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Neuropsychological performance and corpus callosum abnormalities in adolescents with history of prematurity

Thesis presented by

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Dr. Mª Dolors Segarra Castells, professor at the University of Barcelona, CERTIFIES that she has supervised and guided the PhD thesis entitled: "Neuropsychological performance and corpus callosum abnormalities in adolescents with history of prematuriry ", presented by Ana Narberhaus, and asserts that this thesis fulfils the requirements to be defended for the Degree of Doctor.

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To all preterm born babies.

CONTENTS

Foreword

This thesis, presented to obtain the degree of Doctor by the University of Barcelona, is the result of different works carried out at the Department of Psychiatry and Clinical Psychobiology, School of Medicine, University of Barcelona.

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1 INTRODUCTION

1.1. Prematurity

1.1.1. Definition

The American Academy of Pediatrics and the *American College of Obstetrics and Gynecology* define preterm birth as delivery before the completion of 37 weeks of gestation (American Academy of Pediatrics-American College of Obstetrics and Gynecology, 2002). In terms of weight the most frequently used categories are low birthweight (LBW, < 2500g), very low birthweight (VLBW, < 1500g) and extremely low birthweight (ELBW, < 1000g) (Picard et al. 2000).

1.1.2. Epidemiological aspects

Nowadays, the rate of preterm birth in Spain is over 8% (Instituto Nacional de Estadistica de España: www.se-neonatal.es), existing an increment of the 13% of the preterm babies or babies with low birth weight in the last four years (*Sociedad Española de Neonatología*: www.se-neonatal.es).

In the USA, between 1980 and 2000, the infant mortality was reduced 45% with an increased rate of preterm birth (17%), in particular births before 28 weeks of gestation; or of LBW (12%) and VLBW (24%) (Alexander & Slay 2002).

This growth in preterm birth is related to the increase of assisted reproductive therapy and ovulation induction, which increase the risk of multiple births; and to the huge proportion of births among women over 34 years (Lumley 2003).

1.1.3. Prognosis

The prevalence of major neurodevelopmental handicaps, such as cerebral palsy and mental retardation, ranges from 12% to 32% respectively, depending on the birhtweight of the subjects (VLBW or ELBW) (Hack et al. 1996). Moreover studies report an increased risk for behaviour and/or learning disorders at school age and in adolescence, even with an intelligence quotient within the normal range (Botting et al. 1998, Sykes et al. 1997). Particularly among ELBW infants more than 50% have school-age functional educational disabilities (Msall & Tremont 2002).

1.1.4. Medical complications of the newborn preterm baby

The problems that probably have the most impact on the development of the preterm infant's brain are those related to the respiratory and cardiovascular systems.

Following Picard et al. (2000), in the respiratory domain, the immaturity of the lungs, accompanied by a surfactant deficiency, may lead to a hyaline membrane disease. In addition to this, immaturity of the respiratory control centre can difficult the spontaneous respiration, causing apneas. This inadequate respiration produces hypoxia.

In the cardiovascular domain, these low oxygen levels frequently lead to the persistence of the ductus arteriosus of fetal circulation, which improves the hypoxemia. Moreover the immaturity of cerebral autoregulation difficults the adequate adaptation of cerebral blood flow to changes in blood pressure. Under these circumstances the preterm infant is vulnerable to present hypoxic-ischemic encephalopathy.

The cerebral structure most vulnerable to hypoxic-isquemic injury in the preterm infant is the sub-ependymal periventricular germinal matrix. This structure is a richly vascularized end zone and therefore vulnerable to a low blood supply. Moreover the vessels are thin-walled and consequently predisposed to be a ready source of bleeding. In consequence periventricular / intraventricular haemorrhagic lesions can appear (Picard et al. 2000; Volpe 2001a).

The above mentioned clinical aspects should be accompanied by more detailed studies about cognitive and brain structural characteristics of preterm individuals. In the following section we describe the main findings of neuropsychological and brain imaging studies regarding subjects with antecedents of prematurity.

1.2. Neuropsychological studies

The majority of neuropsychological studies about preterm and VLBW children and adolescents report a significant low IQ as well as low specific cognitive performance compared to full-term subjects. However, those works in which standardized scores are provided, the conclusion can be drawn that these individuals are almost always in the normal range, except for IQ and some verbal skills in those subjects weighting less than 750g at birth.

Here we describe the particular studies which report these results mainly following the chronological sequence.

1.2.1. General cognitive ability

Intelligence has been explored using different batteries or tests depending on the samples age.

The Wechsler Intelligence Scales cover the ages ranging from 3 to 74 years: Wechsler Preschool and Primary Scales of Intelligence (WPPSI) and Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R) (3-7); Wechsler Intelligence Scales for Children-Third Edition (WISC-III) and Wechsler Intelligence Scale for Children-Revised (WISC-R) (6-16); and Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) and Wechsler Adult Intelligence Scale-Revised (WAIS-R) (16-74). The intelligence quotient (IQ) is normally distributed with a mean of 100 and a standard deviation of 15. Some studies used the short forms of the WISC-III, WAIS-III or WAIS-R, comprising the subtests Vocabulary and Block design (Spreen & Strauss 1998).

The Kaufman Assessment Battery for Children (K-ABC) is based on theories of intellectual functioning and measures intelligence with the Mental Processing Composite (MPC: 8 subtests), which is subdivided in the Simultaneous Information-Processing Score (SGD) and the Sequential Information-Processing Score (SED). Moreover the Achievement Score (AS: 3 subtests) measures what has been learned by the child. Each of these subscores (MPC, SGD, SED, AS) are standardized at 100 +/- 15 (Wolke & Meyer 1999). This battery assesses the intelligence in subjects with ages ranging from 2 ½ and 12 ½ years. The short form consists of the subtests Hand Movements, Triangles, Word Order and Matrix Analogies (Spreen & Strauss 1998).

Other kind of tests, for instance the Dutch Intelligence test (Leiden Diagnostic Test: LDT; Schroots & Alphen de Veer 1976) or the Schonnel Graded Reading and Spelling Tests (Schonnel & Schonnel 1960), have also been used to assess general cognitive performance in preterm born adolescents.

1.2.1.1. Children

A significantly low general cognitive performance has been observed in VLBW (Korkman et al. 1996; Böhm et al. 2002) and preterm children (Olsén et al. 1998; Pasman et al. 1998; Wolke & Meyer 1999; Burguet et al. 2000; Peterson et al. 2000; Foulder-Hughes & Cooke 2003; Hopkins-Golightly & Raz 2003; Youngmei Peng et al. 2005).

Korkman et al. (1996) obtained IQ values in a sample of 76 VLBW children (5 to 9 years) with a mean birthweight of 1140g, using the WPPSI or WISC-R. Although in the normal range, mean full IQ (FIQ), verbal IQ (VIQ) and performance IQ (PIQ) of these subjects were significantly lower than in controls ranging from 91-96 and 104-105 respectively.

Subsequently, in 42 preterm born children (8 years), also using the WISC-R (10 subtests), Olsén et al. (1998) described a low general cognitive performance. The mean FIQ, VIQ and PIQ of the preterm children were 97.5, 95.4 and 97.5 respectively. So, again, the preterm group showed a normal intelligence but significantly below controls, whose mean IQ indexes were: 103.8 (FIQ), 100.2 (VIQ) and 107.1 (PIQ). When analyzing the ten subtests separately, the differences between the preterm and the control children emerged most clearly in the performance subtests of Picture Completion and Coding, which assesses spatial and visuoperceptual ability. Similar results on FIQ and VIQ were found by Pasman et al. (1998) in 44 preterm born children (5 years) using the LDT.

Low intelligence in preterm children has also been reported using the K-ABC. Wolke & Meyer (1999), in a sample of 264 subjects (6 years), observed a significantly lower performance in the 4 composites of the K-ABC. The lowest mean scores were found in the Simultaneous Information-Processing subscales (1.4 SD below controls). Mean standard scores in each of the composites for preterms and controls were: Mental Processing Composite (MPC): 84.8/99.7; Simultaneous Information-Processing Score (SGD): 83.7/103.2; Sequential Information-Processing Score (SED): 86.9/96.0;

Achievement Score (AS): 84.6/100.9. In contrast to the above mentioned studies, mean intelligence scores were mainly altered.

Again using the Wechsler Batteries, specifically the WPPSI, Burguet et al (2000) described significant differences in 171 preterm children (5 years) compared to controls. However, the FIQ and the PIQ were only 0.8 SD below the values of the controls, and even less (0.5 SD) for the VIQ**.**
In a smaller sample (n = 25) of preterm born children (8 years) and using the WISC-III, Peterson et al. (2000) also observed significant low FIQ scores with a normal mean FIQ (93.2) and a range of 49-126, so including individuals with an IQ < 70. These results could be due to the sample characteristics of the study (very immature subjects; with birthweight between 600 and 1250g). In contrast the full term group showed a mean FIQ of 116.7 and a range of 75-145.

More recently, Böhm et al (2002) obtained significant differences, but with values in the normal range, in a sample of 182 VLBW (mean birthweight 1043g) children (5½ years) compared to controls in the three IQ indexes using the WPPSI-R. The mean IQ scores in preterm subjects and controls respectively were: 91.1/102.3 (FIQ), 96.5/104.6 (VIQ) and 86.6/98.7 (PIQ).

Assessed with the WISC-III, a cohort of 268 preterm children (7 years) showed significant low mean FIQ (89.4), PIQ (87.8) and VIQ (92.9), compared to controls (FIQ: 100.5; PIQ: 99.6; VIQ: 101.2). Again, in this study IQ scores of the preterm group were normal. The four index scores were also significantly different between groups. Mean scores for preterms and controls were: Verbal comprehension: 91 / 99; Perceptual Organization: 87 / 99; Freedom from Distraction: 97 / 106; Processing Speed: 94 / 104. Regarding the subtests subscores, Block Design, Object Assembly and Mazes seem to be the most difficult for the preterm group (Foulder-Hughes & Cooke 2003).

Hopkins-Golightly & Raz (2003) compared 26 preterm children with risk of perinatal hypoxia versus 26 preterm children without risk of hypoxia (6 years) on the basis of 8 subtests out of the 10 included in the Wechsler Batteries. Prorated PIQ score was

obtained with the subtests Object Assembly, Picture Completion, Block design and Mazes; and prorated VIQ with the subtests Vocabulary, Comprehension, Information and Similarities. These authors found significant differences between groups in both IQ scores, although these were normal: 92.35 versus 102.47 for VIQ, and 94.00 versus 105.19 for PIQ.

Recently, Youngmei Peng et al. (2005) explored IQ with the WPPSI in a sample of 101 preterm subjects (5 years). The mean FIQ (105.7) was normal but significantly lower than in controls (114.5). The proportion of subjects with IQ scores ≤ 85 was 0% for controls and 9% for the preterm group.

1.2.1.2. Adolescents

In adolescent samples, significantly low IQ values have also been shown in preterm (Stewart et al. 1999; Roth et al. 2001) and VLBW subjects (Isaacs et al. 2000; Taylor et al. 2000, 2004; Hack et al. 2002).

Isaacs et al. (2000) explored intelligence with the WISC-III in a sample of 11 VLBW (mean birthweight 998g) adolescents (13 years). In addition to VIQ and PIQ, index scores were calculated (Verbal Comprehension, Freedom from Distractibility, Processing Speed). A significant lower score for the preterm group were only obtained for the VIQ (mainly for Arithmetic and Digit Span subtests) and for Freedom from Distractibility. The mean and range for VIQ was 90.0 (79-111) for the preterm and 108.5 (89-133) for the controls. Regarding Freedom from Distractibility these were 94.0 (66-106) and 106.5 (84-140). Impaired VIQ was previously suggested by Stewart et al. (1999) using the Schonnel reading and spelling test in 105 preterm born adolescents (14-15 years).

Using the short forms described at the beginning of the section “General cognitive ability”, a significant low prorated IQ has been reported in VLBW (< 1499g) subjects tested at 11 years (Taylor et al. 2000; n = 115) as well as in a subsample of VLBW (< 750g) subjects tested at 16 years (Taylor et al. 2004; n = 48). Prorated mean IQ for the term born group was 99.14 and 97.94 respectively. In the last mentioned study mean IQ for the VLBW group was 82.5, being in the altered range. A similar result was found

previously in Taylor et al. (2000) for those subjects weighting < 750g, who showed a mean IQ of 78.0.

In 242 VLBW (mean birthweight 1179g) young adults (20 years), Hack et al. (2002) also found significant differences in IQ using the mentioned short forms. The mean prorated IQ was 87 for cases and 92 for controls. 51% of the preterm group showed an IQ in the normal range (≤ 85).

Roth et al. (2001) assessed intelligence with the WISC-R in a sample of 89 preterm adolescents (14-15 years) and obtained a FIQ between 62 and 97 in their sample. Thirty-one % had an IQ of less than 85 and 7.5% of less than 70. The design of this study did not include a control group.

Table 1: Main results on general cognitive ability

Study	Preterm / VLBW sample n, age, GA or birthweight	Test	Results
Korkman et al. (1996)	n = 76, 5-9y, VLBW (mean 1140g)	WPPSI, WISC-R	[FIQ, VIQ, PIQ] [1]
Olsén et al. (1998)	n = 42, 8y, (mean 31w)	WISC-R (ten subtests)	[FIQ, VIQ, PIQ] [1]
Pasman et al. (1998)	n = 44, 5y, ≤ 34w	Leiden Diagnostic Test (LDT)	[LDT-FIQ, LDT-PIQ] [1]
Stewart et al. (1999)	n = 105, 14-15y, < 33w	Schonnel reading and spelling test	VIQ
Wolke & Meyer (1999)	n = 264, 6y, < 32w	K-ABC	[MPC, SGD, AS] [2]; SED [1]
Isaacs et al. (2000)	n = 11, 13y, VLBW (mean 998g)	WISC-III	[VIQ, Freedom from Distraction] [1]
Burguet et al. (2000)	n = 171, 5y, < 33w	WPPSI	[FIQ, VIQ, PIQ] [1]
Peterson et al. (2000)	n = 25, 8y, ≤ 33w	WISC-III	FIQ [1]
Taylor et al. (2000)	n = 115, 11y, VLBW (< 1499g)	WISC-III (short form)	Prorated IQ [1] < 750g group [2]
Roth et al. (2001)	n = 89, 14-15y, < 33w	WISC-R	FIQ: 31% [2] (no control group)
Hack et al. (2002)	n = 242, 20y, VLBW (mean 1179g)	WAIS-R (short form)	Prorated IQ [2]
Böhm et al. (2002)	n = 182, 5½y, VLBW (mean 1043g)	WPPSI-R	[FIQ, VIQ, PIQ] [1]
Foulder-Hughes & Cooke (2003)	n = 268, 7y, < 32w	WISC-III	[FIQ, VIQ] [1]; Verbal Comprehension [1] Perceptual Organization [1] Freedom from Distraction [1] Processing Speed [1]
Hopkins-Golightly & Raz (2003)	n = 26, 6y, ≤ 36 (with risk of hypoxia)	WPPSI-R, WISC-III (8 subtests)	[VIQ, PIQ] [1]
Taylor et al. (2004)	n = 48, 16y, VLBW (< 750g)	WISC-III, WAIS-III (short form)	Prorated IQ [2]
Youngmei Peng et al. (2005)	n = 101, 5y, < 37w	WPPSI	FIQ [1]

Note: all presented results show significant differences
[1] significant differences but normal mean values in the preterm group (Percentile ≥ 10)
[2] significant differences with altered mean values in the preterm group (Percentile < 10)
MPC: Mental Processing Composite, SGD: Simultaneous Information-Processing Score, SED: Sequential Information-Processing Score, AS: Achievement Score

1.2.2. Specific cognitive ability

According to the information available in the scientific literature about preterm born children and adolescents, we have classified the specific cognitive abilities in four groups: perception and constructional functions, verbal functions and language skills, learning and memory, and frontal functions.

