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Increased risk of neuropsychological disorders in children born preterm without major disabilities: a neurodevelopmental model

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Abstract

Over the past 30 years, preterm births have drastically increased and today represent 12.5% of total births. About 1.2% of preterm births characterize very preterm births (GA<32weeks) that, with very low birth weight (BW<1500grams), are constantly found as risk factors of unfavourable neurological outcomes in longitudinal follow up studies. Actually, also "late preterm" children (preterm born from 33 to 36 weeks of gestational age), normally considered at low risk for neurodevelopmental disabilities, are supposed to represent a population of children to be monitored. Previous findings of a general cognitive impairment in children born preterm have gradually addressed the assessment of more specific neuropsychological skills and pointed out the importance to follow these children up to adolescent age. The neuroanatomical prerequisite of an abnormality in frontal lobe development and the correlation with various neuropsychological dysfunctions (fine and gross motor disabilities, executive function and working memory deficits, visual-constructional and attentional dysfunctions) underline the interference of preterm birth with normal brain maturational phases. Though showing more demanding neurodevelopmental pathways than term peers, a large number of preterm children tend to functionally normalize in adolescence. The review supports the hypothesis of a neurodevelopmental model that can be at risk to influence dysfunctional neuropsychological outcome.

Keywords: Preterm infants, Developmental neuropsychology, Executive functions, Working memory, Minor neurological dysfunction

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1. Introduction

A brief report by the U.S. Institute of Medicine, published on July 2006 18th, outlines health costs related to managing the growing morbidity associated with the increase of preterm births and unfavourable outcome in neurocognitive, behavioural and learning areas. They outline figures higher than $26.2 billion, with shares of $51,600 for each child born preterm. This report stresses the significant increase of preterm births over the past 30 years that, with racial differences, today represents approximately 12.5% of total births (I.O.M., 2006).

Births under 32 Gestational Age (GA) and/or Very Low Birth Weight (VLBW<1500 grams) characterize 1.2% of all preterm births, and represent conditions that have been identified as the main neurodevelopmental risk factors in several longitudinal studies (Marlow, Wolke, Bracewell, & Samara, 2005; Lindström, Winbladh, Haglund, & Hjern, 2007). However, for some years, a growing body of scientific literature reports findings of a neurodevelopmental risk even for so-called "near term newborns", better defined today "late preterm" infants, born between the 34th and 36th GA, which account for about 70% of preterm infants (Engle, Tomashek, & Wallman, 2007; Petrini, Dias, McCormick, Massolo, Green, & Escobar, 2009).

Epidemiological data obtained from cohorts of children evaluated from 1998 to 2004 during a follow up at the corrected age 18-24 months, published by the Vermont Oxford Network (VON) – an international network planned among Neonatal Intensive Care Unit (NICU) in more than 25 countries around the world – reveal a higher prevalence (between 25% and 30%) of minor neurodevelopmental dysfunctions (delay in acquisition of motor skills and other various anomalies documented by a Mental Index <70 on the Bayley Scales of Infant Development), than major disturbances (infantile cerebral palsy, severe sensory deficits, microcephaly, mental retardation). In support of this investigation, several other studies in Very Preterm (VP) infants have previously documented a clear prevalence of cognitive disorders and neurological diseases, which appear to characterize the outcome in 35-50% at preschool age (Hadders-Algra, 2003). According to this report, data showing a higher prevalence of a supposed intellectual deficit in children born preterm have often recurred in the literature, variously highlighting a borderline Intellective Quotient (IQ) (Bohm, Katz-Salamon, Smedler, LLagercrantz, & Forssberg, 2002), or behavioural disorders and difficulty in control of attention (Bohm, Smedler, & Forssberg, 2004) or other neuropsychological disorders related to memory and executive functions (Bayless & Stevenson, 2007). Very preterm and VLBW children are considered at high risk to underachieve at beginning of school years, lagging behind their full term peers, because of their bad performances in multiple curriculum areas with most prominent difficulties in math (Pritchard, Clark, Liberty, Champion, Wilson, & Woodward, 2008).

Recent findings are more frequently documenting a tendency to therapeutic interventions or other assistance for delayed school employment even in Low Birth Weight (LBW<2500gr) preterm that have been considered at low risk, eventually showing different developmental pathways to normality from infancy to adolescence than their term peers (Reuner, Hassenpflug, Pietz, & Philippi, 2009).

