

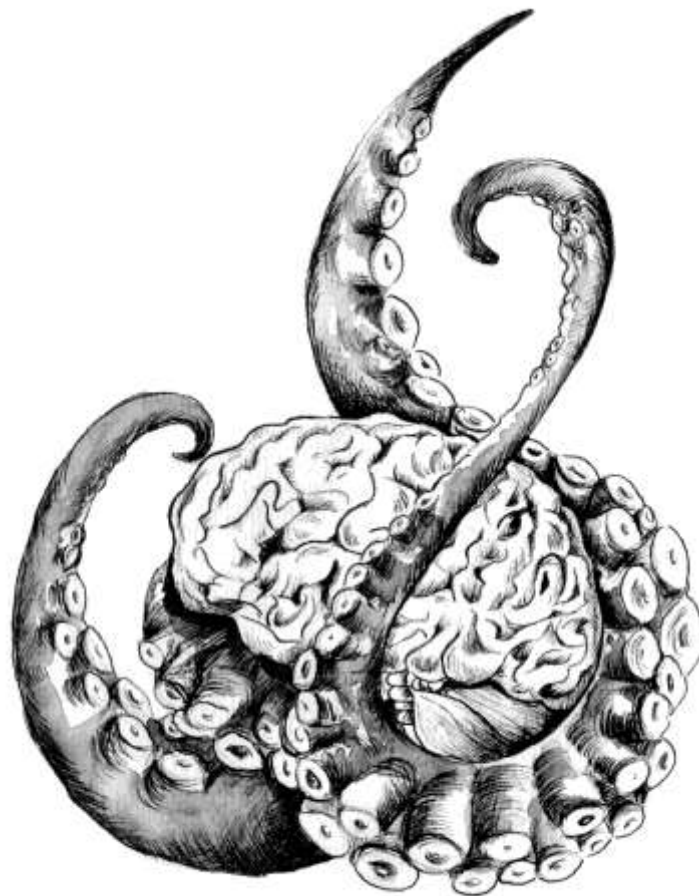
Preterm birth and early life development: the influence of neuropsychology, brain and social factors

Lexuri Fernández de Gamarra Oca

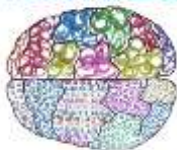
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NeuroLab



Neuropsicología de los Trastornos Médicos Severos
Neuropsychology of Severe Medical Conditions

Doctoral Program in Psychology

Department of Psychology

Faculty of Health Sciences

University of Deusto

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Faculty of Health Sciences

Psychology Doctorate Program

Department of Psychology

**Preterm birth and early life development: the influence of
neuropsychology, brain and social factors**

Doctoral thesis presented by Lexuri Fernández de Gamarra Oca,

To obtain the degree of Doctor by the University of Deusto

In accordance with the requirements of the International PhD Diploma

PhD Student

Lexuri Fernández de Gamarra Oca

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Dr. Leire Zubiaurre Elorza

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Dr. Natalia Ojeda

Bilbao, September 2023

This thesis has been carried out in the Research Group of Neuropsychology of Severe Medical Conditions, in the Department of Psychology, Faculty of Health Sciences, University of Deusto.

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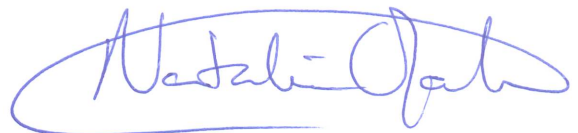
Dr. Leire Zubiaurre Elorza, Professor of the Department of Psychology at the University of Deusto, director of the present thesis; and Dr. Natalia Ojeda, principal investigator of the Neuropsychology of Severe Medical Conditions research team, Full Professor of the Department of Psychology at the University of Deusto, director of the present thesis, certify that the present thesis entitled **“Preterm birth and early life development: the influence of neuropsychology, brain and social factors”** represents an original research work, which is presented by Lexuri Fernández de Gamarra Oca in order to obtain the degree of Doctor.

Director



Dr. Leire Zubiaurre Elorza

Director



Dr. Natalia Ojeda

Bilbao, September 2023

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“Se apaga el carrusel después de otro carnaval

Los conos de papel ensucian el piso

Se apaga el carrusel, deséame suerte”

Vetusta Morla

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Foreword

The present thesis has been presented to obtain the degree of Doctor by the University of Deusto, and is the result of six studies carried out at the Research Group of Neuropsychology of Severe Medical Conditions, at the Department of Psychology, Faculty of Health Sciences, University of Deusto. The following 6 articles have been published on international peer-reviewed journals (4) or are in process of publication (2), as a result of the work performed, with a **global impact factor (IF) of 16.01** (ISI Web of Science, Journal Citation Reports).