Several neuropsychological batteries and tests have been used for the assessment of these abilities. Some of the tests used are described in Lezak et al. (2004) and are listed below; those which are not included in this book are referred in each particular study.

a) Perception and constructional functions: Complex Figure Test (CFT) (copy), Developmental Test of Visual-Motor Integration (VMI), Purdue Pegboard Test and Judgment of Line Orientation (JLO).

b) Verbal functions and language skills: due to the specificity of the test, see particular studies in this section.

c) Learning and Memory: California Verbal Learning Test-Second Edition (CVLT-II), California Verbal Learning Test (CVLT) - Children's Version, Rivermead Behavioural Memory Test (RBMT), Complex Figure Test (CFT) (recall), Auditory Verbal Learning Test (AVLT).

d) Frontal functions: Controlled Oral Word Association Test (COWAT), Category fluency, Cancellation task.

Additionally, studies often used the NEPSY (Korkman 1988a), a comprehensive neuropsychological assessment for children. The original battery consists of 37 subtests divided into five domains: attention and executive functioning, language, sensory-motor functions, visuospatial functions, and learning and memory.

The results obtained in each of these four categories are the following.

1.2.2.1. Perception and constructional functions

Visuospatial and visuoconstructive abilities, perceptual (tactile), and/or perceptual-motor skills, have been studied in VLBW (Waber & Mc Cormick 1995; Korkman et al. 1996) and preterm children (Olsén et al. 1998; Pasman et al. 1998; Briscoe & Gathercole 2001; Foulder-Hughes & Cooke 2003), as well as in VLBW adolescents (Taylor et al. 2000; Taylor et al. 2004).

Several authors demonstrated a low visuospatial and visuoconstructive ability through the copy task of a geometrical figure (CFT or VMI) or through building a complex pattern with cubes, a subtest from the Differential Ability Scales (DAS; Elliot, 1990). Significant differences in performance have been reported in VLBW (Waber and Mc Cormick, 1995: n = 475, 5-9 years, birthweight < 1500g) and in preterm subjects (Olsén et al. 1998: n = 42, 8 years; Pasman et al. 1998: n = 44, 5 years; Briscoe & Gathercole 2001: n = 20, 5 years; Foulder-Hughes & Cooke 2003: n = 280, 7-8 years). Although the performance was low, standard scores were in the normal range in all the studies that provided this information.

A low performance, but also in the normal range, in perceptual (tactile) ability, assessed with the subtest Tactile Finger Discrimination from the NEPSY has also been described in 76 VLBW (mean birthweight 1140g) children (7-10 years) (Korkman et al. 1996) and 42 preterm subjects (8 years) (Olsén et al. 1998). This low performance was only significant in the last mentioned study.

Regarding adolescents, Taylor et al. (2000) observed significant differences between 115 VLBW (< 1499g at birth) early adolescents (11 years) and controls in the copy task of the CFT, indicating some difficulties in visuoperceptual and visuoconstructional abilities for the VLBW group, although z score were in the normal range (-.91). Moreover these authors found significant differences in perceptual-motor skills, assessed with the short form of the Bruininks-Oseretsky Test of Motor Proficiency (Bruininks & Bruininks-Oseretsky, 1978) (T scores), the Purdue Pegboard test (z scores), and the VMI (standard scores). Although the VLBW performed worse, their

scores in each of these tests were again all in the normal range, (T score 40.42, z score -.91 and standard score 83.93).
More recently Taylor et al. (2004) examined a subsample 48 VLBW individuals (16 years) weighting less than 750g at birth, and also reported significant differences in fine motor dexterity (Purdue Pegboard), design copying (VMI, CFT) and spatial judgment (JLO). Results are presented only in raw scores.

1.2.2.2. Verbal functions and language skills

Although in a lesser extend, verbal and language abilities have also been explored in VLBW (Korkman et al. 1996) and preterm children (Wolke & Meyer 1999; Briscoe & Gathercole 2001), as well as in VLBW adolescents (Taylor et al. 2000, 2004).

Korkman et al. (1996) assessed language in 76 VLBW (mean birthweight 1140g) children (5-9 years). Results showed significant differences between these subjects and their full-term peers in the subtests Auditory Analysis of Speech and Naming Body parts of the NEPSY. However, z scores were in the normal range in both groups.

In a bigger sample (n = 262) of preterm children (6 years), Wolke & Meyer (1999) confirmed the existence of language difficulties. These authors used a German test battery (Heidelberger Sprachentwicklungstest, HSET; Grimm & Schöler 1991) for language development. The preterm group performed significantly lower than controls in language comprehension (understanding of grammatical rules and detecting semantically incorrect sentences), expression and articulation. Again, T-scores of the preterm group were normal.

In 20 preterm born subjects (5 years) Briscoe & Gathercole (2001) found a significant poor receptive vocabulary (British Picture Vocabulary: BPVS, Dunn et al. 1982) and bad auditory-verbal comprehension (Test for Reception of Grammar: TROG; Bishop 1989). In both tests the child is required to identify the picture matching either with a word or a sentence, spoken by the experimenter. Although significant differences were found between preterm and term born subjects, only standard score of the TROG was below normality in the preterm group.

In adolescents with VLBW, Taylor et al. (2000) observed significant differences in language skills between 115 VLBW (<1499g) early adolescents (11 years) and controls, using the subtests Oral Directions and Recalling Sentences of the Clinical Evaluation of Language Fundamentals-Revised (Semel et al. 1987). Scaled scores were in the abnormal range (6.51) only for those weighting less than 750g at birth and only in the first mentioned subtest.

In 2004, Taylor et al. also obtained significant differences in language in a subsample of 48 VLBW adolescents (16 years) weighting less than 750g at birth compared to matched full-term controls. Specifically, differences were found for word knowledge (synonyms) and pragmatic judgment (judge the appropriateness of language) (Comprehensive Assessment of Spoken Language: CASL; Carrow-Woolfolk, 1999). Mean standard scores were in the normal range: 90.44 and 85.42 respectively.

1.2.2.3. Learning and Memory

Learning and memory functioning have also been studied in preterm born children (Olsén et al. 1998; Pasman et al. 1998) and adolescents (Giménez et al. 2004), as well as in VLBW adolescents (Isaacs et al. 2000; Taylor et al. 2000, 2004).

Olsén et al. (1998), studying 42 preterm born children at 8 years of age, observed a significant low performance in relation to the controls in immediate visual memory and delayed verbal memory, assessed with the NEPSY. Pasman et al. (1998) used the subtests Word-order and Paper-folding from the Dutch Intelligence test (LDT, Leiden Diagnostic Test: LDT; Schroots et al. 1976) only in a subgroup of 12 preterm born children (5 years) with major neurological abnormalities, and also showed significant differences on visual and verbal memory. In both studies scaled scores of the preterm group were in the normal range.

Isaacs et al. (2000), in a sample of 11 adolescents (13 years) with VLBW (mean birthweight 998g), observed a significant difference compared to controls for scores on verbal learning and everyday memory, assessed with the CVLT-II and the RBMT respectively. Results are presented only in raw scores, but in relation to verbal learning,

authors stated that the difference was sometimes caused by an above-average level of performance by the full-term group and not a below-average score in the preterm group.

In a large sample (n = 115) of VLBW (<1499g) early adolescents (11 years), Taylor et al. (2000) reported a significant low performance compared to controls in verbal learning, assessed with the CVLT; however T scores were in the normal range (44.84). Additionally these authors also found a significant lower visual memory assessed with the CFT, but only for females in the subsample of those subjects weighting < 750g at birth. Z scores were normal (-.66).

Recently, Taylor et al. (2004) also found significant differences in a subsample of 48 VLBW adolescents (16 years), weighting < 750g at birth, in verbal learning and recognition (CVLT-II), and visual memory (Cambridge Neuropsychological Test Automated Battery: CANTAB, CeNeS Cognition 1996). Results are presented only in raw scores.

Our investigation group studied 22 preterm born adolescents (13 years) and showed significant differences versus controls in verbal learning and recognition assessed with the AVLT (Giménez et al. 2004). Again, results are presented in raw scores, however compared with normative data from 14-years-old adolescents (Forrester & Geffen 1991, in Spreen & Strauss 1998) mean scores of the preterm group indicate a normal performance.

1.2.2.4. Frontal functions

Verbal fluency, attention/concentration, executive functioning and processing speed have been explored in preterm born children (Olsén et al. 1998; Pasman et al. 1998; Saavalainen et al. 2006) and adolescents (Allin et al. 2001; Giménez et al. 2006b), as well as in VLBW children (Böhm et al. 2002) and adolescents (Taylor et al. 2000, Taylor et al. 2004).

Regarding verbal fluency, a significant poor performance has been reported for preterm born adolescents of 14-15 years (Allin et al. 2001; Giménez et al. 2006b), as well as for VLBW (mean birthweight 1043g) children of 5½ years (Böhm et al. 2002) and adolescents of 11 years with a birthweight < 1499g (Taylor et al. 2000) and 16 years with a birthweight < 750g (Taylor et al. 2004).

A very recent work of ours reported significant differences in phonetic verbal fluency as well as in category verbal fluency studying a sample of 30 preterm born subjects (Giménez et al. (2006b). In contrast Allin et al. (2001, n = 67) and Böhm et al. (2002, n = 182) reported significant differences only in category verbal fluency, and Taylor et al. (2000, n = 115; 2004, n = 48) in phonetic verbal fluency. In all these studies, this cognitive function was evaluated using the COWAT, the category fluency task or a subtest of the NEPSY. Results are presented in raw scores, except in Taylor et al. (2000). Z scores in this study revealed that the preterm group was in the normal range.

Significant differences in attention/concentration has also been reported in two samples of 42 and 44 preterm born children of 5 and 8 years (Pasman et al. 1998, Olsén et al. 1998), as well as in bigger samples of VLBW children and adolescents; specifically in 182 (mean birthweight 1043g) children of 5½ years (Böhm et al. 2002) and 115 (< 1499g at birth) early adolescents of 11 years (Taylor et al. 2000). These authors used the Bourdon-Wiersma-Vos concentration test for infants (BWVK, Vos 1988), the subtests of the NEPSY, and a cancellation task. The results of Olsén (1998) and Taylor et al (2000) again indicated that the performance of the preterm group was in the normal range, with the lowest z-score being -.68 (Taylor et al. 2000). The other two studies did not provide standard scores.

A significant low performance in executive functioning has also been found in preterm born and VLBW children and/or adolescents. Specifically, studies assessed 182 VLBW (mean birthweight 1043g) children of 5½ years (Böhm et al. 2002), and 115 VLBW (< 1499g at birth) early adolescents (11 years) (Taylor et al. 2000). Moreover this last mentioned investigation group also found significant differences in executive functions in a subsample of 48 adolescents (16 years) weighting less than 750g at birth (Taylor et al. 2004). The following tests have been used: subtests of the NEPSY, WPPSI-R and

CANTAB for assessment of children; and the Planning Test (Taylor et al. 2000), the CANTAB and the Contingency Naming Test (Anderson et al. 2000) for assessment of adolescents.
When results were not presented in raw scores, z scores of the preterm group were in the normal range (-.85) (Taylor et al. 2000).

Significant differences in processing speed have been reported for 42 preterm born children of 8 years (Olsén et al. 1998) and 182 VLBW (mean birthweight 1043) children of 5½ years (Böhm et al. 2002). These authors used the subtests of the NEPSY, and Olsén et al. (1998) indicated that, although the preterm group were slower, they performed in the normal range. Böhm et al. (2002) only provided raw scores.

Saavalainen et al. (2006) used the Rapid Automatic Naming test (Denckla & Rudel 1974) to evaluate processing speed of preterm born children in two different phases of a prospective study: at 9 years (n = 51) and 16 years (n = 40). At the age of 9 years the preterm children were significantly slower than controls in two naming tasks. However at the age of 16 years this difference was no longer significant. Results are presented again in raw scores.

Table 2: Main results on specific cognitive ability

Functions	Study	Preterm / VLBW sample n, age at assessment, GA or birthweight	Test / Results
Perception and constructional functions	Waber & Mc Cormick (1995)	n = 475, 5-9y, VLBW (< 1500g)	Complex Figure Test (CFT)
	Korkman et al. (1996)	n = 76, 5-9y, VLBW (mean 1140g)	Developmental Test of Visual-Motor Integration (VMI) [1]
	Olsén et al. (1998)	n = 42, 8y, (mean 31w)	[VMI; Block Construction, Tactile Finger Discrimination (NEPSY)] [1]
	Pasman et al. (1998)	n = 44, 5y, ≤ 34w	VMI
	Briscoe & Gathercole (2001)	N = 20, 5y, ≤ 32w	Pattern construction subscale (Differential Ability Scales) [1]
	Foulder-Hughes & Cooke (2003)	n = 268, 7y, < 32w	VMI [1]
	Taylor et al. (2000)	n = 115, 11y, VLBW (< 1499g)	[CFT; Bruininks-Oseretsky Test of Motor Proficiency; Purdue Pegboard Test; VMI] [1]
	Taylor et al. (2004)	n = 48, 16y, VLBW (< 750g)	CFT; Purdue Pegboard Test VMI; Judgment of Line Orientation
Verbal functions and language skills	Korkman et al. (1996)	n = 76, 5-9y, VLBW (mean 1140g)	[Auditory Analysis of Speech, Naming Body Parts (NEPSY)] [1]
	Wolke & Meyer (1999)	n = 264, 6y, < 32w	[Plural/singular, Semantics, Sentence production, Grammatical structure (HSET)] [1]
	Briscoe & Gathercole (2001)	N = 20, 5y, ≤ 32w	British Picture Vocabulary [1] Test for Reception of Grammar [2]
	Taylor et al. (2000)	n = 115, 11y, VLBW (< 1499g)	[Oral Directions, Recalling Sentences (Clinical Evaluation of Language Fundamentals-Revised)] [1]; < 750g: Oral Directions [2]
	Taylor et al. (2004)	n = 48, 16y, VLBW (< 750g)	Synonyms, Pragmatic Judgment (CASL) [1]

Note: all presented results show significant differences
[1] significant differences but normal mean values in the preterm group (Percentile ≥ 10)
[2] significant differences with altered mean values in the preterm group (Percentile < 10)
NEPSY: comprehensive neuropsychological assessment for children; HSET: Heidelberger Sparchentwicklungstest; CASL: Comprehensive Assessment of Spoken Language
Continue…

	Study	Preterm / VLBW sample n, age at assessment, GA or birthweight	Test / Results
Learning and Memory	Olsén et al. (1998)	n = 42, 8y, (mean 31w)	[Immediate Memory for pictures, Delayed Verbal Memory for Tests (NEPSY)] [1]
	Pasman et al. (1998)	n = 12, 5y, ≤ 34w	[Word-order, Paper-folding (Leiden Diagnostic Test)] [1]
	Isaacs et al. (2000)	n = 11, 13y, VLBW (mean 998g)	California Verbal Learning Test (CVLT) – II; Rivermead Behavioural Memory Test
	Taylor et al. (2000)	n = 115, 11y, VLBW (< 1499g)	CVLT (children's version) [1]; females < 750: Complex Figure Test (CFT) [1]
	Taylor et al. (2004)	n = 48, 16y, VLBW (< 750g)	CVLT -II; Spatial Span (CANTAB)
	Giménez et al. (2004)	n = 22, 13y, (mean 29w)	Auditory Verbal Learning Test (AVLT)
Frontal functions	Olsén et al. (1998)	n = 42, 8y, (mean 31w)	[Auditory Response Set , Speeded Naming (NEPSY)] [1]
	Pasman et al. (1998)	n = 44, 5y, ≤ 34w	BWVK
	Taylor et al. (2000)	n = 115, 11y, VLBW (< 1499g)	[Phonetic verbal fluency (NEPSY); Cancellation task; Planning Test; Contingency Naming Test] [1]
	Allin et al. (2001)	n = 76, 14-15y, < 33w	Category fluency
	Böhm et al. (2002)	n = 182, 5½y, VLBW (mean 1043g)	Category fluency, Selective attention, Colour-form, Impulse control, Speeded Naming (NEPSY); Animal Pegs (WPPSI-R)
	Taylor et al. (2004)	n = 48, 16y, VLBW (< 750g)	Controlled Oral Word Association Test (COWAT); Solving problems, Spatial working memory, Rapid visual processing (CANTAB); Contingency Naming Test
	Giménez et al. (2006b)	n = 30, 14y, < 33w	COWAT; Category fluency
	Saavalainen et al. (2006)	N = 51, 9y, ≤ 32w	Rapid Automatic Naming Test

Note: all presented results show significant differences
[1] significant differences but normal mean values in the preterm group (Percentile ≥ 10)
[2] significant differences with altered mean values in the preterm group (Percentile < 10)
NEPSY: comprehensive neuropsychological assessment for
children; CANTAB: Cambridge Neuropsychological Test Automated Battery; BWVK: Bourdon-Wiersma-Vos concentration test for infants; WPPSI-R: Wechsler Preschool and Primary Scales of Intelligence-Revised

1.3. Brain imaging studies

Results reported in preterm born individuals regarding general cognitive ability and specific cognitive functions may be related with some subtle cerebral abnormalities. Below we discuss the works that approach this question using neuroimaging techniques.