Therefore, if we consider that Cerebral Palsy (CP), commonly affecting extreme preterm (GA<30) and/or Extremely Low Birth Weight (ELBW<1000gr) in a percentage of 15-25%, has attained incidence of 1.5-3% and that behavioural and cognitive disorders occur in a prevalence of 30-50%, we should expect more frequent effects in the medium and long term on a large amount of children, even at low perinatal risk, not only in terms of physical and/or cognitive functioning, but also on their emotional and psychosocial adaptation (Moster, Lie, & Markestad, 2008).

2. Neurodevelopmental risk and neuroanatomical correlations

During the last century, sophisticated genetics, physiological and neuroimaging techniques have concurred to develop knowledge on the mechanisms that govern a lot of brain functions. Over all, advances in neuroimaging make it possible today to document developmental changes in cerebral structure, and emergent data on brain growth in preterm born infants have recently suggested a correlation with neurobehavioural or cognitive outcome during school age and early adolescence. Among diagnostic methods with high sensitivity in predicting neurological outcome, trans-cranial cerebral ultrasounds allow us to accurately describe the characteristics of lesions in very preterm infants already in the first weeks of post-natal age (Leijser, de Bruïne, Steggerda, van der Grond, Walther, & van Wezel-Meijler, 2009a; Leijser, Steggerda, de Bruïne, van der Grond, Walther, & van Wezel-Meijler, 2009b).

Neuroimaging findings in children born preterm are well documented. White matter abnormalities, referred to as Peri-Ventricular White Matter Abnormalities (PVWMA), have been related to unfavourable neurological outcome in preterm. This assumption is based on the evidence of a time-specific Central Nervous System (CNS) vulnerability, with a complex pathogenetic combination of primary destructive and secondary maturational and trophic disturbances (Volpe, 2009). Recent studies agree that insults to a particular area of developmental brain, the subplate, prematurely lying in the periventricular zone and that addresses cell precursors migrating to the layers of the cortex, could be responsible for neurological outcome. McQuillen and Ferriero (2005) have emphasized the selective sensitivity of subplate neurons to hypoxia-ischemic insults that occurs in the perinatal period. In preterm newborn, according to artery flow distribution

at gestational age between 23 and 32 weeks, a hypoxic-ischemic insult is feasible at the level of the anterior periventricular white matter that, if not leading to characteristic focal lesion - cystic Periventricular Leukomalacia (cPVL) or Intra-Parenchymal Hemorrhage (IPH) - may alter the maturation of cortical structures and establish important adverse effects on function, involving supposed neurotransmitter or fine structural deficits.

Findings on the characteristic motor disorders in preterm born infants have focused the importance of early diffuse damage to subplate neurons. To describe the mechanisms underlying disorders observed during the development of motor behaviour, Hadders-Algra (2007) has assumed that the quality of spontaneous General Movements (GMs) - that have been identified as an early marker of proper functioning or malfunctioning of CNS (Prechtl, Einspieler, Cioni, Bos, Ferrari, & Sontheimer, 1997) - should be probably correlated to subplate maturation. According to Edelman's Theory of Neuronal Group Selection, Hadders-Algra (2000) describes a linear path of typical changes of GMs characteristics during early development, which overlaps with the maturation of subplate. During human subplate maturation from 23 to 35 gestational weeks (see also McQuillen & Ferriero, 2005), GMs show the typical activity - fluent writing and fidgety movements - of a normal motor development in the 4-5 months post-term period. Grading the quality of abnormality of GMs, a motor poor repertoire or clear abnormal stereotypic movements, observed during a possible generic hypoxic-ischemic insult, could depend on a altered reduced selection of functional groups of neurons with consequent decreased normal variability of motor development. The Prechtl's method, when administered at 2-3 months corrected age, shows a very high sensitivity and specificity (over 90%) to detect normal cerebral functioning or a spastic cerebral palsy, but it does not have a high positive predictive value in estimating risk of neurocognitive dysfunctions at preschool age (Einspieler & Prechtl, 2005; Einspieler, Marschik, Milioti, Nakajima, Bos, & Prechtl, 2007).

Other studies are currently orienting their efforts to determine their positive value in predicting neurocognitive outcome at school age and early adolescence. Currently, most of the studies agree on the evidence of a modified development of brain functioning linked to preterm birth (Soria-Pastor, Gimenez, Narberhaus, Falcon, Botet, Bargallo, *et al.*, 2008; Stewart & Kirkbride, 2008). Nosarti, Giouroukou, Healy, Rifkin, Walshe, Reichenberg, *et al*. (2008), using Magnetic Resonance Imaging (MRI) with a voxel-based morphology technique in adolescents born very preterm, documented a decreased grey and white matter volumes proportionately to early gestational age and grade of neurodevelopmental dysfunctions attested by low scores in language and executive functions. According to previous study, Ment, Kesler, Vohr, Katz, Baumgartner, Schneider, *et al.* (2009) using MRI, report reduction in volumes of cerebral grey and white matter in a group of children between 8 and 12 years born very preterm. In normal group MRI

showed a gain of cerebral white matter on the grey matter, regularly deriving from a thickness reduction of the last; this feature was not present in preterm children, in support of the hypothesis of a disorder caused by preterm birth to maturational trajectory of brain development, which is evident in late childhood and early adolescence.

