

The case of late preterm birth: sliding forwards the critical window for cognitive outcome risk

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Abstract: Many survivors of preterm birth experience neurodevelopmental disabilities, such as cerebral palsy, visual and hearing problems. However, even in the absence of major neurological complications, premature babies show significant neuropsychological and behavioural deficits during childhood and beyond. While the clinical tools routinely used to assess neurocognitive development in those infants have been useful in detecting major clinical complications in early infancy, they have not been equally sensitive in identifying subtle cognitive impairments emerging during childhood. These methodological concerns become even more relevant when considering the case of late preterm children (born between 34 and 36 gestational weeks). Although these children have been traditionally considered as having similar risks for developmental problems as neonates born at term, a recent line of research has provided growing evidence that even late preterm children display altered structural and functional brain maturation, with potential life-long implications for neurocognitive functioning. A recent study by Heinonen put forward the hypothesis that environmental factors, in this case educational attainment, could moderate the association between late preterm birth (LPT) and neuropsychological impairments commonly associated with aging. In this paper we bring together clinical literature and recent neuroimaging evidence in order to provide two different but complementary approaches for a better understanding of the “nature-nurture” interplay underlying the lifespan neurocognitive development of preterm babies.

Keywords: Preterm birth; neuroimaging; clinical outcome; neural plasticity

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Preterm birth: a major challenge for health care

Preterm birth, defined as birth before 37 completed weeks of gestation, represents a major health issue. As stated by the World Health Organization, an estimated 15 million newborns worldwide—that is, 1 in 10 babies—born too early every year. Among these, almost 1 million children die due to complications. Many survivors of preterm birth experience neurodevelopmental disabilities, including major neurological deficits such as cerebral palsy, visual and hearing problems (1). Furthermore, several follow-up studies have demonstrated that preterm survivors without major neurological complications show significant

neuropsychological and behavioural deficits during childhood (2). Preterm birth has therefore become a public health priority, especially considering that since the 1990s the survival of preterm infants has significantly improved, mainly thanks to advances in perinatal and neonatal care, including the introduction of drugs such as antenatal corticosteroids and surfactants (1). The improved survival of preterm infants has led to an increase in the prevalence of neonatal problems, in length of hospitalization, and costs of care, as well as increased neurodevelopmental disability (3).

Hence, in recent years attention has increasingly focused on predictors of neurodevelopmental outcome, such as the identification of early prognostic tools which

could delineate possible neurocognitive developmental trajectories in preterm born children. However, while these clinical instruments have been useful in predicting major neurological signs within the first years of life, they have not been entirely successful at predicting behavioural outcomes, including cognitive, neuropsychological and learning difficulties, which may emerge only during school-age or later. Marlow and colleagues (4) evaluated the neurocognitive development of a cohort of extremely preterm newborns (<26 weeks of gestation) who are part of a longitudinal study and reported higher percentages of cognitive deficits at 6-year than at 30-month of age, arguing that the current methods available to researchers to evaluate cognitive functions are quite limited during the first 2 years of life. In fact, developmental tests employed at 1 and 2 years of age, such as the Griffiths and Bayley scales, are largely composed of motor and perceptual-motor items. As such, they might actually be considered as better predictors of perceptual-motor competence at school age than of cognitive development. Consistently, it has been found that all the Griffiths subscales are more highly correlated with the Movement Assessment Battery for Children (Movement ABC) scores than with the Wechsler Pre-school and Primary Scale of Intelligence-Revised (WPPSI) scores (5). In other words, in order to be able to identify predictors of neurocognitive development of preterm babies, we need to develop more refined and specific methods.

The recent application of neuroimaging techniques on the investigation of structural and functional brain development of infants and children born preterm represents a promising avenue to provide novel insight into the mechanisms underlying typical and atypical patterns of brain maturation. These techniques are able to investigate “how the brain is” and “how the brain works” in a premature baby (6). These techniques encompass both classic and well-known tools—such as electrophysiological techniques (7-9), as well as more recently developed methods (such as functional and structural magnetic resonance, magnetoencephalography). Although the exact mechanisms underlying the altered structural and functional neural pathways following preterm birth are unknown, neuroimaging studies suggested a selective vulnerability of specific brain regions associated with both cognitive and psychiatric outcomes (6,10,11). Other studies further hypothesised the existence of a cognitive/psychiatric spectrum in which the selective brain networks affected by early injury (12) interact with social and cultural factors (13) in order to determine the final presentation of the disturbance.

