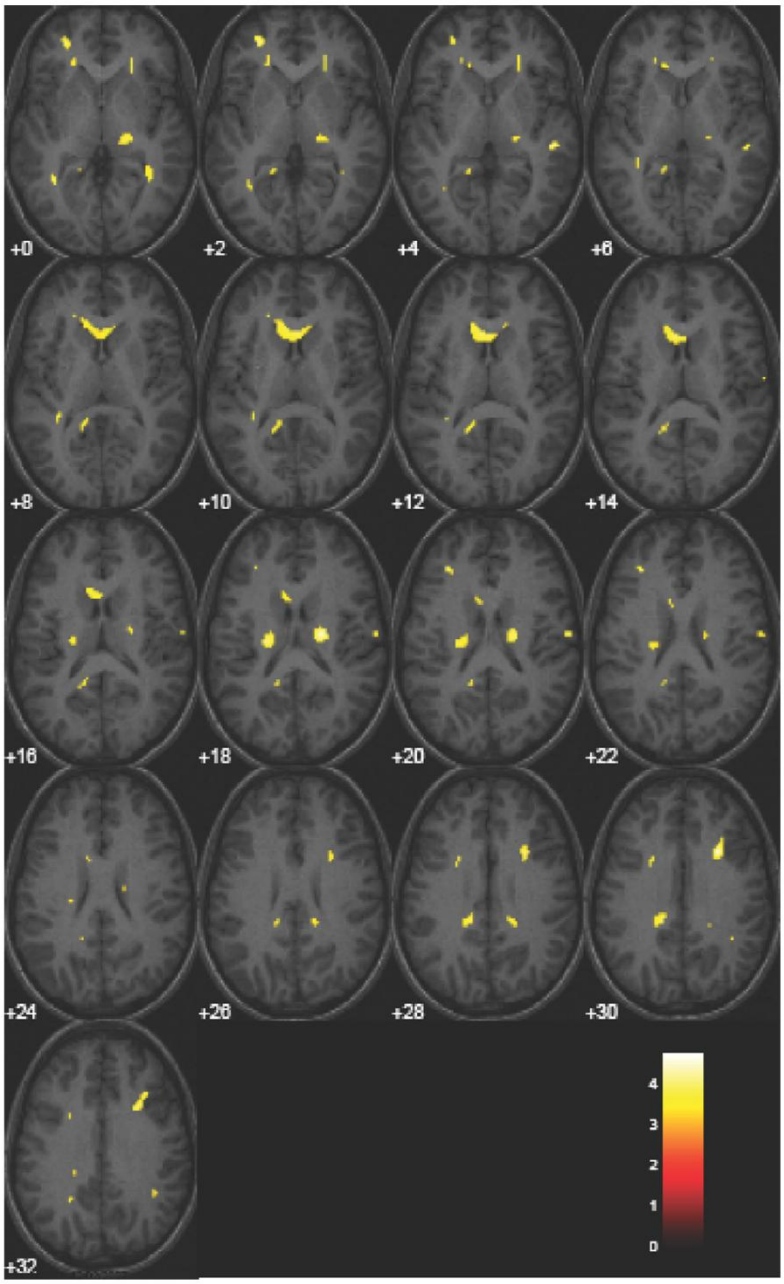


**Fig. 2.** Axial sections of images illustrating WM reductions in the preterm sample with low scores on the Digit Symbol subtest compared to preterm subjects with normal scores on this test. Images are representative slices at the two-slice interval. Differences are mapped onto a brain from a control subject of our sample. The colour bar represents the *t* scores. Results are displayed at uncorrected voxel *P* value threshold of $<0.001$. Statistical parametric maps (SPMs) are represented according to neurological convention (left corresponding to the left hemisphere).

## 4. Discussion

This study provides evidence of the persistence of diffuse WM abnormalities in adolescents who were born VPT, and also reveals the high frequency of these WM abnormalities. Volumetric and MRI-related cognitive outcomes suggest that there are persistent impairments in speed of cognitive processing following early brain damage, despite the existence of developmental plasticity.