3. Motor and neuropsychological dysfunctions

In the past, findings of low IQ scores in very preterm born children have induced a growing interest in detecting neurocognitive disorders in other neuropsychological areas. A low IQ score does not properly explain specific deficits in neuropsychological functioning and often does not provide a clear comprehension of neurodevelopmental outcome in order to justify daily live disabilities or academic failures. Early studies are actually oriented towards an assessment of neuropsychological skills considered at risk in children born preterm at school age. Moreover, children with a normal IQ have been found to lack specific abilities in fine and gross motor functions, executive functions, memory, visual motor integrative abilities, visual perception, spatial skills and attention (Salt & Redshaw, 2006).

3.1 Fine and gross motor functions

The relationship between mild brain damage and neuropsychological disorders can be checked in children who presented an overview of "clumsiness" (i.e., "clumsy child syndrome"). Over the years minor disturbances of motor behavior, predominantly characterized by motor un-coordination, abnormal posture and fine manipulative dysfunction, were variously classified as: "dyspraxia", "developmental apraxia", "minor brain damage", etc. In 1994, a first international consensus meeting approved the definition of "Developmental Coordination Disorder" (DCD). In DSM-IV this definition states, in general, a group of children with normal intelligence and poor motor coordination, with no obvious signs of neurological disease such as cerebral palsy or neuromuscular disease. According to the American Psychiatric Association, this disorder affects "...significantly academic achievements or activities of daily life" (Hadders-Algra, Mavinkurve-Groothuis, Stremmelaar, Martijn, & Butcher, 2004). DCD has frequently been correlated to Attention Deficit Hyperactivity Disorder (ADHD), language, learning and other various developmental disabilities: it does not necessarily represent a condition of brain damage. In 1979, Touwen proposed the term "Minor Neurological Dysfunction" (MND) in replacing "Minimal Brain Damage", to define a syndrome which may not always be related to brain lesion. According to the neurological abnormalities found at Touwen's exam – including assessment of posture and muscle tone, reflexes, dyskinetic movements, coordination and balance, skill in handling, and

other minor neurological signs - two forms of MND are today recognized. The first (MND-1) is the simple one: it reveals minor symptoms, with abnormalities found in at least one, at most two clusters of signs. This form is associated with a moderate risk in recurrence of behavioural disorders (ADHD) and learning disabilities, and it should not represent a condition of strictly organic disease, but a dysfunctional developmental status that could be placed in the extreme tail of the normal distribution of values of a low, non-pathological, quality of brain functioning. This form of MND may have a genetic component to the base of an ill-defined predisposition of Central Nervous System (CNS) to mal adapt to any stress (such as prematurity, Intra Uterine Growth Restriction, mild to moderate perinatal asphyxia (Hadders-Algra, 2002), or eventual prenatal overload resulting from a mother's suffered psychological stress during the evolution period (Touwen, 1979). The second is the complex form of MND (MND-2). It occurs more frequently in at risk preterm children, or in combination with conditions that could cause injuries to the CNS during neurodevelopment. Diagnosis is based on abnormality assessed in more than two clusters of neurological signs. The MND-2 is consistently associated with risk factors such as very preterm birth and very low birth weight, and shows features through minor to moderate disturbances of motor behaviour, with neurological symptoms that, in serious cases, simulate clinical picture of a slight degree of Cerebral Palsy, a borderline CP. In longitudinal follow up studies a quantitative reduction of symptoms in affected children from the pre-pubertal period is frequently observed, with a tendency to persistence of slighter signs belonging to the cluster of more impaired skills (Hadders-Algra, 2002, 2003).

3.2 Executive functions (EF) and working memory (WM)

A growing number of studies points out the impact of Executive Functions and Working Memory deficits in children born preterm at school age and in adolescence.

Executive functions (EF) refer to a group of interrelated processes that support cognitive and adaptive functioning, including the inhibition of acting in response, the appropriate shifting and sustaining of attention for the purposes of goal-directed actions. Most studies are going to confirm their importance in children's developing social competences and academic performance (Blair, Zelazo, & Greenberg, 2005; Carlson, 2005).