In the case of preterm birth brain alterations need to be interpreted within a ‘neuroplastic’ framework, which posits that developmental changes in any brain region may result in a cascade of alterations in several other regions. Indeed, recent research has shifted from the investigation of discrete brain areas to the study of whole brain structural and functional connectomics. These studies have associated preterm birth with alterations in whole brain connectivity, preferentially affecting cortico-striatal and thalamo-cortical connections (14), which could affect an efficient integration between brain regions underpinning different aspects of information processing (15), with long-term implications for cognitive and mental health outcomes (6,11). Furthermore, several studies documented that many of the brain areas showing altered structural and functional maturation in the preterm brain perinatally continue to show alterations up to adulthood (16). Therefore, understanding the exact type and extent of early brain damage in preterm infants and how it affects functional development is essential in order to identify subgroups of individuals who are at increased risk of long-lasting neurodevelopmental problems who could be then closely monitored—to decide if, when and what preventative and rehabilitative strategies may be appropriate (i.e., offer personalised clinical care). This approach is closely related to the study of endophenotypes, namely biological/cognitive markers or subclinical traits that can aid to predict the course of a disorder and inform the type, timing and course of intervention.

An important ongoing study, which aims to detect early biomarkers of typical and atypical development, is the Developing Human Connectome Project, which is constructing the first 4-dimensional atlas of connectivity in the developing human brain using state-of-the art multimodal neuroimaging. This dynamic map of whole brain connectomics from 20 to 44 weeks post-conceptual age will link imaging, behavioural and genetic information, allowing for the identification of early biomarkers of various neurodevelopmental conditions, including as autism and cerebral palsy (<http://www.developingconnectome.org/>).

How much ‘preterm’ is ‘premature’?

By definition, a newborn is preterm if born before 37 gestational weeks. However, several other factors need to be taken into account when considering preterm birth. Perhaps intuitively, a first factor is the gestational development, which includes both gestational age and weight at birth, which *per se* is decisive for survival. That

is, the more 'preterm' a baby is in terms of gestational development, the more biologically 'premature' (i.e., not yet mature) his development is. Historically, this simple assumption led to an initial focus on the study of neurodevelopment of those babies born between 28 and 32 weeks of gestation. This mainly occurred as on the one hand, the survival rate of infants born before 28 weeks was very low prior to the early 1990s, when advances in perinatal and neonatal care improved the survival of babies born at the limits of viability, i.e., of those with an extremely low birth weight (<800 grams) and gestational age <28 weeks (1). On the other hand, for a long time infants born between moderately preterm (MPT; 32^{+0/7} to 33^{+6/7} weeks of completed gestation) and late preterm birth (LPT; 34^{+0/7} to 36^{+6/7} weeks of completed gestation)—representing 6-11% of all births, or 84% of all preterm births (17)—have historically been perceived as having similar risks for developmental problems as neonates born at term (18). This being in spite of the fact that there is good reason to hypothesize that significant brain alterations would exist following interruption of *in utero* brain development. At 34 weeks gestation, the brain weighs only 65% of the weight at 40 weeks gestation and typical brain maturational events that occur during the late preterm period include prominent gyral and sulcal infolding, increasing synaptic density, dendritic arborisation, axonal sprouting, glial cell proliferation and the establishment of neural networks (19).

Up to the last decade LPT babies were largely excluded from long-term follow-ups investigating their structural and functional brain maturation and neurocognitive development at later ages. Only recently, clinicians have realized that although late preterm infants may appear mature and of appropriate size at birth and do not encounter the same serious and chronic conditions as those observed in extremely premature infants, they are however not as healthy as previously thought and are at risk of increased morbidity and mortality compared with term infants (20). With an increased frequency of late preterm deliveries and its associated increase in risk of adverse perinatal complications, recent attention has focused on the neurodevelopmental consequences of LPT birth in terms of short, middle, and long-term outcomes. Several follow-up studies documented that LPT children are more likely to experience educational difficulties and poorer neuropsychological performance compared to term children (21). In spite of this, whilst several on-going studies are attempting to improve specific cognitive

function in very preterm born children, such as working memory and attention, to date no specific intervention has been proposed for late preterm infants at risk for future cognitive impairments.