1.3.1. Qualitative brain imaging studies

Early neuroimaging studies of prematurely born children and adolescents were most often qualitative and poorly controlled. Reports indicate elevated rates of anatomical brain abnormalities which included among others: periventricular leukomalacia (PVL), haemorrhage and cysts (Keeney et al. 1991), delayed myelination (Hüppi et al. 1996), thinning of the corpus callosum (Stewart & Kirkbride 1996, Stewart et al. 1999), ventricular enlargement (Stewart et al. 1999), especially of occipital horns (Olsén et al. 1998), and periventricular lesions (Krägeloh-Mann et al. 1999). More recently Inder et al (2003) described significant diffuse white matter atrophy, and immature gyral development.

Recent quantitative magnetic resonance imaging (MRI) studies have detected more subtle cerebral abnormalities that can not be observed by visual inspection.

1.3.2. Quantitative brain imaging studies

In general, neuroimaging research about preterm and VLBW subjects, report a volume reduction of cerebral white matter, corpus callosum, gray matter, hippocampus, basal ganglia, amygdala and cerebellum, as well as an increased volume of the lateral ventricles.

In the following section we describe the particular studies concerning these data.

1.3.2.1. White Matter

Cerebral white matter abnormalities have been described in preterm born infants (Hüppi et al. 1998, Inder et al. 1999, Peterson et al. 2003, Inder et al. 2005), children (Nagy et al. 2003, Reiss et al. 2004) and adolescents (Giménez et al. 2006a).

One of these studies scanned preterm subjects with associated evidence of white matter injury in the neonatal period (Inder et al. 1999). Specifically these authors reported a significant reduction in the volume of total brain myelinated white matter in 10 preterm infants with periventricular leukomalacia (PVL), scanned during their first 16 days of life. Data were compared with premature infants with no PVL and control term infants. These authors used an advanced automatic quantitative volumetric three-dimensional MRI technique. An apparent compensatory increase in total cerebrospinal fluid volume was also found.

Inder et al. (2005) scanned a large cohort (n = 119) of preterm infants at a mean gestational age of 40 weeks, and following the method described before, the authors described a significant reduction (35%) in the absolute volume of myelinated white matter. Furthermore, when the absolute volume was represented as the percentage of the total intracranial volume, this reduction remained significant.

Peterson et al. (2003) reported white matter reductions, specifically in parieto-occipital and inferior occipital subregions, in 10 preterm infants scanned near birth (mean 35weeks) and compared to full-term controls. Additionally these authors reported that parieto-occipital volumes were larger on the left and smaller on the right in the preterm group. Specific anatomic subregions were manually traced through a region of interest (ROI) analysis.

A significant reduction of cerebral white matter volume were also evident in 65 preterm born children (8 years) reported by Reiss et al. (2004). These authors used a semi-automated whole brain segmentation and quantification using a constrained fuzzy segmentation algorithm that accounts for the proportion of each tissue type in each voxel.

Recently, our investigation group examined regional WM brain abnormalities using the voxel-based-morphometry (VBM) technique in a cohort of 50 preterm born adolescents (14 years). Density analyses detected periventricular WM damage and involvement of the major association fibers, while volume analyses detected WM decreases in regions distant to the ventricular system (Giménez et al. 2006a).

The abnormalities in the microstructure of white matter have been explored using the diffusion tensor imaging (DTI) method in preterm born infants at term (Hüppi et al. 1998) as well as in 11 years-old preterm children (Nagy et al. 2003). Hüppi et al. (1998) reported marked differences in white matter fiber organization between 17 subjects with antecedents of preterm birth and their full-term matched peers, and Nagy et al. (2003) described white matter disturbances, specifically in the corpus callosum and internal capsule in 9 preterm born children.

Related to these disturbances of the white matter, an increased volume of the lateral ventricles has also been reported in preterm born infants (Peterson et al. 2003), children (Peterson et al. 2000, Kesler et al. 2004), adolescents (Nosarti et al. 2002) and early adults (Allin et al. 2004, Fearon et al. 2004). This abnormality may in general indicate white matter loss, although it can also suggest a reduction in gray matter. So, it can only be seen as an indirect measure of white matter abnormalities.

Peterson et al. (2000) showed that the occipital and temporal horns of the lateral ventricles were increased in volume by 300-400%, studying 25 preterm born children of 8 years. Morphometric analysis was performed manually (ROIs) on MRI scans. These differences demonstrate the presence of differential regional vulnerabilities in the developing brain of preterm children.
Subsequently Peterson et al. (2003), using the same procedure, 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.

Kesler et al. (2004) observed a disproportionately enlarged lateral ventricular cerebrospinal fluid volumes in 9 years-old preterm subjects (n = 73) compared to controls. Significant differences between groups were found in the ventricular body and occipital horns. A semi-automated whole brain segmentation and quantification using a constrained fuzzy segmentation algorithm that accounts for the proportion of each tissue type in each voxel was used.

Nosarti et al. (2002) carried out structural MRI on a cohort of 72 adolescents (15 years) with antecedents of prematurity. Using stereological principles, results showed a 42% increase in the size of lateral ventricles in the preterm group compared to controls.

In 23-years-old subjects with VLBW, Allin et al. (2004) (n = 32, automated tissue segmentation algorithm) and Fearon et al. (2004) (n = 33, stereological principles) reported a significant increase in lateral ventricular volumes (41%, and 46% respectively).

1.3.2.2. Corpus Callosum

Corpus callosum is the main interhemispheric commissure of the brain and consists of approximately 180 million fibres (Tomasch 1954).

Corpus callosum reductions have been described in preterm born infants (Argyropoulou et al. 2003), children (Peterson et al. 2000) and adolescents (Nosarti et al. 2004) as well as in VLBW early adults (Fearon et al. 2004).

Argyropoulou et al. (2003) reported a significant reduction of total corpus callosum size in 33 preterm born infants of 1 year of age with PVL, following a manual region of interest (ROI) analysis.

Regarding the other studies, authors have performed a segmentation of the corpus callosum into 5 (Peterson et al. 2000), 4 (Nosarti et al. 2004) or 3 (Fearon et al. 2004) parts, and have quantified the total corpus callosum and its subregions.

Peterson et al. (2000), in a sample of 25 children (8 years), reported a significant reduction in corpus callosum size by as much as 35 %. Regarding the subregions, significant reductions were found in splenium, isthmus, midbody, anterior body and rostrum/genu. Volumetric analysis was performed manually (ROIs) on MRI scans.

More recently, Nosarti et al. (2004) explored a sample of 66 preterm born adolescents (14-15 years) and demonstrated a smaller size of total corpus callosum area (7.5%), mainly in the posterior part (14.7%) and mid-posterior (11.6%) quarters. Preterm

individuals who had experienced periventricular haemorrhages and ventricular dilation in the neonatal period showed the greatest decrease in CC area. The analyses were also performed manually, tracing the regions of interest (ROIs), but measuring areas.

A significant reduction of the posterior corpus callosum (17%), following stereological principles, continues to be evident in 23-years-old VLBW (< 1500g) subjects (Fearon et al. 2004).

1.3.2.3. Gray Matter

Whole cerebral gray matter reductions have been reported for preterm born children (Reiss et al. 2004, Kesler et al. 2004).

Reiss et al. (2004) showed that 65 preterm born children (8 years) presented a significant reduction of cerebral gray matter volume. These authors used a semi-automated whole brain segmentation and quantification using a constrained fuzzy segmentation algorithm that accounts for the proportion of each tissue type in each voxel.
Using this same procedure, Kesler et al. (2004) also found significant differences in cerebral gray matter volume in 73 preterm born children (9 years) compared to controls. Additionally, these authors found a significantly altered profile of cerebral lobe gray volumes in the preterm group. Specifically frontal and parietal lobes were disproportionately increased whereas temporal lobe gray matter volume was disproportionately decreased in this group.

Several studies reported specific reductions in cortical gray matter in preterm born infants (Inder et al. 1999, 2005, Peterson et al. 2003), children (Peterson et al. 2000, Kesler et al. 2006) and adolescents (Nosarti et al. 2002), as well as VLBW adolescents (Isaacs et al. 2003).

Inder et al. showed a marked reduction in cerebral cortical gray matter in 10 preterm infants with PVL (1999) and in a large cohort (n = 119) of preterm born infants (2005), scanning these subjects near birth. Following the method described before, in the last mentioned study the authors described a significant reduction of 22%, which continued

to be significant even when the absolute volume was represented as the percentage of the total intracranial volume.

Peterson et al. (2003) scanned 10 preterm infants near birth and showed cortical gray matter reductions compared to term infants, specifically in the volumes of the sensoriomotor, parieto-occipital and inferior occipital regions. MRI scans were semiautomatically segmented and specific anatomic subregions were manually traced through a region of interest (ROI) analysis.

Cortical gray matter reductions were also evident in 8-years-old preterm born children (n = 25), using the same procedure (Peterson et al. 2000). Significant volume reductions were most prominent in sensoriomotor regions, but also in premotor, midtemporal, parieto-occipital and subgenual cortices. These differences demonstrate the presence of differential regional vulnerabilities in the developing brain of preterm children.

Nosarti et al. (2002) explored a sample of 72 adolescents (15 years) with antecedents of prematurity. Using stereological principles, the preterm group showed an 11.8% decrease in cortical gray matter volume compared to controls.

In a VBM analysis, Isaacs et al. (2003) reported decreased cortical gray matter volumes most prominent in the right ventral extrastriate cortex in 11 VLBW (≤ 1500g) adolescents (15 years) with deficits in a spatial processing task, compared to 11 preterm subjects without these deficits.

As a particular aspect of cerebral cortical development, cortical gyrification has been measured by Kesler et al. (2006) in a sample of 73 children (8 years) with antecedents of prematurity and observed an increased bilateral temporal lobe gyrification index (GyI). This index is defined as the ratio of the inner perimeter of the brain divided by the perimeter of the outer surface. Thus, a larger GyI suggests a higher degree of cortical folding and a smaller gyral width.

Two studies reported significant reductions in whole subcortical gray matter volume in preterm infants (Inder et al. 2005) and children (Kesler et al. 2004).

Inder et al. (2005) described a significant reduction (22%) of deep nuclear gray matter in a large cohort (n = 119) of infants, using an advanced automatic quantitative volumetric three-dimensional MRI technique. However, when the absolute volume was represented as the percentage of the total intracranial volume, this reduction lost significance.

Kesler et al. (2004) observed a significant disproportionately reduced subcortical gray matter volume in 9 years-old preterm subjects (n = 73) compared to controls. A semi-automated whole brain segmentation and quantification using a constrained fuzzy segmentation algorithm that accounts for the proportion of each tissue type in each voxel was used.

1.3.2.4. Gray Matter structures

The volumes of several gray matter structures have been investigated, because of their high vulnerability to be affected in a hypoxic situation, which is a frequent complication in preterm birth.

Specifically, in children and adolescents, studies described significant reductions of the hippocampus (Peterson et al. 2000, Isaacs et al. 2000, Abernethy et al. 2002, Nosarti et al. 2002, Giménez et al. 2004, 2005), amygdala (Peterson et al. 2000), basal ganglia (Peterson et al. 2000, Abernethy et al. 2002, Nosarti et al. 2005), thalamus (Giménez et al. 2004, 2006b) and cerebellum (Peterson et al. 2000, Argyropoulou et al. 2003, Allin et al. 2005).

Peterson et al. (2000) scanned 25 preterm born children (8 years). Results showed that the hippocampus and amygdala were reduced by as much as 30%, and the volumes of the basal ganglia, particularly in their predominantly motor portions (the putamen and globus pallidus) were reduced by 12%. Morphometric analysis was performed manually selecting the regions of interest (ROIs) on MRI scans. These differences demonstrate

the presence of differential regional vulnerabilities in the developing brain of preterm children.

Nosarti et al. (2002) investigated hippocampal reductions in a sample of 72 adolescents (15 years) with antecedents of prematurity. Compared to controls, the preterm group showed a significant decrease in right and left hippocampal volumes; 15.6% and 12.1% respectively. Measurement of this structure was made using stereological principles using the MEASURE software. More recently Nosarti et al. (2005), in the same cohort and using the same volumetric technique, observed that left caudate volume was reduced by 7.3% and right caudate volume by 4.6% in cases relative to control subjects, although these differences were not statistically significant.

Our investigation group reported significant left hippocampal volume reductions, corrected by the intracranial volume, in 22 adolescents (13 years) with history of prematurity with a ROIs approach performing the optimized protocol from the voxel-based-morphometry (VBM) procedures (Giménez et al. 2004), as well as in a subsample

of 14 preterm subjects from the same study using a more precise stereological approach (Giménez et al. 2005). Additionally Giménez et al. (2004) reported significant bilateral thalamic reductions, again corrected by the intracranial volume and using the ROIs approach, which subsequently was also evident in 30 preterm born adolescents (14 years), following the same procedure (Giménez et al. 2006b).

Regarding VLBW adolescents, a significant reduction of the hippocampus was reported in 11 subjects of 13 years (Isaacs et al. 2000, mean birthweight 998g), as well as in 86 adolescents of 15-16-years (Abernethy et al. 2002, birthweight < 1500g). Isaacs et al. (2000) used two quantitative techniques, volumetry and T2 relaxometry; and Abernethy et al. (2002) performed a semiautomatic volumetry. Moreover this last mentioned author also reported a significant reduction of the caudate nucleus in the VLBW group.

The cerebellum is less investigated. Argyropoulou et al. (2003) reported a significant reduction of the volume of this structure in 33 preterm born infants of 1 year of age with

PVL, following a manual ROI analysis. Regarding preterm born children and using the same kind of analysis, this fact has also been reported in a sample (n = 25) of 8-years-old (Peterson et al. 2000). Subsequently, Allin et al. (2005) measured the cerebellum in 67 subjects using stereological principles with the MEASURE software and revealed smaller volumes of the vermis and lateral lobes of the cerebellum in preterm born adolescents (14-15 years), after controlling for whole-brain volumes.

