Anuario de Psicología/The UB Journal of Psychology
2013, vol. 43, nº 3, 285-295

Neuropsychological impairment and brain damage in children and adolescents associated with preterm birth

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Prematurity is defined by the World Health Organization (WHO, 1977) as a delivery occurring before 37 completed weeks of gestation. White matter (WM) abnormalities and periventricular leukomalacia (PVL) are the most prominent pathologies in the preterm neonate. Compared with their term-peers, children born preterm have lower intelligence quotient (IQ) scores, although within the normal range. Moreover, domain-specific measures of neuropsychological abilities such as executive functions, visuoperceptual and linguistic skills are often impaired. Preterm children with PVL have a similar profile, with lower IQ scores and poorer executive functions, mental calculation and visuoperceptual skills than controls. Cerebral structural gray matter (GM) abnormalities that might contribute to the poor performance of preterm samples are localized in the frontal, parietal, temporal and occipital lobes. The cerebellum and deep gray matter structures such as the caudate nuclei, the thalami and the hippocampus are also altered. Over the past few years, magnetic resonance imaging and neuropathological studies have shown that, in addition to the classical WM injury seen in preterm samples with PVL, cortical and subcortical GM injury may also contribute to the impaired cognitive performance.
Keywords: *Intelligence, preterm, neuroimaging, neuropsychology, magnetic resonance imaging,*

Alteraciones neuropsicológicas y daño cerebral en la infancia y adolescencia asociados al nacimiento prematuro

La prematuridad es definida por la Organización Mundial de la Salud (OMS, 1977) como el parto que ocurre antes de las 37 semanas de gestación. La alteración de la sustancia blanca (SB) es la principal característica de daño cerebral

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y la leucomalacia periventricular (LPV) es el hallazgo patológico más común en estudios de resonancia magnética Los niños nacidos prematuros comparados con los niños nacidos a término presentan un cociente de inteligencia (CI) con puntuaciones menores pero dentro de la normalidad. Las funciones neuropsicológicas específicas más afectadas son las ejecutivas, visuo-perceptivas y lingüísticas. Los niños prematuros con LPV, también muestran puntuaciones más bajas en el CI, en las funciones ejecutivas, en el cálculo mental y en las capacidades visuoperceptivas. Las alteraciones cerebrales estructurales de sustancia gris (SG) que pueden contribuir a una peor ejecución cognitiva en estas muestras de prematuros implican regiones en los lóbulos cerebrales temporal, parietal, frontal y occipital. Además, el cerebelo y diversos núcleos grises subcorticales tales como el núcleo caudado, el tálamo y el hipocampo están también afectados. En los últimos años, los estudios de resonancia magnética y neuropatológicos, están demostrando que además de la alteración clásica de SB, los niños prematuros con LPV presentan daño en la SG tanto cortical como subcortical a los cuales se les atribuye una implicación directa en la peor ejecución cognitiva.

Palabras clave: *inteligencia, prematuro, neuroimagen, neuropsicología, resonancia magnética.*

Introduction

The World Health Organization (World Health Organization [WHO], 1977) defines preterm birth as a delivery occurring prior to 37 completed weeks of gestation. The incidence of preterm birth in Spain has risen from 4.75% of all live births in 1996 to 6.88% in 2010 (National Statistics Institute of Spain, 2010, www.ine.es). The reasons for this increment in preterm deliveries remain unclear, although it has been proposed that an increase in multiple gestations associated with in vitro fertilization therapy is in part responsible (Blondel & Kaminski, 2002) as well as the improvements in antenatal and neonatal care (Simmons, Rubens, Darmstadt, & Gravett, 2010).

Preterm birth has negative consequences on normal brain maturation processes, which may lead to neurocognitive and behavioral problems in childhood (Bhutta, Cleves, Casey, Cradock, & Anand, 2002) and in adolescence and adulthood (Marlow *et al.,* 2004) The time window during childhood and adolescence is particularly sensitive; at this time age-related social and academic demands increase, and emerging sequelae manifest themselves or pre-existing ones are intensified (Aylward, 2005).