Our results showed that in preterm subjects without clinical evidence of WM impairment in the MRI assessment, the frequency of reductions in WM concentration was very high. Interestingly, these subjects are considered clinically to be a low-risk preterm sample. However, individual VBM analyses revealed significant reductions in 35 of 44 preterms (80%). These results suggest that WM reductions are common, even in those preterm subjects without motor impairment and who follow normal schooling. Our findings are consistent with those of other studies documenting the prevalence of WM damage. Stewart et al. (1999) reported that MRI at 14–15 years of age detected many more abnormalities in preterms than in full-term controls. WM lesions were noted in 36 of 40 children with abnormal MRI, confirming that brain damage in VPT infants predominantly occurs in WM. Counsell et al. (2003) claimed that diffuse WM injury with subsequently impaired WM development is extremely common in small premature infants. These authors suggested that WM susceptibility to injury may be attributed to the low blood flow to cerebral WM in preterm infants, and to the susceptibility of immature oligodendrocytes to injury from free radicals, certain cytokines and glutamate toxicity. Our results also agree with those reported in a study of low-risk preterm infants without magnetic resonance-visible brain injury which demonstrated a reduction in myelinated WM, thus suggesting an adverse influence of early birth on WM development (Mewes et al., 2006). Recently, Constable et al. (2008) showed that compared with control subjects, prematurely born children with no neonatal ultrasound evidence of WM injury manifest changes in neural connectivity at 12 years of age. In agreement with these findings, our results suggest that WM changes occurring during pregnancy or the perinatal period persist until adolescence after a long period of cerebral changes.

Our individual analyses showed patterns of reduced WM, mainly in PV areas and the centrum semiovale, the latter being the most frequently affected region, followed by posterior PV areas. According to Taylor (2006) the nature of cognitive outcomes may depend on damage to WM vs. GM, or on the extent to which insults are localized in PV brain regions; these authors pointed out that preterm children or those with very low birth weight can have both global and selective cognitive deficits.

The cognitive assessment showed significant differences between VPT and full-term adolescents. In agreement with previous reports (e.g., Peterson et al., 2000; Cooke and Foulder-Hughes, 2003), preterms obtained lower scores on all the IQ scales. Although their intellectual performance was within the normal range the preterm population experience learning disabilities more often than full-terms do (Olsen et al., 1998), and they also require more extra educational provision (e.g., Botting et al., 1998; O'Brien et al., 2004). As in other studies (e.g., O'Brien et al., 2004; Isaacs et al., 2000, 2003; Abernethy et al., 2004) we found lower scores on the PIQ scale than on the VIQ scale. Within PIQ the most affected subtest was Digit Symbol. The Digit Symbol subtest of Wechsler Intelligence Scales, in which subjects fill in the symbols as fast as they can, is commonly used to assess processing speed (Kail and Salthouse, 1994). Rose et al. (2002) found that the deficits shown by preterm infants in processing speed are already present during the first year of life. Rose and Feldman (1996) also reported that preterm children at 11 years were slower on selected aspects of processing speed but not on motor speed, and concluded that a deficit in processing speed could be a central mechanism underlying the several cognitive impairments reported in the preterm population. In contrast, a recent study by Saavalainen et al. (2007) found no differences in processing speed between preterm and full-term adolescents at age 16, as assessed by the Coding subtest of the WAIS-R and by the verbal automatisms of the Wechsler Memory Scale III.

As Colom et al. (2006) pointed out, a number of published reports address the neural basis of human intelligence by using several imaging methods. Gignac et al. (2003) used structural imaging to demonstrate a significant correlation between total brain volume (GM and WM) and intelligence. Moreover, these authors hypothesized that whole-brain WM may be more correlated to intelligence than is whole-brain GM. In our study, the analysis of correlations between whole-brain native volumes (GM, WM and ICV) and IQ scales showed that in preterm adolescents there were several significant correlations between IQ scales and both GM and WM volumes; however, the most robust correlation was observed between the whole WM volume and the PIQ scale. Our results are consistent with those of Allin et al. (2001), who also reported correlations between intelligence and whole-brain volume in VPT adolescents. Recently, using a DTI approach, Yung et al. (2007) concluded that whole-brain WM volume and FA were independent variables significantly affecting Full Scale IQ.