Table 3: Main results of quantitative brain imaging studies

	Study	Preterm / VLBW sample n, age at scan, GA or birthweight	Technique/Approach	Specific findings
White matter (WM)	Hüppi et al. (1998)	n = 17, at term, preterm	Diffusion Tensor Imaging (DTI)	Low relative anisotropy in posterior limb of the internale capsule
	Inder et al. (1999)	n = 10, first 16 days after birth, mean 29w; with PVL in neonatal period	Automatic volumetric analysis	Total brain myelin volume reduction
	Peterson et al. (2003)	n = 10, near term (mean 35w), mean 29w	Manual volumetry (ROI)	Global WM reductions
	Nagy et al. (2003)	n = 9, 11y, mean 29w	Diffusion Tensor Imaging (DTI)	Disturbances in the internale capsule and CC
	Reiss et al. (2004)	n = 65, 8y, mean 28w	Semiautomatic volumetry	Global WM reductions
	Inder et al. (2005)	n = 119, mean 40w, ≤ 32w	Automatic volumetric analysis	Total brain myelin volume reduction
	Giménez et al. (2006a)	n = 50, 14y, ≤ 32w	Voxel-based morphometry (VBM)	Periventricular WM damage / WM decrease in several regions
Lateral ventricles	Peterson et al. (2000)	n = 25, 8y, ≤ 33w	Manual volumetry (ROI)	Increased occipital & temporal horns
	Nosarti et al. (2002)	n = 72, 15y, < 33w	Stereology	Increased lateral ventricles volume
	Peterson et al. (2003)	n = 10, near term (mean 35w), mean 29w	Manual volumetry (ROI)	Increased midbody, occipital & temporal horns
	Kesler et al. (2004)	n = 73, 9y, mean 28w	Semiautomatic volumetry	Enlarged lateral ventricular cerebrospinal fluid volumes
	Allin et al. (2004)	n = 32, 23y, VLBW (mean 1260g)	Manual volumetry (ROI)	Increased lateral ventricle volumes
	Fearon et al. (2004)	n = 33, 23y, VLBW (< 1500g)	Stereology	Increased lateral ventricle volumes

Continue….

	Study	Preterm / VLBW sample n, age at scan, GA or birthweight	Technique/Approach	Specific findings
Corpus Callosum (CC)	Peterson et al. (2000)	n = 25, 8y, ≤ 33w	Manual volumetry (5 ROIs)	Reductions in: splenium, isthmus, midbody, anterior body & rostrum/genu
	Argyropoulou et al. (2003)	n = 33, 1y, mean 31w; with PVL	Manual area measurement (ROI)	Reduction of the CC
	Nosarti et al. (2004)	n = 66, 14-15y, < 33w	Manual area measurements (4 ROIs)	Reduction total CC, posterior & mid-posterior quarter
	Fearon et al. (2004)	n = 33, 23y, VLBW (< 1500g)	Stereology	Reduction of posterior CC
Gray Matter (GM)	Inder et al. (1999)	n = 10, first 16 days after birth, mean 29w; with PVL in neonatal period	Automatic volumetric analysis	Reduction in cortical GM
	Peterson et al. (2000)	n = 25, 8y, ≤ 33w	Manual volumetry (ROI)	Reduction in sensoriomotor, premotor, mid-temporal, parieto-occipital & subgenual cortical regions
	Nosarti et al. (2002)	n = 9 , 15y, < 33w; with IVH & ventricular dilation in neonatal period	Stereology	Decrease in cortical GM
	Peterson et al (2003)	n = 10, near term (mean 35w), mean 29w	Manual volumetry (ROI)	Reduction in sensoriomotor, parieto-occipital & inferior occipital cortical regions
	Isaacs et al. (2003)	n = 11, 15y, VLBW (≤ 1500g)	Voxel-based morphometry (VBM)	Decrease of cortical GM in the right ventral extrastriate cortex
	Reiss et al. (2004)	n = 65, 8y, mean 28w	Semiautomatic volumetry	Reduced cerebral GM volume
	Kesler et al. (2004)	n = 73, 9y, mean 28w	Semiautomatic volumetry	Reduced subcortical GM
	Inder et al. (2005)	n = 119, mean 40w, ≤ 32w	Automatic volumetric analysis	Reduction in cortical GM
	Kesler et al. (2006)	n = 73, 8y, mean 28w	Gyrification index	Increased temporal lobe gyrification

PVL: periventricular haemorrhage; IVH: intraventricular haemorrhage
Continue….

	Study	Preterm / VLBW sample n, age at scan, GA or birthweight	Technique/Approach	Specific findings
Gray matter structures	Peterson et al. (2000)	n = 25, 8y, ≤ 33w	Manual volumetry (ROI)	Reduction of the hippocampus amygdala, putamen, globus pallidus, & cerebellum
	Isaacs et al. (2000)	n = 11, 13y, VLBW (mean: 998g)	Volumetry	Reduction of the hippocampus
	Abernethy et al. (2002)	n = 86, 15-16y, < 1500g	Semiautomatic volumetry	Reduction of the hippocampus & caudate nucleus
	Nosarti et al. (2002)	n = 72, 15y, < 33w	Stereology	Reduction of hippocampus bilaterally
	Argyropoulou et al. (2003)	n = 33, 1y, ≤ 36	Manual volumetry (ROI)	Reduction of the cerebellum
	Giménez et al. (2004)	n = 22, 13y	Voxel-based morphometry (VBM) & ROI analysis	Reduction of left hippocampus & thalamus
	Giménez et al. (2005)	n = 14, adolescents, mean 29w	Stereology	Reduction of left hippocampus
	Allin et al. (2005)	n = 67, 14-15y, < 33w	Stereology	Reduction of the cerebellum
	Giménez et al. (2006b)	n = 30, 14y, < 33w	Voxel-based morphometry (VBM) & ROI analysis	Reduction of thalamus bilateral

2 APPROACH

The specific background for each of the studies carried out in this thesis, is briefly summarized in the following paragraphs.

VLBW subjects are at high risk of brain injury in the perinatal period, and consequently of later neurological, cognitive, and behavioural impairments (Taylor et al. 2000, Fearon et al., 2004). Between 30% and 40% of these survivors experience learning disabilities or behavioural problems during their early school years (Abernethy et al. 2002), which persist into adolescence and are apparent even in those of normal intelligence and without neurological impairments (Hack et al. 2002). In adolescence cognitive task difficulties increase. In consequence memory functioning becomes more critical and its influence on school performance rises. There have been few studies about verbal, visual and everyday memory in VLBW adolescents, and these are contradictory. Moreover the effect of intelligence on memory performance has often been neglected. These facts enhance the importance to study memory functioning in VLBW adolescents, relating it to their IQ (study 1).

Our first study demonstrated that not birthweight but gestational age per se is a good predictor for general cognitive performance and this result took us to explore in the sample of preterm born subjects the underlying brain structure, which could be responsible for this deficit.

Prematurity involves a high risk of cerebral lesions. In preterm children, cerebral gray and white matter volume reductions have been described (Peterson et al. 2000). Abnormalities of white matter, especially common in the corpus callosum, persist at long term follow-up (Stewart & Kirkbride 1996, Stewart et al. 1999), and can account for the behavioural impairments shown by preterm born adolescents (Stewart et al. 1999). Corpus callosum is easy to measure and reflect the general cognitive performance (Peterson et al. 2000).

In adolescents and using quantitative MRI techniques, studies in literature are scarce. To our knowledge only one investigation group applied this method to explore corpus

callosum anomalies in preterm born adolescents (Nosarti et al. 2004). These authors particularly described corpus callosum reductions of the posterior regions and related these reductions with verbal IQ (but assessed at 8-years of age) and phonetic verbal fluency. But there are no studies that asses different cognitive abilities and relate it to corpus callosum volume reductions in preterm born adolescents (study 2).

Gestational age is a predictive factor for global cognitive performance in adolescence (study 1), and has a strong correlation with FIQ and corpus callosum reduction (study 2). These results took us to investigate the importance of being born at different gestational ages for long term corpus callosum atrophy, as well as for general cognitive performance.

Gestational age has been associated with corpus callosum damage in preterm-born babies (Anderson et al. 2005). These authors measured the length of the corpus callosum in 64 very preterm infants at birth, and established three different groups depending on the gestational age: 23-25 weeks, 26-29 weeks and 30-33 weeks. Results were compared with the expected growth rate from antenatal data. The authors concluded that the corpus callosum grows at a much lower rate post-natally than in utero among very preterm infants. There is no study in literature that specifically explores corpus callosum reductions and general cognitive performance in adolescents regarding different gestational ages at birth (study 3).

In summary, the aims of the studies carried out in this thesis are:

1) To explore memory deficits in relation to intelligence in VLBW adolescents.
2) To study corpus callosum abnormalities and cognitive performance in adolescents being born at 33 weeks or less.
3) To explore the specific influence of gestatinal age on corpus callosum reduction and cognitive outcome in preterm born adolescents.

3 METHODOLOGY

In the following section we go through those aspects which the three studies described in this thesis have in common.

3.1. 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 2500g, gestational age < 37 weeks, and current age between 11 and 17 years.

The Paediatric Division of this hospital registered 857 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). 30 cases did not fulfil inclusion criteria/clinical data were missing/or they died. 88 cases were excluded either because of updated address or telephone number were not available, or because of subjects were not found by phone or mail. 14 cases declined to enroll (or parents refused permission). 50 subjects were included in our sample.

In order to increase the number of preterm subjects born at a gestational age < 33, we contacted the Pediatric Division of the Hospital Vall d'Hebron and selected subjects with antecedents of prematurity from the population born between 1988 and 1989 at this hospital. The inclusion criteria were the same as the above mentioned, changing only the gestational age. The preterm born population at this hospital comprised 213 subjects. Hundred and thirteen cases did not fulfil inclusion criteria/clinical data were missing/ or they died. Either because of updated address or telephone number was not available, or because of subjects were not found by phone and mail, 56 cases were excluded. 11 cases declined to enroll (or parents refused permission). 33 subjects were included in our sample.

The total sample for our research project comprised 83 preterm born subjects. Additional information obtained from the clinical histories described that 41% of these subjects presented apneas and/or hyaline membrane syndrome, and administration of oxygen, indicating a possible risk of perinatal hypoxia; and 6% additionally presented intraventricular haemorrhage (IVH) grade III, indicating ventricular dilation.

The clinical histories used for these studies frequently gave fragmented information about the clinical status at birth and until discharge of the subjects. Additionally, both hospitals did not use the same protocols when applying the diagnostics. These facts hinder the correct and homogeneous characterization of the sample.

Table 4: Characteristics of the preterm born sample (N = 83)

Number	CA (y)	GA (w)	BW (g)	Apgar 1’	Apgar 5’	Apgar 10’	Umbilical artery pH	Respiratory distress	O_2	Tone	Reflexes	ECO/CT
1	9	33	2380	6	9	9	-	-	-	Hypotonia	Weak	N
2	10	33	1430	8	9	9	-	-	-	Hypotonia	N	N
3	10	35	2630	6	9	10	-	-	No	Hypotonia	Weak	N
4	10	35	2700	6	7	10	-	-	Yes	Hypotonia	N	-
5	10	34	2700	8	5	10	-	-	-	-	-	-
6	11	29	1155	4	7	9	7,34	Yes	Yes	Hypotonia	-	-
7	11	29	1180	6	9	-	7,29	Yes	Yes	Hypotonia	N	N
8	11	33	2000	9	10	10	-	-	-	Hypotonia	N	N
9	11	28	950	2	10	10	7,38	Yes	Yes	Hypotonia	Absent	IVH III bilateral
10	11	31	1470	3	9	10	7,3	Yes	Yes	Hypotonia	N	IVH III
11	11	33	1250	2	9	9	-	-	Yes	Hypotonia	N	N
12	12	31	1360	9	10	-	N	No	No	N	N	-
13	12	25	850	9	10	-	7,29	Yes	Yes	N	-	IVH III
14	12	32	1860	4	8	10	-	Yes	Yes	-	Weak	-
15	12	31	1560	7	10	-	N	Yes	Yes	Hypotonia	N	N
16	12	33	1450	7	10	-	-	-	-	Hypotonia	Absent	IVH I
17	12	34	1830	4	9	-	-	-	Yes	Hypotonia	Weak	N
18	12	34	2080	3	7	10	-	-	Yes	Hypotonia	Absent	N
19	12	32	1200	4	10	-	7,22	Yes	Yes	Hypotonia	N	N
20	12	27	890	1	7	8	7,05	Yes	Yes	Hypotonia	Absent	Cortical/subcortical atrophy

CA: chronological age; GA: gestational age; BW: birthweight; Apgar Test; Respiratory distress include: apnea, cyanosis or hyaline membrane disease; ECO: ecography; CT: computed tomography; -: no data; N: normal; IVH: Intraventricular haemorrhage

Continue….

Number	CA (y)	GA (w)	BW (g)	Apgar 1’	Apgar 5’	Apgar 10’	Umbilical artery pH	Respiratory distress	O_2	Tone	Reflexes	ECO/CT
21	12	29	1200	-	-	-	7,31	Yes	Yes	Hypotonia	Absent	N
22	12	32	1220	7	9	10	7,27	Yes	Yes	Hypotonia	Weak	N
23	13	31	1220	3	7	9	7,6	Yes	Yes	Hypotonia	Weak	-
24	13	28	870	3	7	10	7,11	Yes	Yes	-	-	N
25	13	28	800	4	8	-	-	Yes	Yes	N	-	N
26	13	31	1060	3	7	8	7,31	Yes	Yes	Hypotonia	Absent	-
27	13	31	1670	8	9	-	7,18	Yes	Yes	Hypotonia		IVH III, PVL
28	13	28	820	3	7	8	-	Yes	Yes	N		IVH I
29	13	31	1420	3	7	7	7,24	Yes	Yes	Hypotonia	-	IVH I bilateral
30	13	25	840	2	8	9	-	Yes	Yes	Hypotonia	Absent	IVH III bilateral
31	13	32	1800	8	10	-	7,24	No	No	N	N	-
32	14	26	760	9	10	10	7,27	Yes	Yes	N	-	IVH II-III
33	14	32	1470	6	7	9	-	Yes	Yes	-	N	IVH I (left)
34	14	31	2160	-	2	-	-	Yes	Yes	Hypotonia	Absent	IVH III bilateral, PVL
35	14	29	1380	8	10	-	-	No	No	N	N	N
36	14	31	1600	7	9	-	-	No	No	N	N	-
37	14	32	1650	7	8	-	7,2	No	No	N	N	-
38	14	32	2010	9	10	10	7,33	No	No	N	N	-
39	14	32	1700	7	9	-	-	No	No	N	N	-
40	14	29	1130	7	8	-	7,34	Yes	Yes	-	N	PVL

CA: chronological age; GA: gestational age; BW: birthweight; Apgar Test; Respiratory distress include: apnea, cyanosis or hyaline membrane disease; ECO: ecography; CT: computed tomography; -: no data; N: normal; IVH: Intraventricular haemorrhage; PVL: periventricular leukomalacia

Continue….