Paper I

Fernández de Gamarra-Oca, L., Zubiaurre-Elorza, L., Junqué, C., Solana, E., Soria-Pastor, S., Vázquez, E., Delgado, I., Macaya, A., Ojeda, N., Poca, M.A. (2021). Reduced hippocampal subfield volumes and memory performance in preterm children with and without germinal matrix-intraventricular hemorrhage. *Scientific Reports*, 11, 2420. DOI: 10.1038/s41598-021-81802-7 [IF = 4.997, JCR = Q2 Multidisciplinary Sciences].

Paper II

Fernández de Gamarra-Oca, L., Ojeda, N., Loureiro, B., Sierra-Ibarbia, A., García-Guerrero, M.A., Peña, J., Ibarretxe-Bilbao, N., Zubiaurre-Elorza, L. (2022). Maternal care and general cognitive functioning in moderate and late preterm-born children. *Cognitive Development*, 64, 101247. DOI: 10.1016/j.cogdev.2022.101247 [IF = 1.800, JCR = Q3 Psychology, Developmental].

Paper III

Fernández de Gamarra-Oca, L., Ojeda, N., Gómez-Gastiasoro, A., Peña, J., Ibarretxe-Bilbao, N., García-Guerrero, M.A., Loureiro, B., Zubiaurre-Elorza, L. (2021). Long-term neurodevelopmental outcomes after moderate and late preterm birth: a systematic review.

The Journal of Pediatrics, 237, 168-176. DOI: 10.1016/j.jpeds.2021.06.004 [IF = 6.314, JCR = Q1 Pediatrics].

Paper IV

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Paper V

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Paper VI

Fernández de Gamarra-Oca, L., Lucas-Jiménez, O., Ontañón, J.M., Loureiro, B., Peña, J., Ibarretxe-Bilbao, N., García-Guerrero, M.A., Ojeda, N., Zubiaurre-Elorza, L. Amygdala Structure and Function and Its Associations with Social-Emotional Outcomes in a Low-Risk Preterm Sample. (Submitted).