As regards the analysis of processing speed, we observed an interesting correlation between Digit Symbol performance and WM concentration in the right sub-gyral WM region of the temporal lobe. This region was also involved as one of the areas showing reduced WM concentration in the preterm group with abnormal Digit Symbol scores compared with preterms whose scores were normal. In this regard, the study by de Groot et al. (2000) with an adult sample found a relationship between PV but not subcortical WM lesions and cognitive function, the most affected tasks being those involving speed of cognitive processes. Moreover, studies of leukoaraiosis (Junque et al., 1990; Ylikoski et al., 1993) support the relationship between PV WM lesions and processing speed, which may be due to the high density of pathways running through PV regions and interconnecting distant cortical structures (Desmond, 2002).

A number of aspects of the present study require further mention. As Ridgway et al. (2008) pointed out in their comment paper, in performing a VBM study many methodological options are available, so according to their work and following their recommendations we have tried to report the core principles and the information that should be included when reporting a VBM study in order to improve the level of transparency and to permit the reader to assess the validity of our work and compare it to similar literature in the field. Additionally, it is important to notice that one limitation of our study is implicit in the VBM procedures. A critique of VBM is that it is sensitive to systematic shape differences attributable to mis-registrations from the spatial normalization step. Moreover, this software was not initially designed to evaluate structural abnormalities and, although the algorithms in SPM are considered robust, imperfect registration may lead to inaccuracy (Bookstein, 2001). To minimize the problems arising from this procedure, we performed the entire normalisation subject by subject, ensuring that all subjects were well adapted to the T1 SPM template. Furthermore, we cannot avoid the fact that spatial normalization of paediatric brains is influenced by standard adult references.

Although smoothing is used to improve the validity of statistical inferences and to reduce inter-individual variation, it is important to use the appropriate size of the smoothing filter, because variations in smoothing can produce very different results (Jones

et al., 2005). Since non-normality in the error terms can be an issue in the individual use of VBM (Salmond et al., 2002) we decided to use different sizes of smoothing kernel depending on the type of comparison: 12 mm or 6 mm kernels for individual vs. group or between-groups comparisons, respectively. Although we focused on WM lesions and cognitive performance in preterm adolescents it is important to remember that cognition requires higher cortical functions (Dammann et al., 2002). In this regard, a study by Inder et al. (1999) of preterm infants showed that WM damage is commonly accompanied by GM involvement; in fact, the pattern of cerebral alterations has been reported to be related to the degree of immaturity at birth and to concomitant WM injury (Inder et al., 2005). Although we found WM abnormalities in preterm adolescents compared to controls these differences were apparently not relevant for daily living, since our subjects received normal schooling. Indeed, as Desmond (2002) noted, some studies have suggested that cognitive deficits are related to the total volume of the WM lesion, with a threshold that perhaps needs to be surpassed before clinically meaningful deficits are evident. As regards methods of cognitive assessment a limitation of our study is the lack of a widespread neuropsychological assessment, with an emphasis on executive functions and, in particular, measures of cognitive processing speed. Future prospective studies are thus required in order to investigate a possible cause-and-effect relationship between WM lesions and cognitive deficits in the preterm population. Finally, it should be noted that the pathological basis of WM abnormalities identified with VBM remains uncertain and awaits further investigation, including correlative neuropathological studies (Woermann et al., 1999a).

In summary, although the nature of the relationship between diffuse WM injury and cognitive/behavioural deficits is complex and not entirely understood (Volpe, 2003) our results suggest that WM abnormalities are partially related with worse PIQ scores and slower speed of processing. Therefore, we conclude that diffuse WM loss in preterm children may be responsible for long-term cognitive outcome.

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