Number	CA (y)	GA (w)	BW (g)	Apgar 1’	Apgar 5’	Apgar 10’	Umbilical artery pH	Respiratory distress	O_2	Tone	Reflexes	ECO/CT
41	14	29	1200	3	9	-	N	Yes	Yes	Hypotonia	Weak	SAH
42	14	34	3000	1	3	6	-	-	Yes	Hypotonia	Absent	N
43	14	34	2350	7	9	-	-	-	No	-	Weak	-
44	14	36	2500	-	-	-	-	-	-	-	-	-
45	14	36	2800	9	10	10	-	-	No	N	N	N
46	14	34	2240	9	10	10	-	-	-	-	-	-
47	15	32	1570	7	9	-	7,2	Yes	Yes	-	Absent	-
48	15	29	1230	5	8	10	7,14	Yes	Yes	Hypotonia	Weak	-
49	15	27	900	6	8	-	-	Yes	Yes	-	Weak	-
50	15	31	1330	5	7	-	-	Yes	Yes	-	-	-
51	15	27	1240	5	8	-	7,35	Yes	Yes	Hypotonia	N	-
52	15	31	1030	-	-	-	-	Yes	Yes	-	-	-
53	15	30	1400	6	6	-	7,3	Yes	Yes	-	Weak	-
54	15	29	1300	4	6	-	-	Yes	Yes	-	Absent	-
55	15	33	2860	10	-	-	-	Yes	-	Hypotonia	Weak	-
56	15	36	2200	8	10	-	-	-	-	N	N	N
57	15	31	1270	7	9	-	6,9	Yes	Yes	Hypotonia	Weak	IVH I
58	15	31	1530	4	6	-	7,16	Yes	Yes	-	changeable	IVH I bilateral
59	15	29	1230	6	7	-	7,14	Yes	Yes	-	-	IVH I
60	15	31	1800	3	7	-	-	Yes	Yes	-	N	IVH III, PVL

CA: chronological age; GA: gestational age; BW: birthweight; Apgar Test; Respiratory distress include: apnea, cyanosis or hyaline membrane disease; ECO: ecography; CT: computed tomography; -: no data; N: normal; SAH.: subarachnoid haemorrhage; IVH: Intraventricular haemorrhage; PVL: periventricular leukomalacia

Continue….

Number	CA (y)	GA (w)	BW (g)	Apgar 1’	Apgar 5’	Apgar 10’	Umbilical artery pH	Respiratory distress	O_2	Tone	Reflexes	ECO/CT
61	15	27	700	4	-	-	7,28	Yes	Yes	N	N	-
62	15	27	1220	5	8	-	7,35	No	No	N	N	-
63	15	31	1600	6	8	-	7,31	Yes	Yes	N	N	-
64	15	32	1390	8	10	-	-	No	No	N	N	-
65	15	32	1670	8	10	-	-	No	No	N	N	N
66	15	32	1750	9	10	-	-	No	No	N	N	N
67	15	32	1510	8	9	-	-	No	No	N	N	N
68	15	32	1450	7	9	-	7,26	No	No	N	N	-
69	16	30	1430	7	8	-	-	Yes	Yes	-	N	N
70	16	32	1610	4	7	-	-	Yes	Yes	-	-	N
71	16	34	2280	10	-	-	-	-	Yes	Hypotonia	-	IVH I
72	16	34	2120	9	10	-	-	-	-	Hypotonia	N	N
73	16	27	690	-	-	-	7,24	Yes	Yes	-	-	IVH II
74	16	30	1100	4	8	-	7,29	Yes	Yes	N	N	-
75	16	30	1190	6	8	10	-	No	No	N	N	N
76	16	31	1330	6	9	10	7,38	No	No	N	N	-
77	16	32	1700	9	10	-	-	No	No	N	N	-
78	16	32	1530	7	8	-	-	No	No	N	N	N
79	17	32	1400	4	6	-	7,39	Yes	Yes	Hypotonia	Absent	-
80	17	28	950	3	9	-	7,44	Yes	Yes	N	N	-
81	17	28	1200	5	8	9	7,27	Yes	Yes	-	-	SAH
82	17	29	1000	2	4	4	6,39	Yes	Yes	-	-	-
83	18	30	1350	3	6	9	7,31	Yes	Yes	Hypotonia	-	IVH I

CA: chronological age; GA: gestational age; BW: birthweight; Apgar Test; Respiratory distress include: apnea, cyanosis or hyaline membrane disease; ECO: ecography; CT: computed tomography; -: no data; N: normal; IVH: Intraventricular haemorrhage; SAH: subarachnoid haemorrhage

Exclusion criteria applied in our studies were: mental deficiency (FIQ < 70); history of focal traumatic brain injury, cerebral palsy or other neurological diagnosis; motor or sensorial disability that precluded neuropsychological assessment; metal orthodontic prosthesis; and claustrophobia or anxiety levels high enough to require sedation.

The control group was composed by relatives or acquaintances of the study sample or of university students. These subjects were all full-term with normal pre-, peri- and postnatal data. Patients and controls were matched by age, gender, educational level, socio-economical status and ethnic origin.

The study was approved by the Ethics Committee of the University of Barcelona and all the subjects or their family gave written informed consent prior to participating in the study.

3.2. Neuropsychological assessment

The same psychologist (A. N.) assessed all the participants in the study in two different sessions of 90min. Intelligence and several types of specific cognitive abilities were evaluated. General cognitive performance was assessed with the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler 1974) or the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler 1997), depending on the subject's age.

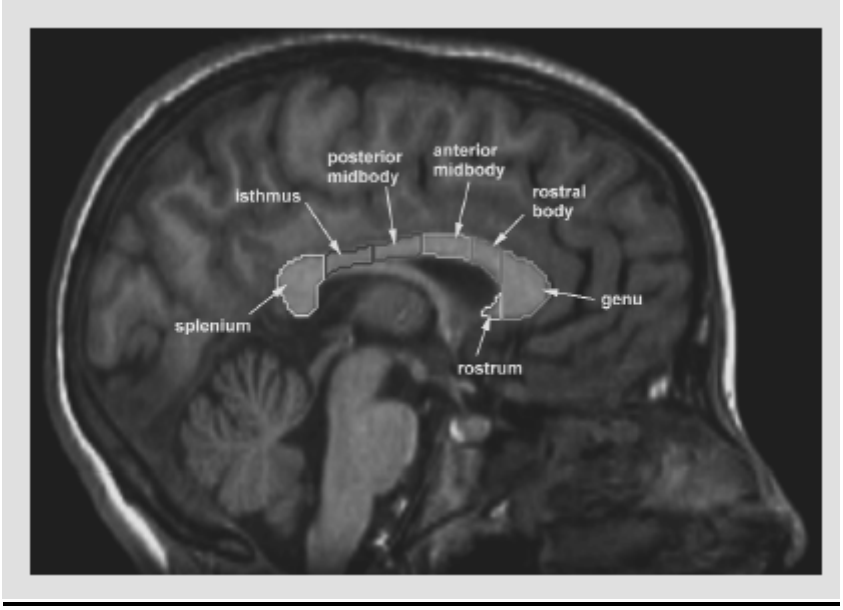
Verbal learning and memory were assessed by using a modified version of the Auditory Verbal Learning Test (AVLT) (Rey 1958); visual memory with the retention task of the Complex Figure Test (CFT) (Rey 1980); and everyday memory with the Rivermead Behavioral Memory Test (RBMT) (Wilson 1985). Visuoperceptive and visuoconstructive functioning were evaluated with the copy task of the CFT (Rey 1980).

Phonetic verbal fluency was assessed with a modified version of the Controlled Oral Word Association Test (COWAT) (Benton & Hamsher 1989); and for the category verbal fluency, a task was used in which participants were required to produce as many names of animals as they could within a time frame (1min).

3.3. Magnetic Resonane Imaging (MRI) acquisition and analysis

T1 weighted morphological images were acquired on a 1.5 T Signa GE (Milwaukee, WI) using a 3D FSPGR-IR sequence (TR = 12 ms; TE = 5.2 ms; TI = 300 ms; 1 NEX; FOV = 24 x 24 cm; matrix size = 256 x 192) yielding partitions of 1.5 mm of thickness. All the images were reoriented in order to place them in the same position. A midsagittal slice in which the anterior and posterior commissures, as well as the fornix were clearly identifiable was selected in order to draw the corpus callosum. This was semiautomatically segmented in 7 parts (rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus and splenium) following the approach described by Witelson (1989), using Analyze 5.0 / 6.0 (Biomedical Imaging Resource, Mayo Clinic) (see figure below). The area of each part was calculated by computer. To obtain the total callosum area a sum of the different parts was performed.

In addition, images were segmented using SPM2 (Wellcome Department of Cognitive Neuroscience, London, UK) running on Matlab 6.0 (Mathworks, Natick, MA) in order to obtain gray matter, white matter and cerebrospinal fluid volumes. These three values were added together to obtain the intracranial volume for each subject.
We also obtained the mid-sagittal area to correct corpus callosum size.



Corpus callosum segmentation following Witelson (1989).

4 RESULTS

4.1. STUDY 1: MEMORY PERFORMANCE IN VLBW ADOLESCENTS

Objective

The aim of the present study was to investigate memory functioning in a sample of VLBW adolescents, relate it to their general cognitive performance, and to determine factors that may predict them.

Participants

The sample for this study comprised 44 preterm born adolescents with a birthweight < 1500g (VLBW). Forty-four controls were matched to this group for comparison; one by one and attending to the criteria described in the "METHODOLOGY"
Characteristics of the sample are detailed in Table 1.

Table 1: Characteristics of the very-low-birth-weight (VLBW) group and controls

	VLBW	CONTROLS
	Mean (SD) (Range)	Mean (SD) (Range)
Birth weight (g)	1149.67 (227.93) (690-1470)	3438.95 (429.8) (2400-4300)
Gestational age (weeks)	29.25 (1.94) (25-32)	39.73 (1.44) (37- 43)
Multiple birth	19 yes/25 no	-
Gender (M: male/ F: female)	22 M / 22 F	23 M/ 21 F
Age at assessment (years)	14.14 (1.85) (11-18)	14.43 (1.91) (11-18)

Neuropsychological assessment

Verbal learning and verbal, visual and everyday memory, were evaluated for memory functioning. Additionally we explored intelligence in order to observe its influence on memory performance. The tests used for this assessment are described in the section "METHODOLOGY".

Procedure

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS Win., v. 11.0). First we used one-way analysis of variance (ANOVA) between groups, applying Bonferroni correction, setting the significance threshold at $p < .007$. Analysis of covariance (ANCOVA), using FIQ as covariate, removed the effect of intelligence on memory performance. A stepwise multiple linear regression analysis tested the impact of different clinical and demographic factors on the neuropsychological results. Birth weight, gestational age, assisted ventilation, IVH, Apgar score at one and five minutes, and gender were entered in the analysis. Significance threshold for this analysis was set at $p < .05$.

Results

The results of all the administered tests were worse for VLBW subjects than controls. Although within normal ranges, the VLBW group showed significantly lower mean FIQ ($p < .001$), VIQ ($p < .001$), and PIQ ($p = .003$) than the controls. On the memory tests, their performance on verbal learning, recognition and visual memory was not significantly different to the controls. In contrast in the RBMT the VLBW group performed significantly lower ($p = .004$), but applying the ANCOVA analysis these everyday memory deficits lost significance ($p = .075$). (Table 2)

The regression analysis showed that gestational age predicted performance on FIQ ($p = .03$); and everyday memory (global score) ($p = .01$). In contrast birth weight was not a predictive factor for any cognitive variable.

Table 2: Neuropsychological performance comparisons with and without FIQ as a covariate

		VLBW		CONTROLS		ANOVA		ANCOVA	
		M	SD (Range)	M	SD (Range)	F	p	F	p
WISC-R / WAIS-III:	FIQ	100.05	15.78 (72 -135)	113.18	10.15 (88-125)	21.58	< .001	-	-
	VIQ	103.07	19.27 (51-145)	117.77	10.60 (95-141)	19.67	< .001	-	-
	PIQ	97.34	12.61 (74 -125)	105.5	10.67 (92-133)	9.57	< .003	-	-
AVLT:	Learning	52.00	7.76 (36 -66)	55.50	6.41 (42-67)	5.32	ns	1.94	ns
	Recognition	13.95	1.12 (11-15)	14.36	1.06 (10-16)	3.10	ns	0.52	ns
CFT:	Visual memory	21.99	5.64 (10-36)	24.55	5.55 (11.5-36)	4.50	ns	1.23	ns
RBMT:	Everyday memory	10.43	1.50 (9-12)	11.20	0.82 (9-12)	8.97	< .004	3.25	ns

After Bonferroni correction significant threshold was set at p < .007. WISC-R: Wechsler Intelligence Scale for Children-Revised; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; AVLT: Auditory Verbal Learning Test; CFT: Complex Figure Test; RBMT: Rivermead Behavioural Memory Test; FIQ: Full Scale Intelligence Quotient; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; ANOVA = analysis of variance; ANCOVA = analysis of covariance

Discussion

Research findings have described a disadvantage of VLBW adolescents in verbal memory (specifically verbal learning and recognition) and visual memory functioning (Taylor et al. 2004). However, a normal performance have also been described in verbal learning (Rushe et al., 2001), recognition and visual memory (Isaacs et al. 2000); our results agree with these last findings.

Global intelligence can influence the performance of specific abilities, and this effect has often been neglected in studies reporting long term memory deficits of low birth weight subjects. Isaacs et al. (2000) reported that VLBW adolescents perform worse in everyday memory and found no relationship between these deficits and the low scores in VIQ. We also observed a low everyday memory and VIQ, but in contrast to these authors we additionally found significant low mean PIQ and FIQ scores. Moreover we observed that this intelligence index accounted for the RBMT performance.

The ANCOVA showed that FIQ explains the low performance in everyday memory functioning, and the regression analysis showed that gestational age is a good predictor of FIQ, indicating that prematurity per se (independent of birthweight) can affect global cognitive performance. Although the mean IQ of the VLBW subjects was normal, this group showed a wide range of IQ scores, basically due to the low scores in the inferior range.

4.2. STUDY 2: CORPUS CALLOSUM SIZE AND NEUROPSYCHOLOGIC IMPAIRMENT IN ADOLESCENTS WHO WERE BORN PRETERM

Objective

The aim of the present study was to investigate the possible corpus callosum (CC) reductions and cognitive deficits in adolescents who were born preterm

Participants

The sample for the present study consisted of 25 adolescents born before 33 weeks gestational age.

Twenty-five subjects comprised the control group and were matched to the preterm group attending to the criteria described in "METHODOLOGY".

Characteristics of the sample are detailed in Table 1.

Table 1: Characteristics of the preterm group and controls

	PRETERM	CONTROLS
	Mean (SD) (Range)	Mean (SD) (Range)
Gestational age (weeks)	29.48 (2.52) (25-32)	39.9 (1.41) (38-42)
Birth weight (g)	1236.8 (549.7) (690-2860)	3403.2 (538.9) (1450-4180)
Gender (M: male/ F: female	15 M/ 10 F	13 M/ 12 F
Age at assessment (years)	13.44 (1.94) (11-18)	13.96 (2.51) (10-18)

MRI acquisition and analyses

This procedure is described in the section "METHODOLOGY". One rater drew the region of interest. Twenty subjects were assessed on two separate occasions so as to check intrarater reliability, which was .97.

Neuropsychological assessment

As in the first study, we evaluated verbal learning, visual memory, everyday memory and intelligence. Moreover, we extended the specific cognitive assessment choosing some of the main studied cognitive abilities in preterm born subjects. We included the evaluation of the visuoperceptive and visuoconstructive ability, as well as verbal fluency (phonetic and category). These cognitive functions were assessed using the tests mentioned in the section "METHODOLOGY".

Procedure

Statistical analyses were performed using SPSS 10.0 for windows. Student's t tests for independent samples were used to explore for differences in morphological and neuropsychological measures between the two groups. Pearson's product moment correlations were performed for the preterm group to assess possible associations between the cerebral measures and low neuropsychological performance. Additionally we performed a stepwise multiple linear regression analysis to explain CC size. The independent variables used were: age at assessment, gestational age, gender, peri/intraventricular haemorrhage, white matter volume, gray matter volume and whole brain volume. The significance threshold was set at $p < .05$ bilaterally for all the analyses.