In a recent birth-cohort study published in *Pediatrics*, Heinonen and colleagues (22) addressed one of the most clinically relevant questions about prematurity. That is, if and to what extent LPT birth may affect neuropsychological impairments commonly associated with aging. In particular, Heinonen and colleagues used data from an epidemiological sample, the Helsinki Birth Cohort Study, to test the performance of individuals in their late 60s who were born late preterm on the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB). Based on the observation that LPT birth has been associated with lower level of education throughout the lifespan, the authors further investigated a possible moderating role of educational level on the association between LPT birth and neurocognitive performance. Older adults who were born LPT showed worse performance on selected neuropsychological subscores than those born at term, including word list recognition, with differences at trend levels of significance on a summary memory score. Perhaps not surprisingly, individuals with a lower level of education scored worse on most CERAD-NB subscores than peers with a higher level of education.

The impact of lifespan experience on preterm babies' neurocognitive functioning

In their study, Heinonen and colleagues did not find significant differences in maximum attained level of education between LPT and term individuals, a result that is perhaps inconsistent with the findings of studies investigating younger LPT samples, i.e., at school-age, which reported lower reading scores, math skills and higher requirement of special education support in later preterm compared to term born children (21). However, one remarkable finding documented by Heinonen and colleagues refers to the possible moderating role of education on the association between LPT and late life neuropsychological functioning. Among those individuals who had lower lifetime attained education level, LPT birth was associated with lower scores on several CERAD-NB items, including episodic memory and executive function, and had a higher risk of mild cognitive impairment compared to term controls. However, among those individuals who had higher lifetime attained education

level, LPT was not significantly associated with lower neuropsychological performance.

The authors interpreted such results in the context of higher levels of education facilitating the attainment of neurocognitive reserve, as in the literature investigating the aetiology of Alzheimer's disease, higher educational level has been associated with later age of onset. Such findings in relation to LPT may reflect the fact that individuals with higher educational attainment may possess higher cognitive reserve which protects them from age-related cognitive declines.

An alternative explanation to these findings could be that greater environmental stimulation in the form of higher educational attainment could facilitate adaptive neuroplasticity in the developing brain, so as to maximise the utilization of compensatory neural pathways following early disruption to typical patterns of brain maturation. Support to this hypothesis could be provided by studies looking at the neuroanatomy of high order cognitive functions in late preterm samples, as there is recent evidence that LPT children, even in the absence of overt neuropsychological impairments, display alterations in prefrontal cortical connectivity (23). In higher risk samples (individuals born very preterm; <33 weeks of gestation) in adult life, an investigation of the dynamic formation of visual memory associations revealed that what are normally regarded as memory deficits can be understood in the context of neuroanatomical alterations occurring during learning (24). This study showed altered learning patterns in very preterm individuals in a standard episodic memory network, as well as other cortical areas, suggesting a possible reorganisation of the learning and memory system by adulthood. Specifically, Brittain *et al.* demonstrated reduced recruitment of the hippocampus, parahippocampal cortex and posterior cingulate gyrus in very preterm adults during learning of visual paired associates compared to controls, but also an increased recruitment of superior frontal areas, possibly reflecting a search for alternative strategies due to suboptimal engagement of the core episodic memory network.

Neural plasticity can be regarded as the capacity of the Central Nervous System (CNS) to reorganize itself as a product of the interaction of genetically predetermined constraints and the impact of the experience. Even in adulthood, the brain shows a great potential to reshape its neural architecture depending on particular demands and afferent inputs. From a lifespan perspective this is quite important as there is increasing evidence demonstrating

that the cortex may modify its structural and functional organization in response to experience on both a macroscopic (i.e., cortical pathway redeployment relying on changes in cortical connectivity) and microscopic (i.e., synaptic re-shaping) level (25). In other words, our individual and daily experience interacts with our brain in order to create a biologically unique and inimitable organism. Hence, the process generating human behaviour is extremely complex and oscillates between genetically predetermined and experience induced events. Within this framework the concept of 'education' in its broader meaning assumes a crucial importance not only in the early phases of life but also in the adulthood and even later, during elderly age.

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