Glossary of abbreviations

ACE = Adverse Childhood Experiences

ACE-IQ = Adverse Childhood Experiences Questionnaire

AD = Axial Diffusivity

ASR = Adult Self Report

BET = Brain Extraction Tool

BOLD = Blood-Oxygenation-Level-Dependent

BW = Birth Weight

CA = Cornu Ammonis

CBCL = Child Behavior Checklist

CCT = Children's Color Trails Test

CD-RISC = Connor-Davidson Resilience Scale

CP = Cerebral Palsy

CPRS = Conners' Parent Rating Scale

CTh = Cortical Thickness

CUS = Cranial Ultrasound

DDT = Delay Discounting Test

DTI = Diffusion Tensor Imaging

ELBW = Extremely Low Birth Weight

EPT = Extremely Preterm

ERQ = Emotion Regulation Questionnaire

eTIV = Total Intracranial Volume

FA = Fractional Anisotropy

FC = Functional Connectivity

fMRI = Functional Magnetic Resonance Imaging

FOV = Field of View

FSL = FMRIB Software Library

GA = Gestational Age

GC-DG = Granule Cell Layer of Dentate Gyrus

GM = Gray Matter

GM-IVH = Germinal Matrix-Intraventricular Hemorrhage

HATA = Hippocampal-Amygdalar Transition Area

HR = Hazard Ratio

IQ = Intelligence Quotient

IUGR = Intrauterine Growth Restriction

IVH = Intraventricular Hemorrhage

LBW = Low Birth Weight

LGA = Large for Gestational Age

MD = Mean diffusivity

MedFC = Medial Frontal Cortex

MJT = Moral Judgment Test

MLPT = Moderate and Late Preterm

MRI = Magnetic Resonance Imaging

M-WCST = Modified Wisconsin Card Classification Test

NICU = Neonatal Intensive Care Unit

OR = Odd Ratio

PB = Preterm Birth

PHH = Posthemorrhagic Hydrocephalus

PHVD = Posthemorrhagic Ventricular Dilatation

PPVT-III = Peabody Picture Vocabulary Test III

pre-OLs = Premyelinating Oligodendrocytes

PVI = Periventricular Hemorrhagic Infarction

PVL = Periventricular Leukomalacia

RAVLT = Rey Auditory Verbal Learning Test

RD = Radial Diffusivity

ROI = Region of Interest

RPM = Raven's Advanced Progressive Matrices

RR = Relative Risk

rs-fc = Resting State Functional Connectivity

SES = Socioeconomic Status

SGA = Small for Gestational Age

SPSS = Statistical Software Package for Social Sciences

SWLS = Satisfaction with Life Scale

SWLS-C = Satisfaction with Life Scale-Child

TBSS = Tract-Based Spatial Statistic

TE = Echo Time

TFCE = Threshold-free Cluster Enhancement

TMT = Trail Making Test

TR = Repetition Time

VLBW = Very Low Birth Weight

VPT = Very Preterm

WAIS-IV = Wechsler Adult Intelligence Scale IV

WHO = World Health Organization

WISC-V = Wechsler Intelligence Scale for Children V

WM = White Matter

I. Abstract

1. Abstract

Preterm birth (PB) alters brain development influenced by neurological damage, environmental circumstances, and the timing of their occurrence. Based on weeks of gestation, there are newborns considered moderate and late preterm (MLPT) who are born between 32 to 36 weeks of gestation. This group is of increasing interest as it comprises more than 84% of all PBs. However, there is a paucity of research converging neurodevelopmental outcomes in well-characterized samples in terms of clinical manifestations at birth, which would allow researchers to assess the effect of PB *per se* and brain injury on cognition and cerebral development. Especially, considering that only a small percentage of MLPT children present a profile of developmental difficulties close in phenotype to those born at a lower gestational age. Nevertheless, the existing neurodevelopmental consequences may contribute to lower education, employment status and income during adulthood in this population, leading to decreased well-being and poorer mental and physical health. Aside from the presence or absence of neonatal brain injury, some environmental factors may also place PB at even greater risk for adverse long-term development.

This thesis is composed of six studies and analyzes PB taking into account different degrees of neonatal immaturity, with the first two studies focusing on childhood and the following four on adolescence and young adulthood. More specifically, it addresses the impact of PB on the neuropsychological profiles of preterm born children, adolescents and young adults according to their clinical manifestations at birth. On the other hand, it assesses the potential role of early life environmental factors on cognitive development, such as socioeconomic status, parental bonding, and adverse childhood experiences. In turn, a systematic review and meta-analysis is conducted with the aim of gaining insight into the long-term neurodevelopmental outcomes of MLPT adults in

relation to cognitive functioning and psychiatric disorders. Finally, it studies the brain after PB at different developmental stages, with special emphasis on the hippocampus and amygdala taking into account the importance of both structures on cognition and social-emotional outcomes.

These studies mentioned here provide different neuropsychological profiles and brain indicators in the prognosis of short- and long-term development of PB. For instance, children, adolescents, and young adults born prematurely, with or without neonatal brain injury, continued to lag behind their full-term peers in a variety of cognitive domains. However, the effects of MLPT on psychiatric illnesses are frequently small during adolescence and adulthood, even none regarding social-emotional problems at different developmental stages. At brain level, in the absence of neonatal brain injury, differences in normative structural brain development and regional white matter microstructure were found during young adulthood. Moreover, increased functional connectivity was also displayed in brain areas related to social-emotional outcomes. Although much work remains to be done regarding the inclusion of neuropsychological and brain adverse outcomes in PB care, the present thesis suggests that the use of standardized long-term follow-up may be potentially useful, even at a lower risk for developing negative developmental consequences, without ignoring the impact of different environmental factors during the first years of life.

Keywords: preterm birth, neuropsychological profiles, emotional-behavioral problems, environmental factors, neuroimaging, brain structure and function.

Resumen

El nacimiento prematuro puede alterar el cerebro por daños neurológicos, circunstancias ambientales y al momento en que se producen. De acuerdo a las semanas de gestación, hay recién nacidos considerados prematuros moderados y tardíos que nacen entre las semanas 32 y 36. Este grupo es de gran interés, ya que comprende más del 84% del total de nacimientos prematuros. Sin embargo, hay una escasez de investigaciones con muestras bien caracterizadas en términos de manifestaciones clínicas al nacer, lo que permitiría a los investigadores evaluar el efecto del nacimiento prematuro *per se* y del daño cerebral sobre la cognición y el cerebro. Especialmente, si se tiene en cuenta que pocos niños prematuros moderados y tardíos presentan un perfil de dificultades de desarrollo cercano al fenotipo de los prematuros nacidos con una menor edad gestacional. No obstante, las consecuencias existentes en el neurodesarrollo pueden contribuir a una menor educación y peor situación laboral e ingresos durante la edad adulta, lo que conlleva una disminución del bienestar y una peor salud mental y física. Asimismo, algunos factores ambientales también pueden exponer a los recién nacidos prematuros a un riesgo aún mayor de desarrollo adverso a largo plazo.