Neuropsychological profile in children/adolescents born preterm

A meta-analysis of studies published between 1980 and November 2001 (Bhutta *et al.,* 2002) focusing on the cognitive and behavioral outcomes of school-aged preterm children showed that preterm birth is associated with low cognitive scores in childhood. During the last decade, with the decrease in mortality and the

increasing recognition of neurodevelopmental disabilities, termed by Aylward (2002) as "high prevalence/low severity dysfunctions", contemporary cohorts provide evidence of a similar pattern of low intelligence quotient (IQ). A meta-analysis by Kerr-Wilson, Mackay, Smith, & Pell (2012), covering studies from 1980 to 2009, found preterm delivery to be associated with a 12 point reduction in IQ scores. Therefore, it seems that preterm children, although within the normal range (Johnson, 2007), showed lower IQ scores than their term peers and that improvements in obstetric and neonatal practice have not reduced the impact of preterm delivery on IQ.

Domain-specific measures of neuropsychological abilities have also been studied although it is obvious that some of these cognitive functions may be strongly related to IQ. Executive dysfunctions are commonly evidenced in preterm samples (Mulder, Pitchford, Hagger, & Marlow, 2009); rather than a global deficit, they constitute a single profile of affected and non-affected areas. Executive function abnormalities comprise: (a) anticipation and deployment of attention; (b) impulse control and self-regulation; (c) initiation of activity; (d) working memory; (e) mental flexibility and utilization of feedback; (f) planning ability and organization, and (g) selection of efficient problem-solving strategies. Moreover, very preterm children are at high risk for executive dysfunctions such as working memory deficits and processing speed dysfunctions which may impact academic achievement and inattention and impulsive behavior (Mulder *et al.,* 2009; Mulder, Pitchford, & Marlow, 2010; Mulder, Pitchford, & Marlow, 2011).

Preterm birth also negatively affects visual recognition memory, visuospatial memory and visuospatial perception in childhood (Jongbloed-Pereboom, Janssen, Steenbergen, & Nijhuis-van der Sanden, 2012). As regards the language development in children born preterm without cerebral damage, linguistic abnormalities were found at the end of the preschool years (Guarini *et al.,* 2009) in addition to language (reading comprehension, lexical production and phonological awareness) and literacy problems (reading comprehension, reading and writing) by the age of eight years (Guarini *et al.,* 2010).

In addition to cognitive problems, preterm children are at high risk for behavioral problems (Bhutta *et al.,* 2002). Attention deficit-hyperactivity disorder (ADHD) is the primary abnormal outcome. Specifically, there is a 23% prevalence and nearly threefold increased risk for psychiatric disorders such as ADHD, emotional problems and autism spectrum disorders at 11 years of age in extremely preterm children (Johnson *et al.,* 2007).

Neuropsychological profile of children born preterm with periventricular leukomalacia

Periventricular leukomalacia (PVL) is the prototypical lesion in the encephalopathy of prematurity and the most prevalent type of brain injury affecting cerebral

white matter (WM). It leads to long-lasting cognitive and sensory-motor impairments in this population; 25-50% of very low birth weight infants present cognitive and behavioral deficits and 5-10% present cerebral palsy (Volpe, 2008, 2009).

It has been shown that preterm children who suffered a neonatal periventricular injury display sub-optimal scores compared to full-term children in performance and verbal intelligence quotients at 11 years. Those with severe damage evidenced worse reading and spelling skills, which are both related to working memory deficits (Downie, Frisk, & Jakobson, 2005). High-risk preterm children with poor reading skills may be likely to show executive dysfunctions (Frye, Landry, Swank, & Smith, 2009). Low scores for mental calculation have also been found in adolescents who suffered periventricular brain damage (Pavlova, Sokolov, & Krageloh-Mann, 2009).

Selective deficits in visuospatial and visuomotor integration have been found in preterm children with PVL (Olsen *et al.,* 1998) and are attributed to a malfunctioning of the dorsal stream (Fazzi *et al.,* 2004). Interestingly, Fazzi *et al.* (2009) have pointed out that PVL preterm children at 8 years showed involvement of both dorsal and ventral streams, reflected in deficits mainly in visual-object recognition, visual imagery, visuospatial skills and visual memory.

There are two main possibilities for explaining cognitive deficits after PVL (Kostovic & Judas, 2006). First, diffuse perinatal WM lesions can be so extensive as to involve a variety of motor, sensory and corticocortical pathways (Counsell *et al.,* 2003) and second, the focal component selectively affects a topographically condensed periventricular crossroad of mixed motor, sensory and associative pathways (Judas *et al.,* 2005). Thus, this combination of extensive and more restrictive damage may be linked with the variable cognitive performance evidenced in infants with perinatal brain lesions.