Results

Corpus callosum measurements. Student's t test yielded a significant difference in the size of the whole corpus callosum between premature and full-term children ($p = .004$), the size of the corpus callosum being smaller in the preterm group. After adjusting the total corpus callosum size for the mid-sagittal area, the difference between groups remained significant ($p = .006$). In relation to the subregions, the splenium ($p < .001$),

genu (p = .004), and posterior midbody (p = .016) also achieved statistical significance. No differences between groups were observed in the rest of CC subregions. (Table 2) The regression analysis showed that only gestational age predicted CC size (p = .001).

Table 2: Corpus callosum areas and intracranial volumes

		PRETERM		CONTROLS			
		Mean	(SD)	Mean	(SD)	t	p
Corpus callosum (expressed in mm^2)	Total Corpus callosum	565.28	(111.71)	657.29	(101.54)	3.05	.004
	Rostrum	23.04	(9.44)	24.4	(7.44)	0.56	.580
	Genu	120.7	(30.8)	144.21	(23.38)	3.04	.004
	Rostral body	81.6	(23.44)	83.85	(19.54)	0.37	.710
	Anterior midbody	74.64	(14.13)	81.7	(12.7)	1.85	.070
	Posterior midbody	64.9	(9.55)	72.86	(12.74)	2.50	.016
	Isthmus	70.37	(17.37)	80.78	(22.77)	1.82	.075
	Splenium	129.99	(34.05)	169.49	(31.48)	4.26	<.001
Intracranial volumes (expressed in cm^3)	Total intracranial volume	1459.19	(131.76)	1579.08	(119.66)	3.37	<.001
	White matter	360.79	(45.75)	404.85	(37.37)	3.73	<.001
	Gray matter	784.86	(61.82)	834.72	(66.46)	2.74	.009
	Cerebrospinal fluid	313.54	(50.81)	339.51	(39.10)	2.03	.048

Neuropsychological results. The results of all the administered tests were worse for preterm children than controls. As in the first study the preterm group had an intelligence score within the normal range but showed significantly lower mean FIQ (p < .001), VIQ (p < .001), and PIQ (p = .004) than the controls. We observed normal performance in visual memory and an impaired verbal learning (p = .002) and everyday memory (p = .005). As regards the visuoperceptive and visuconstructive ability no

differences were observed. In verbal fluency, only category verbal fluency achieved statistical significance ($p < .001$). (Table 3)

Table 3: Neuropsychological results

		PRETERM		CONTROLS			
		Mean	(SD)	Mean	(SD)	t	p
WISC-R/ WAIS-III:	FIQ	96.04	16.8	113.28	12.16	4.16	<.001
	PIQ	93.48	12.95	104.84	13.84	3.01	.004
	VIQ	99.84	21.5	118.16	10.09	3.86	<.001
AVLT:	Learning	49.52	7.7	56.16	6.48	3.30	.002
CFT:	Visual memory	22.2	6.87	24.5	6.11	1.25	.217
	Visuoperceptive-constructive	33.14	3.22	34.56	2.06	1.86	.07
RBMT:	Everyday memory	10.12	1.616	11.20	0.816	2.98	.005
COWAT:	Phonetic verbal fluency	27.08	8.36	32.12	11.84	1.74	.088
	Category verbal fluency	16.4	4.09	21.32	4.05	4.27	<.001

Wechsler Intelligence Scale for Children-Revised; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; AVLT: Auditory Verbal Learning Test; CFT: Complex Figure Test; RBMT: Rivermead Behavioural Memory Test; FIQ: Full Scale Intelligence Quotient; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient

Correlations. Pearson's analysis revealed a significant correlation between total corpus callosum area and PIQ ($r = .50$) and everyday memory ($r = .47$). Gestational age at birth strongly correlated with total corpus callosum size ($r = .62$) and full intelligence quotient ($r = .65$). (Table 4, Figure 1 and 2)

Table 4: Correlations between MRI and neuropsychological data

	VIQ	PIQ	FIQ	AVLT	RBMT	Category fluency
Total Corpus callosum area	.27	.50**	.38	.04	.47*	.08
Intracranial volume	.33	.39	.43*	.01	.47*	.03
White matter	.31	.56**	.48*	.31	.52**	.23
Gray matter	.50*	.37	.56**	-.11	35	.06

VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; FIQ: Full Scale Intelligence Quotient; AVLT: Auditory Verbal Learning Test; RBMT: Rivermead Behavioural Memory Test; * $p \leq .05$; ** $p \leq .01$

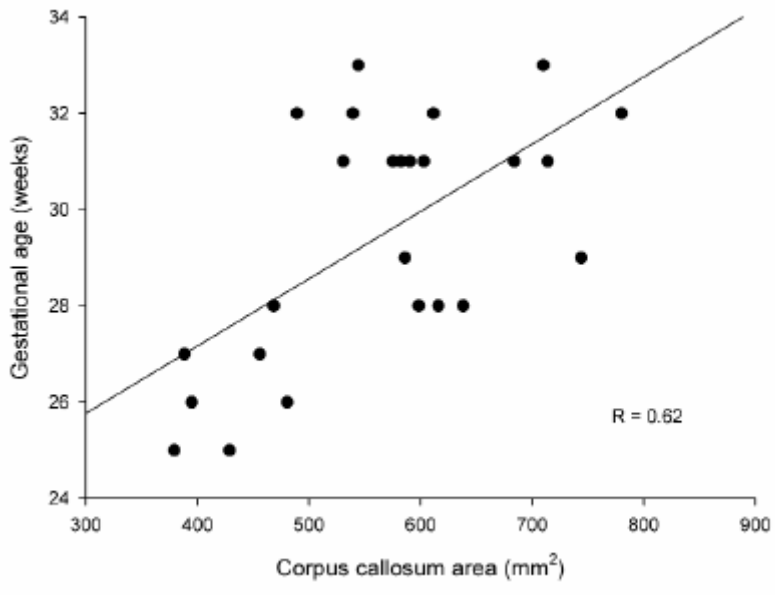


Figure 1: Correlation between gestational age and corpus callosum area

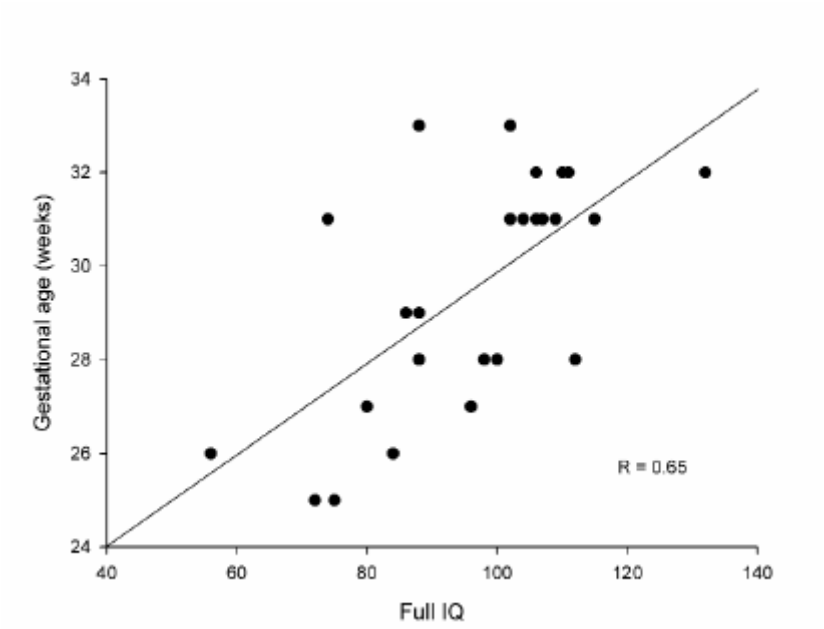


Figure 2: Correlation between gestational age and Wechsler Full-Scale IQ

Discussion

Corpus callosum reduction is an abnormality that is commonly found in MRI scans of prematures (Volpe 2001). Three previous studies have performed a volumetric analysis of the corpus callosum, segmenting it into five, four or three subregions (Peterson et al. 2000; Nosarti et al. 2004; Fearon et al. 2004). In the first study, authors found significant differences in preterm children compared to controls in all the analyzed parts of the corpus callosum (splenium, isthmus, midbody, anterior body and rostrum/genu), the anterior body being the most preserved region. In contrast to these generalized reductions, in our adolescents we found a more selective decreased volume mainly in the splenium and genu.

Nosarti et al. (2004), also exploring preterm adolescents, found that corpus callosum reductions were only observed in the posterior part. This difference could be related to the smaller chronological age of some subjects in our sample.

The third mentioned study, about 23-years-old VLBW individuals, also reported a reduction only in the posterior corpus callosum volume (Fearon et al. 2004).

The neuropsychological assessment also revealed significant differences between preterm and full-term adolescents.

Regarding intelligence there are previous reports describing low IQ levels in preterm born children (Olsén et al. 1998, Krägeloh-Mann et al. 1999, Burguet et al. 2000, Peterson et al. 2000, Böhm et al. 2002, Foulder-Hughes & Cooke 2003, Youngmei Peng et al. 2005). We extend these studies demonstrating that low IQ scores continue to be evident in preterm born adolescents, a finding previously suggested by Stewart et al. (1999) reporting impaired reading age in these subjects.

In relation to our results about the specific cognitive functions, we agree with some previous studies. We corroborate the results about deficits in verbal learning (Narberhaus et al. 2003, Giménez et al. 2004) and about a normal visual memory (Giménez et al. 2004). Regarding the low performance in everyday memory and category verbal fluency, but normal performance on phonetic verbal fluency, we extend Isaacs et al. (2000) and Allin et al. (2005) findings in VLBW adolescents respectively.

We obtained a very interesting relationship between corpus callosum size and gestational age at birth. The regression analysis showed that gestational age predicted corpus callosum size. Corpus callosum is an important component of white matter, which has been described as particularly vulnerable in the extremely premature infant. Infants of < 26 weeks' gestational age exhibited a pattern of cerebral white matter abnormalities, characterized by ventriculomegaly and a marked reduction in white matter volume (Inder et al. 2003).

4.3. STUDY 3: GESTATIONAL AGE AT PRETERM BIRTH IN RELATION TO CORPUS CALLOSUM AND GENERAL COGNITIVE OUTCOME IN ADOLESCENTS

Objective:

Our third study was aimed to further investigate the impact of different gestational ages at birth on corpus callosum volume reduction and general cognitive performance at adolescence.

Participants

The sample for this study comprised 64 adolescents born prior to 37 weeks' gestational age. In order to explore differences regarding their gestational age, we divided these subjects into four groups.

Fifty-three controls were enrolled for comparison following the criteria described in the "METHODOLOGY".

A description of the 4 preterm groups, and of the control group, is shown in Table 1.

Table 1: Characteristics of the preterm sample and controls

	PRETERMS (N = 64)				CONTROLS (N = 53)
	PRETERMS Group 1 N = 9 Mean (SD) (Range)	PRETERMS Group 2 N =19 Mean (SD) (Range)	PRETERMS Group 3 N = 25 Mean (SD) (Range)	PRETERMS Group 4 N =11 Mean (SD) (Range)	Group 5 N = 53 Mean (SD) (Range)
Gestational age (weeks)	26.4 (0.88) (25-27)	29.0 (0.78) (28-30)	31.72 (0.68) (31-33)	34.64 (0.92) (34-36)	39.6 (1.49) (37- 43)
Birth weight (g)	898.9 (202.5) (690-1240)	1139.7 (195.1) (800-1430)	1534.4 (361.1) (1030-2860)	2445.5 (302.2) (2080-3000)	3419 (424.3) (2340-4300)
Gender M: male F: female/	7M / 2F	8 M /11 F	11 M / 14 F	7 M / 4 F	26 M / 27 F
Age at assessment (years)	14.1 (1.45) (12-16)	14.6 (2.06) (11-18)	13.8 (1.78) (10-17)	13.55 (2.01) (10-16)	14.32 (2.21) (10-19)

MRI acquisition and analyses

This procedure is described in the section "METHODOLOGY". Moreover, in order to be more precise, in this study we also acquired the data of the total corpus callosum as well as each sub-region corrected to the mid-sagittal area. Inter- and intra-rater reliability, performed on 11 randomly selected independent ratings of total corpus callosum area, were 0.98 ($p < 0.0001$) and 0.95 ($p < 0.0001$) respectively.

Neuropsychological assessment

General cognitive performance (FIQ, PIQ and VIQ) was explored with the intelligence batteries described in the section "METHODOLOGY".

Procedure

Statistical analyses were performed using the SPSS 11.0 for windows. For all these analyses corpus callosum data were adjusted for mid-sagittal area. To test for differences in morphological and neuropsychological measures between the five groups, we used a one-way analysis of variance (ANOVA) with honestly significantly different (HSD) Tukey post-hoc. Pearson's product moment correlations were performed to explore the associations between cerebral measures, intelligence and gestational age. Significance threshold for the analyses was set at $p < .05$.

Results

Corpus callosum measurements. The ANOVA showed a significant difference between groups in total corpus callosum ($p<.001$). Regarding the subregions, the splenium ($p<.001$), genu ($p=.001$), isthmus ($p=.006$), posterior midbody ($p=.01$), and anterior midbody ($p=.02$) also reached statistical significance. All these significant differences were mainly due to the smaller measurements in preterm group 1 (≤ 27 weeks) compared to the control group and/or other preterm groups. Additionally, the post-hoc analysis showed a significant difference between preterm group 2 (gestational age between 28 and 30) and the control group for the splenium. No differences between groups were observed in rostrum and rostral body. (Table 2)

Table 2: One-way analysis of variance with honestly significantly different (HSD) Tukey post-hoc for corpus callosum areas and intracranial volumes

		Group 1 n = 9 Mean (SD)	Group 2 n = 19 Mean (SD)	Group 3 n = 25 Mean (SD)	Group 4 n = 11 Mean (SD)	Group 5 n = 53 Mean (SD)	F	p	p post-hoc
Corpus callosum corrected by mid-sagittal area (expressed in mm²)	Total Corpus callosum	3.445 (0.60)	4.298 (0.54)	4.286 (0.58)	4.673 (0.64)	4.467 (0.66)	6.17	< .001	.008 (1,2); .006 (1,3); < .001 (1,4;1,5)
	Rostrum	0.128 (0.03)	0.142 (0.05)	0.140 (0.06)	0.179 (0.06)	0.154 (0.45)	1.78	.14	
	Genu	0.718 (0.15)	0.976 (0.16)	0.947 (0.20)	1.007 (0.22)	1.002 (0.18)	4.88	.001	.006 (1,2); .01 (1,3); .006 (1;4); < .001 (1,5)
	Rostral body	0.540 (0.11)	0.645 (0.13)	0.598 (0.11)	0.677 (0.14)	0.586 (0.13)	2.4	.05	
	Anterior midbody	0.437 (0.04)	0.518 (0.08)	0.512 (0.09)	0.560 (0.12)	0.520 (0.10)	3.0	.02	.007 (1,4)
	Posterior midbody	0.401 (0.05)	0.511 (0.10)	0.491 (0.08)	0.530 (0.07)	0.4954 (0.09)	3.41	.01	.01 (1,2); .05 (1,3); .008 (1,4); .02 (1,5)
	Isthmus	0.388 (0.11)	0.509 (0.10)	0.531 (0.12)	0.582 (0.08)	0.547 (0.14)	3.86	.006	.03 (1,3); .006 (1,4); .005 (1,5)
	Splenium	0.833 (0.25)	0.997 (0.18)	1.067 (0.19)	1.122 (0.22)	1.164 (0.21)	6.3	< .001	.03 (1,3); .02 (1,4; 2,5); <.001 (1,5)
Intracranial volumes (expressed in cm³)	White matter	312090.8 (57942.9)	377197.1 (57942.9)	372016.8 (52090.2)	389824.6 (45057.9)	381568.2 (35713.4)	5.51	< .001	.003 (1,2); .004 (1,3); .001 (1,4); < .001 (1,5)
	Gray matter	733390.9 (54683.7)	771292.1 (133165.7)	778113.8 (72113.5)	780336.5 (69904.0)	783905.5 (65474.7)	0.77	.55	
	Cerebrospinal fluid	309307.0 (87707.0)	339976.6 (115093.7)	295124.6 (56761.1)	303166.8 (66429.1)	295507.13 (56544.2)	1.46	.22	
	Intracranial volume	1354789 (174094.0	1488466 (164942.3)	1445255 (146393.9)	1473328 (148372.0)	1460981 (134603.6)	1.39	.24	