Esta tesis se compone de seis estudios y analiza el nacimiento prematuro teniendo en cuenta diferentes grados de inmadurez neonatal, centrándose los dos primeros estudios en la infancia y los cuatro siguientes en la adolescencia y la adultez temprana. Más concretamente, aborda el impacto del nacimiento prematuro en los perfiles neuropsicológicos de niños, adolescentes y adultos jóvenes en función de sus manifestaciones clínicas al nacer. Por otro lado, evalúa el papel potencial de los factores ambientales en las primeras etapas sobre la cognición, como son el estatus socioeconómico, el vínculo parental y las experiencias adversas en la infancia. A su vez, se lleva a cabo una revisión sistemática y un metaanálisis con el objetivo de conocer los

resultados del neurodesarrollo a largo plazo de los adultos prematuros moderados y tardíos en relación con el funcionamiento cognitivo y los trastornos psiquiátricos. Por último, se estudia el cerebro tras el nacimiento prematuro en diferentes etapas del desarrollo, con especial énfasis en el hipocampo y la amígdala teniendo en cuenta la importancia de ambas estructuras en la cognición y el funcionamiento socioemocional.

Los estudios aquí mencionados aportan diferentes perfiles neuropsicológicos e indicadores cerebrales en el pronóstico de la evolución a corto y largo plazo del nacimiento prematuro. Los niños, adolescentes y adultos jóvenes nacidos prematuramente, con o sin lesión cerebral neonatal, siguieron puntuando por debajo en comparación con sus homólogos nacidos a término en diversos dominios cognitivos. Sin embargo, los efectos del nacimiento prematuro moderado y tardío sobre las enfermedades psiquiátricas suelen ser pequeños durante la adolescencia y la edad adulta, incluso ninguno en relación con los problemas socioemocionales en diferentes etapas del desarrollo. A nivel cerebral, se encontraron diferencias en el desarrollo estructural cerebral y en la microestructura regional de la sustancia blanca durante la adultez temprana. Además, también se mostró una mayor conectividad funcional en áreas cerebrales relacionadas con resultados socioemocionales. Aunque aún queda mucho trabajo por hacer en lo que respecta a la inclusión de resultados neuropsicológicos y cerebrales adversos en la atención del nacimiento prematuro, la presente tesis sugiere que el uso de un seguimiento estandarizado a largo plazo, incluso en aquellos con un menor riesgo de desarrollar consecuencias negativas en el desarrollo, sin ignorar el impacto de los diferentes factores ambientales durante los primeros años de vida.

Palabras clave: nacimiento prematuro, perfiles neuropsicológicos, problemas emocionales-conductuales, factores ambientales, neuroimagen, estructura y función cerebral.

II. Introduction

2. Introduction

The shift from fetal to neonatal periods is critical in terms of physiological adaptation. A succession of critical processes, ending in labor, enable the fetus to prepare for life outside the womb, leaving the uterus, and, in most cases, adapting to an extrauterine environment acceptably. In general terms, an abrupt transition occurs in 10 to 15% of births, predisposing these neonates to life-threatening difficulties (e.g., congenital abnormalities, birth injuries, or disease) (Askin, 2002; Swanson & Sinkin, 2015). As an example, adaptation abnormalities are commonly discovered after preterm birth (PB), with resuscitation rooms being required in some cases to help the newborn through this transition (Hillman et al., 2012). However, there is still much unknown about the role of different environmental determinants in both the early and long-term neuropsychological and brain development following PB. Therefore, such a thesis is highly justified, since the public health system stills need to enhance its' knowledge of the possible consequences for this population.