Mechanisms that underlie the complex functioning of EF have been strictly associated to Working Memory (WM) that essentially represents the ability to maintain the online memory information. Planning and operational skills, requesting attentive and memory performance, are consistent with a well functioning working memory. As reviewed in recent studies, Working Memory involves central executive functions that are linked to brain maturational functions of frontal lobes that, as accurately document-

ed by neuroimaging techniques, are constantly activated during performances in skills as inhibition, verbal fluency, memory, strategic problem solving that have been classified as executive functions. Among tests of clinical assessment, two of main evaluated WM skills are inverse span in verbal fluency and in visual-constructional memory. A classical model of Working Memory functioning assumes that verbal material is maintained into a phonological loop and visual-spatial material into a visual-spatial sketchpad. Currently from a neurodevelopmental point of view, a central executive panel seems to operate during preschool age and early adolescence, and it should not represent a defined memory store, but an attentional monitor involved in tasks that require attentional shifts and processing of information. Employing multiple tasks, this functioning could require more efforts for attentional capacity and absorb most of the time to perform. In older children and adults, instead, phonological loop and visual-spatial sketchpad become independent from central executive panel, requiring less time for attentional processes. (Conklin, Luciana, Hooper, & Yarger 2007; Saavalainen, Luoma, Bowler, Määttä, Kiviniemi, Laukkanen *et al.*, 2007). Another recent study has documented a developmental process relating to performance in cognitive abilities assessing Event-Related brain Potentials (ERPs) activation. In the early stages of skill acquisition, ERPs are widely temporally and spatially distributed. It seems that neural activation travels across multiple brain sites that communicate continuously in flux with each other. When a skill is mastered, temporal and spatial relationships stabilize (Molfese DL, Molfese VJ, Beswick, Jacobi-Vessels, Molfese PJ, Key *et al.*, 2008). The old epigenetic Hebbian model (Hebb, 1949) to explain brain development may have to adapt to these more recent findings.

Although early appearing of EF abilities during development is difficult to test, a recent study has attempted to document some abnormalities in infants born preterm during their first 2 years of life. A significant difference in executive functioning was found between born preterm infants and full term peers, but it obviously needs to be confirmed by longitudinal assessment and follow up at preschool age (Sastre-Riba, 2009).

In assessing EF during development, various critical aspects emerge in outlining an interrelation with deficits observed in many other areas. Extremely preterm born children pay the highest price in terms of deficit in executive functions and motor disorders (Bayless & Stevenson, 2007). In a study on motor hyperactivity and ADHD, difficulties in impulse control, working memory and other executive functions have been confirmed in preterm children when starting school. Two of the most important predictors for executive functions were gender (male) and visual impairment; these data invite us to better investigate the visual function (Böhm, Smedler, & Forssberg, 2004). Marlow *et al.* (for the EPICure Study Group, 2007) evidenced a very high prevalence of impairment in visual-spatial, perceptual-motor, attention-executive, and gross motor function at early

school age in extremely preterm without major disability (CP, sensory impairment). They assume that neuropsychological deficits do not depend on motor impairment, but motor and executive-function difficulties together make an important additional contribution to worse school performance. A positive aspect is that motor abilities can be improved by therapeutic or educative strategies (Marlow, Hennessy, Bracewell, & Wolke, 2007); as recently reviewed, early motor intervention programs show they positively influence cognitive outcomes in the short to medium term (Spittle, Orton, Doyle, & Boyd, 2007). Korkman, Mikkola, Ritari, Tommiska, Salokorpi, Haataja *et al.* (2008) have well documented the interrelation between neuromotor performance and grade of neuropsychological impairment. Children with slight motor coordination problems show a widespread neuropsychological impairment, while most important motor disturbances, as reported in children with neurological abnormalities and CP, are related to evident neuropsychological dysfunctions in attention and EF, and in manual and visual-constructional tasks. They conclude that, in spite of average intelligence, the degree of motor disturbances could predict neuropsychological disorders.