M: mean; SD: standard deviation

Intelligence quotient assessment. The ANOVA showed significant differences in mean FIQ ($p < .001$), VIQ ($p < .001$), and PIQ ($p < .001$), mainly due to the poor performance of group 1 (≤ 27 weeks) compared to the control group and to some other preterm groups. Additionally, premature subjects in group 2 (GA between 28 and 30) showed a significantly low performance in comparison to controls on both FIQ ($p = .005$) and VIQ ($p = .006$). Furthermore, premature subjects in group 3 (GA between 31 and 33) presented significant differences compared to the controls on FIQ ($p = .02$). (Table 3)

Table 3: One-way ananlysis of variance with honestly significantly different **(**HSD**)** Tukey post hoc for intelligence

		Group 1 n =9 M (SD)	Group 2 n = 19 M (SD)	Group 3 n =25 M (SD)	Group 4 n =11 M (SD)	Group 5 n = 53 M (SD)	F	p	p post-hoc
WISC-R / WAIS-III	FIQ	91.4 (14.4)	100.5 (16.2)	103.2 (15.7)	112.7 (13.8)	113.6 (11.5)	7.94	< .001	.007 (1,4); < .001 (1,5); .005 (2,5); .02 (3,5)
	VIQ	98.7 (20.4)	102.4 (18.4)	106.7 (19.8)	118.6 (13.6)	117.3 (12.7)	5.79	< .001	.05 (1,4); .01 (1,5); .006 (2,5)
	PIQ	85.9 (6.6)	99.5 (12.8)	98.4 (13.5)	102.6 (14.7)	106.2 (10.7)	6.57	< .001	.04 (1,2); .02 (1,4); < .001 (1,5)

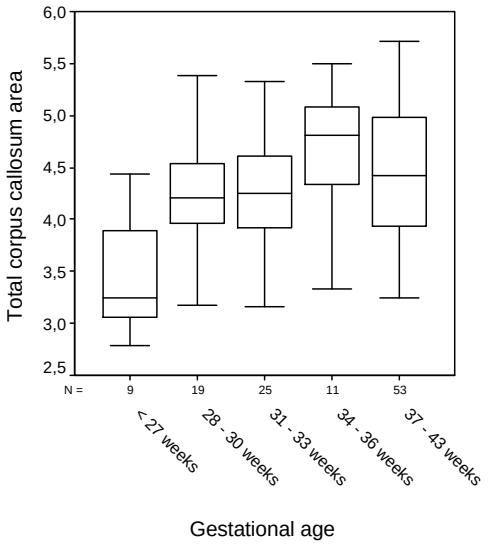
Correlations. Pearson's analysis revealed a significant correlation between total corpus callosum area and PIQ (r = .35) and FIQ (r = .27). Regarding the specific corpus callosum subregions, the genu and isthmus correlated with PIQ (r = .36; .27 respectively), and the splenium with VIQ (r = .36), PIQ (r = .31) and FIQ (r = .36). In relation to gestational age, this variable correlated with all three intelligence indexes (VIQ: r = .31; PIQ: r = .28; FIQ: r = .36). Moreover it appeared to be strongly correlated with total corpus callosum area (r = .53) and with all corpus callosum sub-regions (except the rostrum). (Table 4, Figure 1)

Table 4: Correlations between CC, intelligence and gestational age

CC	VIQ	PIQ	FIQ	GA
Total	.19	.35**	.27*	.53**
Rostrum	-.22	-.13	-.22	.20
Genu	.10	.36**	.21	.37**
Rostral body	.11	.23	.17	.29*
Anterior midbody	.10	.20	.14	.42**
Posterior midbody	-.00	.22	.09	.39**
Isthmus	.15	.27*	.22	.51**
Splenium	.36**	.31**	.38**	.45**
GA	.31*	.28 *	.36**	1
WM	.29*	.32**	.36**	.40**

CC: corpus callosum; VIQ: verbal intelligence quotient;
PIQ:performance intelligence quotient; FIQ: full intelligence quotient ;
GA: gestational age; WM: white matter; * $p \leq .05$; ** $p \leq .01$

Figure 1: Distribution of total corpus callosum data in relation to gestational age



Discussion

We report here that only preterm subjects born at a gestational age of 30 weeks or less present corpus callosum and total white matter volume reductions at adolescence, a finding that was most marked and generalized in those born at 27 weeks or below. This result could be related to the alteration of normal oligodendroglial development. Between 18 and 27 weeks of gestation the late oligodendrocyte progenitors are predominant, and between 28 and 41 weeks an increase in immature oligodendrocyte is expected accompanied by a progressive increase in myelin sheaths (Back et al. 2001). Preterm birth during the first mentioned period or very early in the second, could lead to the interruption of normal myelination development (Peterson et al. 2003), which may result in a less well myelinated corpus callosum, with a lower integrity of the fibres crossing in this structure.

The pattern of posterior reduction observed in the present study agrees with previous reports, which describe a volume decrease mostly in this part of the corpus callosum in preterms (Peterson et al. 2000; Nosarti et al. 2004). Our contribution is that this reduction is not a general feature of prematurity, but rather seems to depend on the gestational age. We extend this findings by demonstrating that only the more immature subjects (gestational age ≤ 27) present a significant reduction of the whole posterior part (posterior midbody, isthmus and splenium), while in adolescents born between 28 and

30 weeks this decrease is limited to the splenium. In higher gestational ages we did not find differences in corpus callosum size.

Although we have found a simultaneous affectation of the CC and IQ in subjects born before 31 weeks gestational age, our study also shows that individuals born with a gestational age between 31 and 33 weeks, even without corpus callosum reductions, have a low full IQ. This result agrees with the findings of Stewart et al. (1999), who report an impaired reading age (used as a surrogate of intelligence) in adolescents born before 33 weeks gestational age without any cerebral abnormality in their MRI scans. Better MRI methods, such as diffusion tensor imaging (DTI), could elucidate the relationship between brain structural and functional outcomes. Nagy et al. (2003) detected white matter microstructure anomalies in 11-years-old preterm subjects using DTI. Therefore, this method would be able to detect subtle white matter anomalies, which could explain the low IQ findings.

Nosarti et al. 2004 suggested a relationship between IQ (assessed at 8 years of age) and the posterior part of the corpus callosum (assessed at 14-15 years of age) in very preterm born subjects. Our results improve these data by revealing that the splenium is the specific sub-region which most strongly correlates with IQ (both explored in adolescence).

5 GENERAL DISCUSSION

Related to the neuropsychological results, our preterm sample show significant differences compared to the term-born subjects on general cognitive ability (IQ) and on some specific cognitive functions (everyd
ay memory, verbal learning and category verbal fluency). However, it is necessary to emphasize that their performance is always in the normal range, agreeing with the neuropsychological results described in section 1.2.

In this line it is reasonable that we have even observed the lack of significant differences for some other cognitive functions (verbal memory, visuoperceptive-constructive abilities, visual memory and phonetic verbal fluency). Similarly, in one of the most exhaustive studies, Rushe et al. (2001) reported that 75 preterm born adolescents showed normal performance on several measures of attention, memory, perceptual skill, and visuomotor and executive function, and impairment only in verbal fluency, stating that long-term cognitive deficits of preterm birth appear to be minor in this population.

Even though in everyday memory, verbal learning and category verbal fluency our preterm subjects perform in the normal range, they do always in the low part of the normal scale, establishing a difference with the control group that reaches statistical significance. We consider several reasons to explain this fact.

On one hand, it has been suggested that the IQ can influence specific cognitive ability. However it is unusual to find investigations that explicitly assessed this relationship. In the reviewed literature only four studies controlled for IQ in their analyses (Wolke & Meyer 1999, Isaacs et al. 2000, Taylor et al. 2000, Taylor et al. 2004) and the results are unclear. Sometimes statistical differences between prematures and controls disappeared, after IQ influence was removed. This is the case of language functions (Wolke & Meyer 1999, Taylor et al. 2000), perceptual-motor skills, verbal learning and attention (Taylor et al. 2000). In contrast, differences did remain significant after controlling for IQ for perception and constructional functions (Taylor et al. 2000), as well as for phonetic verbal fluency (Taylor et al. 2004) and everyday memory (Isaacs et al. 2000). Regarding executive functioning and visual memory the results are unclear; data from the same group showed contradictory results (Taylor et al. 2000, 2004). In our sample of study 1,

subjects scored worse than controls in everyday memory, but the significance disappeared after IQ was controlled by means of covariance analysis.
On the other hand, another possible explanation for the significant differences between preterms and controls could be the extent of white matter damage, with a consequent decrease in the speed of processing information and low cognitive performance. Verbal learning depends on with white matter circuitry of the phonological system, which is a component of the verbal working memory system (Clark & Wagner 2003). Besides, in agreement with this explanation, previous findings of our research group on long term consequences of preterm birth, showed significant correlations between a worse category verbal fluency and reductions of several thalamic nuclei connecting with prefrontal cortex (Giménez et al. 2006b). In study 2 all the preterm born subjects presented risk of hypoxia in the perinatal period, what could cause white matter lesions (Volpe, 2001b) and consequently can be related to their low cognitive performance.

Related to white matter commissural fibers, the corpus callosum (CC) is by far the largest in the human brain and contains more than 300 million fibers (Susumu et al. 2005). This commissure integrates the activities of the two hemispheres by transferring sensory and higher processed information (Giedd et al. 1996). As the difficulty of cognitive requirements increases, the integrated activity of both hemispheres and so the CC functioning becomes more important (Levy & Trevarthen 1981).

Regarding the specific relationship between general cognitive performance and CC in preterm born subjects, we observe a significant correlation between low IQ measures and thinning of the CC in preterm born adolescents (studies 2 & 3). There are two previous studies that similarly observed this relationship. Peterson et al. (2000) described significant correlations between low IQ measures and reduced volume of CC in 8 years-old subjects, and Nosarti et al (2004) reported that IQ (assessed at 8 years) was positively associated with total CC size in 14-15-years-old adolescents.

An interesting study of very long-term plasticity in prematurity comes from Fearon et al. (2004). These authors observed that CC is neither fully completed in 23-years-old preterm subjects. These results suggest that CC volume reduction is a long term sequela

of prematurity and that, despite gradual although slow corpus callosum growth during life span, the structural impairment produced by prematurity is not completely compensated in early adulthood. Therefore, it would be interesting to study preterm born adults in their fourth decade of life in order to explore the possibility of compensation at a later stage.

According to Volpe (2001a), corpus callosum development in humans begins at 9 weeks after conception. By bidirectional growth beginning at the interface of the genu and body, the entire CC develops (genu first, followed by the body, isthmus, splenium and rostrum). Subsequently CC growth happens through neuronal migration (3 to 5 months after conception) and establishment of the appropriate circuitry with important glial proliferation and differentiation (5 months after conception to postnatal years). From birth to years postnatally the CC continues to show morphologic changes related to the ongoing myelination of interhemispheric fibers. Giedd et al. (1996) suggested that the the posterior CC shows greater age related changes consistent with the continued maturation of higher association areas well into adulthood.

Analyzing the corpus callosum subdivisions, our studies showed a decrease of the anterior (genu) and posterior (posterior midbody and splenium) part. Related to the findings of Peterson et al. (2000) with preterm born children (8 years), and Nosarti et al. (2004) with preterm born adolescents (14-15 years), it is noteworthy that our sample comprised mainly 10 to 13-years-old subjects. This fact suggests a chronological age effect, explaining that our individuals show less CC reductions than in Peterson' study, but more CC affectation than in the work of Nosarti.
It seems that through life span the CC compensates its volume reduction differently for each of its parts. The anterior part could be the first to reach normal volume; and the posterior could be the last part to compensate, as has been suggested by Giedd et al (1996).

The immaturity at birth can be a contributing factor to corpus callosum reductions. Exploring the relationship between gestational age at birth, corpus callosum size and general cognitive performance (study 3), we observed that only preterm subjects born at a gestational age of 30 weeks or less present CC volume reductions. In concrete, those

subjects born at 27 weeks or less present a decrease of the total CC size as well as of the subregions previously found in study 2 (genu, posterior midbody and splenium), with an additional significant volume decrease in the anterior midbody and isthmus. The interruption of normal myelinated development during this period could be more stressing and lead to a more generalized CC volume decrease. Moreover, this preterm group showed the lowest IQ levels. So, these preterm born individuals are the group of risk for long-term brain structural abnormalities and functional deficits.

In contrast the subjects born between 28 and 30 weeks show a reduction only in the splenium, and adolescents born at a gestational age of more than 30 weeks do not show a CC volume reduction. It is important to mention however, that those subjects born between 28-30 and 31-33 weeks gestational age show lower IQ levels than full-term individuals; a fact that is not noticeable in those subjects born between 34 and 36 weeks.

We can not exclude that all these subjects could additionally have other subtle brain abnormalities not seen in our MRI study. More powerful techniques such as the diffusion tensor imaging (DTI), detecting alteration of the microstructure of white matter, may be used for this goal. This kind of disturbances has been found in preterm born (24 to 36 gestational age) newborns (Partridge et al. 2004).

In summary, our results in study 3 suggest a gestational age effect in the preterm born adolescent sample with a worse structural and functional outcome in the more immature individuals.

6 CONCLUSIONS

1. Preterm born adolescents show long term functional disadvantages and structural brain abnormalities, which could be more related to their gestational age than to their birthweight.

2. Adolescents with antecedents of prematurity show memory deficits that can be partially explained by their general cognitive dysfunction.

3. Intelligence, everyday memory, verbal learning and category verbal fluency are the functions most sensitive to the effects of prematurity.

4. Even though statistical significant differences are evident between preterm born subjects and controls, the mean scores of the preterm group are in the normal range.

5. The corpus callosum reduction, previously observed in preterm born infants, remain after at least 16 years of cerebral reorganization.

6. The genu, posterior midbody and splenium are the subregions which are most affected by prematurity.

7. Gestational age at birth is clearly related to corpus callosum abnormalities and low general cognitive performance. Subjects born at 27 weeks or less show a reduction of the total corpus callosum, genu, anterior midbody, posterior midbody, isthmus and splenium. Those born between 28-30 weeks present only a reduction of the splenium. After this age corpus callosum and intelligence quotient are similar to full-term controls.

SUMMARY OF THE THESIS

(in spanish)

RESUMEN DE LA TESIS:

Rendimiento neuropsicológico y anormalidades del cuerpo calloso en adolescentes con antecedentes de prematuridad

1. INTRODUCCIÓN

La definición de prematuro es la de recién nacido de edad gestacional inferior a 37 semanas (*American Academy of Pediatrics* y *American College of Obstetrics and Gynecology*, 2002). En relación al peso se utilizan con frecuencia las categorías: bajo peso (< 2500g), muy bajo peso (< 1500g) y extremadamente bajo peso (< 1000g) (Picard et al. 2000).