Predictors of long-term cognitive outcome in children/adolescents born preterm

The nature of cognitive development in the preterm infant is influenced by genetic, sociodemographic and congenital factors (Luciana, 2003). Among the main predictors of long-term outcome during childhood and adolescence, brain immaturity, lower birth weight (BW) and gestational age (GA) have been commonly reported (Bhutta *et al.,* 2002). It has been reported that early GA predicts the loss of around 1.5 to 2.5 IQ points per week in very preterm children (Johnson, 2007). In a recent study by the EPIPAGE group (Beaino *et al.,* 2011), the authors concluded that social factors such as low parental socio-economic status and lack of breastfeeding were significant predictors of mild cognitive dysfunctions. Both these factors, as well as biological factors including the presence of cerebral lesions, being small for GA and having a large number of siblings predicted severe cognitive deficiency. In addition, in a sample of extremely low BW

children maternal education was found to be the strongest predictor of long-term neurodevelopmental outcome between 6 and 10-13 years of age, followed by the presence of brain damage (Voss, Jungmann, Wachtendorf, & Neubauer, 2012). Another biological factor such as early motor repertoire has been identified as a good marker for intelligence performance from 7 to 11 years (Bruggink, Van Braeckel, & Bos, 2010). As far as executive functions are concerned, postnatal growth (for spatial span and planning) and parental education (for verbal fluency) were the main predictors of executive functions (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, Oosterlaan, & van Goudoever, 2013).

A good predictor of IQ in early adolescence is a previous IQ score at an early age (Botting, Powls, Cooke, & Marlow, 1998). However, it is still not clear whether early childhood cognitive performance is predictive of long-term consequences, since numerous cognitive functions emerge later in life and others are in the early stages of development (Anderson & Doyle, 2008). Furthermore, longitudinal studies have not found evidence of catch-up growth in comparison with term peers; rather, worsening outcomes have been reported over time (Johnson, 2007). In contrast, in a longitudinal study comprising a sample of very low BW infants Ment *et al.* (2003) found an improvement in verbal and IQ test scores in middle childhood.

MRI studies of brain morphology: Update and their cognitive correlates in preterm children and adolescents

Sulcal impairments

MRI techniques have been used in preterm subjects to investigate sulcal and gyral abnormalities. In subjects with evident abnormalities such as parenchymal hemorrhages and cystic PVL (Battin *et al.,* 1998), preterm birth seems to affect the staging of normal gyrification; furthermore, when quantitative measures are used, impairments in gyration are seen even in subjects without perinatal complications (Kesler *et al.,* 2006; Gimenez *et al.,* 2006a). Kesler *et al.* (2006) reported that children born prematurely showed an impaired gyrification index in the temporal lobe, affecting reading skills. In an adolescent sample, Gimenez *et al.* (2006a) found a significantly lower maximum depth in the orbitofrontal sulcus, but not in the primary olfactory sulcus.

The cause of the sulcal abnormalities associated with prematurity is still unknown. It has been suggested that the specific location and shape of sulci are determined by the global minimization over the brain of the visco-elastic tensions from WM fibers connecting cortical areas (Van Essen, 1997). This question was addressed by Dubois *et al.* (2008a), who compared 25 preterm subjects with clinically normal MRI and 10 subjects with WM lesions, observing a trend towards higher sulcation indices in the frontal lobe in subjects with WM lesions.

Regional gray and white matter abnormalities

Areas previously associated with GM abnormalities using quantitative volumetric MRI techniques were: temporal lobe bilaterally, parietal cortices (Peterson *et al.,* 2000; Soria-Pastor *et al.,* 2009), frontal and occipital areas (Nosarti *et al.,* 2008), cerebellum (Allin *et al.,* 2001), caudate nucleus (Abernethy, Cooke, & Foulder-Hughes, 2004), thalamus (Nosarti *et al.,* 2008) and hippocampus (Gimenez *et al.,* 2004). Impairment of any of these areas has the potential to disrupt normal neurodevelopment. MRI studies during childhood and adolescence have shown WM reductions in the brainstem (Hargitai *et al.,* 2004), internal capsule (Partridge *et al.,* 2004), subthalamic nuclei, the pons, temporal and frontal regions (Gimenez *et al.,* 2006b) and the corpus callosum (Peterson *et al.,* 2000). These differences in GM and WM volumes appear to be gender-specific, with males presenting greater impairment (Kesler *et al.,* 2008) and directly related to neonatal factors (GA and BW) during childhood (Soria-Pastor *et al.,* 2009).