Other studies concerning working memory have been conducted in preschoolers, but the evidence that developmental maturation of the prefrontal regions continues into adolescence validates prolonged follow up studies. Saavalainen *et al.* (2007), in a group of 16 yrs old adolescents born very preterm and without cognitive impairment, report findings of minor neuropsychological disorders regarding only spatial WM deficit. In a longitudinal study, 16 yrs old adolescents born very preterm without major disabilities showed a good outcome in school performance, if compared to their full term peers (Saavalainen, Luoma, Laukkanen, Bowler, Määttä, Kiviniemi *et al.*, 2007a). Though results are encouraging in observing only minor neuropsychological deficits in very preterm born individuals up to adolescence, we have to argue that participants enrolled to the study according their gestational age, birth weight and Apgar score at 1' and 5' as the main risk factors, do not have a documented clinical picture or concurrent disorder. Authors properly consider that, in spite of the documented good school performance, individual history can enfold a specific impairment and that parental monitoring or remedial support may have affected positively the good outcome highlighting the role of environmental variables.

3.3 Visual, attention and memory dysfunctions

Visual, attention and memory dysfunctions have already in part been discussed above as concurrent aspects of working memory dysfunctions.

Visual cognition occupies an important role among major dysfunctions affecting children born preterm, but significant differences demonstrate that visual perception seems to be less affected than visual-constructional skills. These findings suggest a neurodevelopmental disorder

in children born preterm that has been associated with specific dorsal-stream pathway vulnerability. The dorsal-stream pathway is a brain area (projecting from primary visual cortex to the parietal lobe) that is specialized for processing spatial information and in visual-motor planning. The theory of dissociation between the dorsal-stream pathway and the ventral pathway (projecting from primary visual cortex to the temporal lobe), primarily associated with perceptual recognition of shape, form, objects and faces, has received strong support from both animal research as well as neuropsychological studies on patients with localized brain damage (Santos, Duret, Mancini, Gire, & Deruell, 2009). As already reported above, visual spatial and constructional abilities are variously interrelated to dysfunctions observed in motor and working memory performances Saavalainen *et al.* (2007).

Attention deficits are commonly associated to ADHD that has frequently been reported in very preterm born children (Bayless & Stevenson, 2007; Conklin, Luciana, Hooper, & Yarger, 2007). Selective attention deficits and behavioural disorders have been documented in a group of 7-9 yrs age preterm children, using selective spatial and visual tests and ADHD rating questionnaire for parents and teachers. Selective visual and spatial attention deficits showed to be significantly related to ADHD rating scores (Shum, Neulinger, O'Callaghan, & Mohay, 2008). The problem to differentiate ADHD and selective attentional deficits dwells in its difficulty to assess a developmental process of ADHD. Early minor motor difficulties in very preterm infants at 2 yrs corrected age have longitudinally been related to selective attention deficits at 7-9 yrs (Jeyaseelan, O'Callaghan, Neulinger, Shum, & Burns, 2006). As previously described, at this age central executive panel for working memory request more attentional resources and prolonged time employment (Saavalainen *et al.*, 2007).

Memory dysfunctions more frequently appear to be a component of the malfunctioning in other areas, especially in working memory or visual spatial memory. Functional neuro-anatomy of the hippocampus and the head of the caudate nucleus has been studied using a functional Magnetic resonance Imaging (fMRI) technique during administration of memory tasks in a group of adolescents born very preterm. Findings demonstrate no statistical difference with control group in activation of hippocampus and caudate nucleus, supporting the hypothesis that spatial memory span deficits may represent a dysfunction in executing a planned motor sequence, rather than a deficit in the ability to remember the spatial sequence. It also raises questions on the normative processes of brain maturation and potential influence of perinatal hypoxic-ischemic stress in preterm infants (Curtis, Zhuang, Townsend, Xiaoping, & Nelson, 2006). An other study supports evidence of a non-specificity of memory deficits, bringing together memory deficits with impairment in general cognitive performances (Narberhaus, Segarra, Giménez, Junqué, Pueyo, & Botet, 2007).

4. Conclusions

The review addresses the topic of neurodevelopmental risks in preterm children. In order to analyze effective dysfunction in children born preterm without major disabilities (CP, mental retardation) previous findings of a general cognitive impairment in this population of children has not received consistent scientific agreement and has encouraged further research in this area to better assess specific neuropsychological skills and extend follow up to adolescent age.

Neuroanatomical findings are consistent with developmental brain frontal lobe abnormalities and correlate with minor neurological dysfunctions which typically affect fine and gross motor development, executive function and working memory, visual-constructional and attentional performances, while memory seems to work in interconnection with other functions. Preterm birth could interfere with normal developmental brain maturational steps with functional adjustments resulting in minor dysfunctions that are more evident in preschoolers born very preterm. The large number of preterm children that tend to normalize in adolescence, with more demanding neurodevelopmental pathways than term peers, support the hypothesis of a neurodevelopmental adaptation that risks to drop into dysfunctional neuropsychological outcome.

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