En la actualidad, la tasa de partos prematuros en España se sitúa entorno al 8% (Instituto Nacional de Estadística de España: www.se-neonatal.es), existiendo un incremento del 13% de los niños prematuros o de bajo peso en los últimos cuatro años (*Sociedad Española de Neonatología*: www.se-neonatal.es).

Siguiendo a Picard et al. (2000), las complicaciones médicas que pueden tener un mayor impacto sobre el desarrollo cerebral de los niños prematuros, son aquellas relacionadas con la inmadurez de sus sistemas respiratorio y cardiovascular, lo cual puede producir hipoxia. Además, y debido a la vulnerabilidad de la matriz germinal, pueden aparecer lesiones hemorrágicas peri/intraventriculares.

La mayoría de estudios neuropsicológicos acerca del rendimiento cognitivo general en sujetos prematuros indican una valoración significativamente más baja en esta población respecto al grupo control. Concretamente estos resultados se han obtenido en niños de muy bajo peso (Korkman et al. 1996; Böhm et al. 2002), así como en niños prematuros (Olsén et al. 1998; Pasman et al. 1998; Wolke & Meyer 1999; Burguet et al. 2000; Peterson et al. 2000; Foulder-Hughes & Cooke 2003; Hopkins-Golightly & Raz 2003; Youngmei Peng et al. 2005).

En cuanto a los adolescentes, la literatura es más escasa. Sin embargo, algunos estudios también muestran un coeficiente de inteligencia (CI) significativamente más bajo en

adolescentes de muy bajo peso al nacer (Taylor et al. 2000, 2004; Hack et al. 2002) ó con antecedentes de prematuridad (Stewart et al. 1999, Roth et al. 2001).

Asimismo, en relación a las funciones cognitivas específicas frecuentemente los estudios muestran que los sujetos prematuros rinden peor que los controles. Específicamente, en niños de bajo peso ó prematuros se han obtenido estos resultados para percepción y funciones constructivas (Korkman et al. 1996; Olsén et al. 1998; Pasman et al. 1998; Briscoe & Gathercole 2001; Foulder-Hughes & Cooke 2003), funciones verbales y lenguaje (Korkman et al. 1996; Wolke & Meyer 1999; Briscoe & Gathercole 2001), aprendizaje y memoria (Olsén et al. 1998; Pasman et al. 1998), y para las funciones frontales (Pasman et al. 1998; Böhm et al. 2002; Saavalainen et al. 2006). En estas dos últimas funciones se ha observado también un rendimiento significativamente más bajo en adolescentes con antecedentes de prematuridad (Allin et al. 2001; Giménez et al. 2004; Giménez et al. 2006b).

Por último, en relación a los adolescentes con bajo peso al nacer, Taylor et al. (2000, 2004) han demostrado que éstos rinden peor que los nacidos a término en todas las funciones específicas anteriormente citadas

Tanto en el rendimiento cognitivo general, como en el de funciones específicas, la valoración de los prematuros suele situarse dentro del rango considerado como normal, exceptuando las funciones verbales y lenguaje (Taylor et al. 2000) de aquellos individuos con un peso < 750g al nacer.

En referencia al posible sustrato estructural de estas disfunciones neuropsicológicas, las técnicas cuantitativas de neuroimagen han evidenciado, en sujetos de bajo peso al nacer ó prematuros, anomalías estructurales ya presentes durante el período perinatal (Inder et al. 1999; Peterson et al. 2003), que pueden persistir tanto en la niñez (Peterson et al. 2000, Kesler et al. 2004; Reiss et al. 2004), como en la adolescencia (Nosarti et al. 2002, 2004; Giménez et al. 2006a,b) y etapa adulta (Fearon et al. 2004; Allin et al. 2004).

En relación a los adolescentes con antecedentes de prematuridad, nuestro grupo de investigación (Giménez et al. 2000a,b), ha observado lesiones periventriculares, así como un descenso del volumen de la sustancia blanca en diversas regiones cerebrales.

Nosarti et al. (2004) ha observado una disminución del tamaño total del cuerpo calloso (CC), especialmente de algunas de sus subregiones.

Finalmente, varios estudios han aportado datos acerca de reducciones de la sustancia gris cerebral total, (Nosarti et al. 2002; Isaacs et al. 2003), y de diversas estructuras subcorticales como: el hipocampo (Isaacs et al. 2000; Abernethy et al. 2002; Giménez et al. 2004) y el núcleo caudado (Abernethy et al. 2002), además del cerebelo (Allin et al. 2005).

2. OBJETIVOS

En síntesis, los objetivos de los estudios realizados en esta tesis son:

1. Explorar los déficits de memoria en adolescentes con bajo peso al nacer y el papel que pueda desempeñar el coeficiente de inteligencia en relación a los mismos.
2. Estudiar las anormalidades del cuerpo calloso y el rendimiento en diversas funciones cognitivas, en adolescentes con antecedentes de prematuridad, correlacionando ambos tipos de datos.
3. Explorar la influencia específica de la edad gestacional al nacer sobre las anomalías del cuerpo calloso así como sobre el rendimiento cognitivo general, en los mismos sujetos antes citados.

3. METODOLOGIA

Los sujetos que componen la muestra total de estudio (N = 83), fueron seleccionados de la población de prematuros nacidos en el Hospital Clinic y el Hospital de la Vall d'Hebron, ambos en Barcelona. Los criterios de selección fueron: peso al nacer < 2500g, edad gestacional < 37 semanas y edad actual entre 11 y 17 años. En cuanto a los criterios de exclusión, hemos utilizado: deficiencia mental (CIT < 70), antecedentes de traumatismo craneoencefálico, parálisis cerebral u otro diagnóstico neurológico,

dishabilidades motoras y/o sensoriales que impidiesen la exploración neuropsicològica, prótesis dentales y claustrofobia o nivel de ansiedad elevado.
El grupo control se compone de familiares o conocidos de los sujetos de estudio ó de estudiantes universitarios. Estos sujetos nacidos a término y con una historia clínica normal, han sido emparejados por edad, género, nivel de educación, estado socio-económico y origen étnico, con la muestra de estudio.

La evaluación neuropsicológica de todos los participantes ha sido llevada a cabo por un mismo explorador (A.N.) en dos sesiones de 90min cada una. Los tests utilizados para medir el rendimiento cognitivo general y específico son los siguientes: a) coeficiente de inteligencia: WISC-R (Wechsler 1974) ó WAIS-III (Wechsler 1997), dependiendo de la edad del sujeto; b) aprendizaje verbal y memoria: "Auditory Verbal Learning Test" (Rey 1958); c) funciones visuoperceptivas / visuoconstructivas y memoria visual: tarea de copia y reproducción del Test de la Figura Compleja de Rey (Rey 1980); d) memoria de la vida cotidiana: Test de Memoria Cotidiana Rivermead (Wilson 1985); e) fluencia verbal: versión modificada del Controlled Oral Word Association Test (Benton & Hamsher 1989), y mediante una tarea de fluencia semántica a través de la generación de palabras a partir de una consigna categórica (animales).

En relación al estudio de neuroimagen, se adquirieron imágenes por resonancia magnética potenciadas en T1. El cuerpo calloso se midió en el corte sagital medial en el que las comisuras anteriores y posteriores, y el fórnix, fueran claramente visibles. Se siguió el modelo de segmentación de Witelson (1989) analizando 7 subregiones ("rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus and splenium"), de forma semiautomática, a través del programa ANALYZE 5.0/6.0 (Biomedical Imaging Resource, Mayo Clinic).
Además se utilizó el programa de procesamiento automático SPM2 (Wellcome Department of Cognitive Neuroscience, London, UK) para obtener los volúmenes de sustancia blanca, gris y líquido cefalorraquídeo.

El análisis estadístico se realizó a través del programa SPSS 10.0/11.0 (Statistical Package for the Social Sciences).

4. RESULTADOS

Estudio 1:

En el primer estudio se compara el rendimiento en memoria de 44 adolescentes de bajo peso al nacer con 44 sujetos nacidos a término. Los resultados muestran que los primeros presentan un rendimiento normal en aprendizaje verbal, memoria de reconocimiento y memoria visual. Por otra parte se observa una diferencia significativa en el Test de Memoria Cotidiana, que sin embargo desaparece al covariar (ANCOVA) por el coeficiente de inteligencia total (CIT). Además se observa, a través de un análisis de regresión, que no es el peso al nacer, sino la edad gestacional, la variable clínica que mejor predice el CIT.

Estudio 2:

En este estudio se seleccionan 25 sujetos con una edad gestacional < 33 semanas y 25 sujetos control. El análisis de neuroimagen muestra una diferencia significativa entre los grupos en el cuerpo calloso total, así como en varias subregiones (genu, posterior midbody y splenium). Asimismo aparece una diferencia significativa en el CI, aprendizaje verbal, memoria de la vida cotidiana y fluencia verbal semántica. Todos estos datos muestran un rendimiento más bajo del grupo prematuro. Por otro lado, se observa una correlación estadísticamente significativa de la edad gestacional con el tamaño del cuerpo calloso total y con el rendimiento cognitivo del sujeto. Por último, el análisis de regresión muestra que la edad gestacional es la variable que mejor predice el tamaño del cuerpo calloso.

Estudio 3:

Para este estudio se seleccionan 64 prematuros con una edad gestacional (EG) < 37 semanas, clasificados en 4 grupos atendiendo a su EG. El grupo control se compone de 53 sujetos nacidos a término. Los resultados muestran que los sujetos nacidos antes de la semana 27 presentan un adelgazamiento del cuerpo calloso total, así como de 5 subregiones (genu, anterior midbody, posterior midbody, isthmus and splenium), y un CI bajo. Los sujetos que nacen entre la semana 28 y 30, también presentan un bajo CI, pero únicamente presentan una reducción del tamaño del splenium. Los prematuros que

nacen con una EG entre 31 y 33 semanas, no muestran diferencias con los controles en cuanto al cuerpo calloso, pero sí en relación al CI, que es inferior en los prematuros. Finalmente, aquellos sujetos nacidos con 34 ó más semanas de gestación, no muestran ninguna diferencia con los nacidos a término. Además existe una correlación significativa de la EG con el cuerpo calloso y con el CI.

5. DISCUSIÓN GENERAL

Los resultados neuropsicológicos indican que nuestra muestra de prematuros tiene un rendimiento significativamente más bajo que los controles en el CI y en memoria de la vida cotidiana, aprendizaje verbal y fluencia verbal semántica. Sin embargo, cabe destacar que sus puntuaciones se sitúan dentro del rango considerado normal.

Por otra parte, no se observan diferencias significativas entre los grupos de estudio en: memoria verbal y visual, funciones visuoperceptivas y visuoconstructivas, y fluencia verbal fonética). Estos resultados son comparables a los obtenidos por Rushe et al (2001) en un amplio estudio neuropsicológico, que concluye sugiriendo que los déficits cognitivos a largo plazo en sujetos prematuros son leves.

Las diferencias observadas en las funciones específicas, están por un lado, relacionadas con el CI (memoria de la vida cotidiana, estudio 1). Por otro lado, con la posible afectación de la sustancia blanca, que ocasionaría una disminución en la velocidad de procesamiento de la información y un bajo rendimiento cognitivo, evidente en las funciones prefrontales citadas (aprendizaje verbal y fluencia verbal semántica, estudio 2. Cabe destacar que todos los prematuros de este estudio presentan un riesgo de hipoxia)

En relación a los estudios de neuroimagen, la presente tesis muestra que existe una correlación significativa entre el CI y el tamaño del cuerpo calloso en adolescentes con antecedentes de prematuridad. Estudios previos obtienen este resultado en niños (Peterson 2000) y adolescentes –si bien el CI empleado es el de los 8 años- (Nosarti et al. 2004).

Específicamente, nosotros encontramos un adelgazamiento del cuerpo calloso total así como de su parte anterior (genu) y posterior (posterior midbody y splenium). Este hallazgo diferente al de Nosarti et al. (2004), que sólo aporta una disminución de la

parte posterior en prematuros de 14-15 años, puede deberse a que nuestra muestra se compone también de sujetos menores de 14 años, llegando incluso a los 10. En este sentido, Peterson et al. (2000) observó una afectación de todas las partes del cuerpo calloso analizadas en niños de 8 años.

Ante estos resultados, podría decirse que las dimensiones del cuerpo calloso se recuperan de forma diferente a lo largo de la ontogenia; empezando por la parte anterior, y siendo la posterior la última en compensarse, tal y como sugirieron Giedd et al. (1996).

En cuanto a la relación entre edad gestacional (EG), cuerpo calloso y rendimiento cognitivo, nuestro estudio 3 muestra que los adolescentes que nacen con una EG $\leq$ 27 semanas son el grupo de mayor riesgo para presentar anormalidades estructurales así como déficits cognitivos. Este resultado puede relacionarse con la interrupción de los procesos normales de mielinización, cuyas consecuencias parecerían más acusadas de ocurrir en este período precoz del desarrollo. Entre las semanas 18-27 de gestación predominan los progenitores tardíos de la oligodendroglia, y entre las semanas 28-41 se esperaría un aumento del número de oligodendrocitos inmaduros, así como un aumento progresivo de las capas de mielina (Back et al. 2001).

Los sujetos que nacen entre las semanas 28 y 30 presentan únicamente una reducción del splenium, y a partir de la semana 31 ya no se observan alteraciones estructurales. Es de destacar sin embargo que los sujetos entre 28 y 33 semanas presentan un CI significativamente más bajo que los controles; lo cual no ocurre en los prematuros de más de 33 semanas de gestación.

No podemos excluir que los sujetos de nuestra muestra presenten además otras anormalidades cerebrales más sutiles no detectables en nuestros análisis de resonancia magnética. Nuevas modalidades de neuroimagen como la que utiliza tensores de difusión (DTI-en inglés-), podrían detectar alteraciones de la microestructura de la sustancia blanca, como ha sido efectivamente observado en recién nacidos prematuros con una EG entre 24-36 semanas (Partridge et al. 2004).

6. CONCLUSIONES

1. Adolescentes con antecedentes de prematuridad presentan dificultades cognitivas y anormalidades estructurales a largo plazo, que podrían estar más relacionadas con la edad gestacional que con el peso al nacer.

2. Adolescentes que nacieron prematuramente tienen déficits de memoria que pueden explicarse parcialmente por sus disfunciones en el rendimiento cognitivo general.

3. Inteligencia, memoria de la vida cotidiana, aprendizaje verbal y fluencia verbal semántica, son las funciones cognitivas más sensibles a la prematuridad.

4. Aún en el caso de observarse diferencias estadísticas significativas entre los grupos de estudio, la media de las puntuaciones de los sujetos prematuros se sitúa en el rango normal.

5. La reducción de tamaño del cuerpo calloso, observada con anterioridad en prematuros recién nacidos, se mantiene como mínimo después de 16 años de reorganización cerebral.

6. El genu, posterior midbody y splenium, son las subregiones más afectadas por la prematuridad.

7. La edad gestacional al nacer presenta una clara relación con las anormalidades del cuerpo calloso y con el bajo rendimiento cognitivo general. Los sujetos que nacen con una edad gestacional inferior o igual a 27 semanas, presentan una reducción del cuerpo calloso total, genu, anterior midbody, posterior midbody, isthmnus y splenium. Aquellos sujetos que nacen entre las semanas 28-30 sólo presentan una reducción del splenium. Después de esta edad, el cuerpo calloso y el coeficiente de inteligencia es similar a los sujetos nacidos a término.

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