Although cortical and subcortical regions with reduced GM have been described in preterm samples at school age and in adolescence, few reports have isolated samples of preterm children with PVL in order to investigate cerebral GM at this time of life. Interest in this field is increasing, and a recent review concluded that PVL WM injury is often accompanied by diffuse neuronal/axonal disease affecting cortical and subcortical GM (Volpe, 2009). The first study to provide evidence of GM damage in association with PVL was carried out by Inder *et al.* (1999) in a group of 10 neonates with this condition, highlighting that decrements in total myelinated WM were accompanied by global cortical GM reductions. Although PVL characteristically affects cerebral WM (Kwaja & Volpe, 2008), neuropathological studies have shown that GM lesions are frequent in infants with PVL, indicating that WM injury is often accompanied by GM abnormalities (Pierson *et al.,* 2007). Quantification of neuronal loss in a PVL post-mortem study showed that the structure with the largest GM reduction was the thalamus, which presented a loss of 38% compared with one of 21% in the cerebral cortex (Pierson *et al.,* 2007). Thala-mic damage is also a common finding in PVL neuropathological studies (Pierson *et al.,* 2007; Ligam *et al.,* 2009), and in MRI studies (Ricci *et al.,* 2006); its dorsomedial and pulvinar regions have been reported to be the most frequently affected areas (Nagasunder *et al.,* 2011).

Previous quantitative MRI studies in preterm children found that regional GM changes in regions such as sensorimotor, middle temporal and postcentral gyri correlated with IQ scores (Peterson *et al.,* 2000; Soria-Pastor *et al.,* 2009). It has also been reported that frontal and temporal volume decrements correlate with verbal IQ decline in preterm children, while decreases in temporal and occipital cortical regions are associated with a decline in performance IQ (Isaacs *et al.,* 2004). White matter volume has been directly related to performance IQ in preterm adolescents (Soria-Pastor *et al.,* 2008). In PVL children, neurodevelopmental outcome

correlated with the severity of MRI findings (Serdaroglu, Tekgul, Kitis, Serdaroglu, & Gokben, 2004). Moreover, parieto-occipital periventricular lesions of preterm children with PVL lead to long-term disturbances in visual perceptual system functioning (Pavlova, Sokolov, Birbaumer, & Krageloh-Mann, 2006) whereas frontal lesions in the right hemisphere are linked with visual navigation disabilities (Pavlova *et al.,* 2007), and right temporal periventricular lesions are related to the ability for perception and understanding of others' actions (Pavlova, Sokolov, Birbaumer, & Krageloh-Mann, 2008).

Increases and decrements in cortical thickness

Normal development in childhood is accompanied by an increase in CTh (Cortical Thickness) in almost all brain areas, whereas during adolescence there is a progressive cortical thinning (Shaw *et al.,* 2008). Studies of neurodevelopmental disorders have reported both thicker and thinner cortical regions. For instance, cortical thickening has been described in autism (Raznahan *et al.,* 2010) whereas cortical thinning has been found in ADHD (Shaw *et al.,* 2007).

Two previous studies in preterm adolescents measuring CTh have shown cortical thickening and thinning, and a greater impact with lower BW and shorter GA (Martinussen *et al.,* 2005; Nagy Lagercrantz, & Hutton, 2011). Intelligence levels correlated with CTh maturation trajectories in both children and adolescents (Shaw *et al.,* 2006). A recent study performed in a large sample of normal developing brains found positive bilateral correlations between intelligence and CTh localized in frontal, parietal, temporal and occipital lobes in adolescence (Karama *et al.,* 2012). Moreover, positive correlations have been found between IQ and CTh in areas in ventro-lateral frontal, parietal and temporal lobes in very low BW late teenagers (Bjuland, Lohaugen, Martinussen, & Skranes, 2013), and entorhinal cortical thinning has been associated with low IQ and reduced perceptual and executive functions in preterm adolescents (Skranes *et al.,* 2012).

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