2.1. Preterm birth (PB)

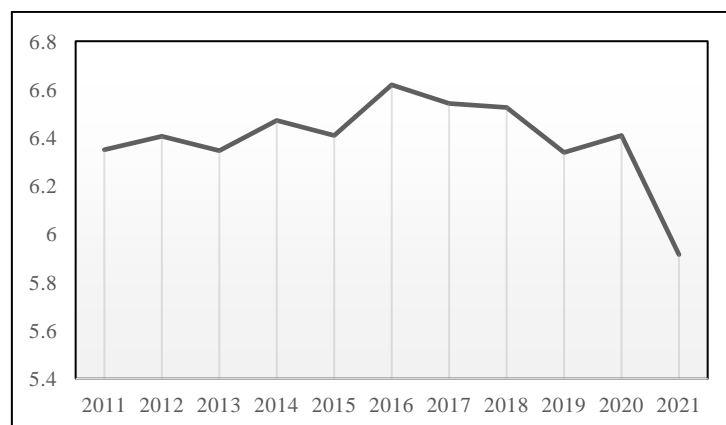
According to the World Health Organization (1977), PB occurs before 37 weeks of gestation or within 259 days of the date of a woman's last menstrual period. Numerous maternal risk factors have been associated with PB, including sociodemographic, obstetrical, psychological and genetic factors, as well as paternal and environmental factors (Torchin & Ancel, 2016). Nevertheless, the majority of women who gave birth to a preterm newborn had low-risk pregnancies (i.e., no maternal and population risk factors identified) (Kiserud et al., 2017). Based on its definition, PB is well-defined as a condition characterized by the interruption of gestation before 37 weeks, instead of the existence of particular signs or symptoms (Kramer et al., 2012). This means PB may be regarded as a

negative consequence of pregnancy (i.e., after a fetus is unable to reach its in utero growth potential) or a chosen consequence (i.e., after effectively preventing a miscarriage). Therefore, PB itself is a risk factor for newborn development including optimal adult development, well-being, and health (Vogel et al., 2018).

The number of PBs worldwide was around 14.8 million in 2014, or 10.6% of all live births (Chawanpaiboon et al., 2019). In Spain, by contrast, prevalence was 5.9% in 2021 (see Figure 1). Since the majority of PB-related deaths occur in the newborn period, it is the leading cause of mortality in children under the age of five (Walani, 2020). Hence, preterm newborns present higher mortality and morbidity rates than term newborns, with the worst outcomes occurring after the shortest gestation periods (Saigal, & Doyle, 2008; Teune et al., 2011). Additionally, those infants born preterm who survive are at higher risk of adverse neurologic and developmental outcomes during adulthood compared to infants born full term (Raju et al., 2017). Even though certain neurologic and developmental abnormalities are emerging less frequently owing to advances made in prenatal and neonatal care units, preterm newborns still present higher rates of adverse developmental delays (Chung et al., 2020).

Figure 1

Prevalence of PB in Spain from 2011 to 2021



Note: Figure created based on data from Instituto Nacional de Estadística (INE).

2.2. PB classifications

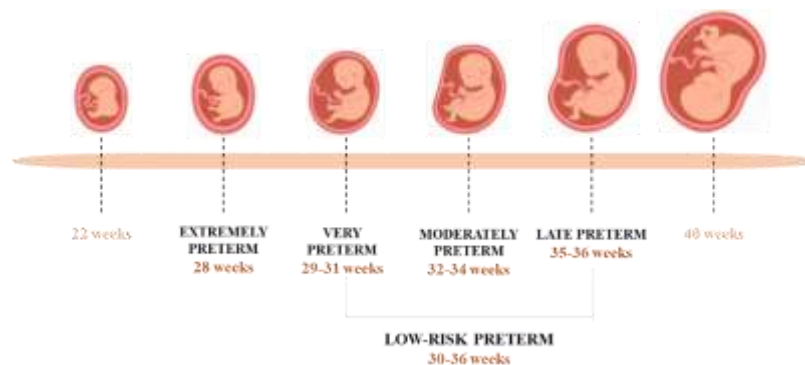
PB can be classified attending to its clinical etiology (i.e., medically induced, preterm premature rupture of the membranes, and spontaneous preterm labor resulting in PB); however, without fully explaining all deliveries. Despite well-known distinctions in the etiologic pathways leading to PB, there has not been any adequate epidemiologic research (Ananth & Vintzileos, 2006). Because of the evident heterogeneity of PB, plausible biological processes should be more clearly defined (Moutquin, 2003). That is to say, further knowledge of the epidemiology and the risk factors thought to be related to the etiology are needed to develop new treatments (Frey & Klebanoff, 2016). The different classifications of PB based on the clinical factors of gestational age (GA) and birth weight (BW) are presented below.

2.2.1. Gestational age (GA)

PB can be divided into four categories based on GA at birth: extremely preterm (EPT) (< 28 weeks); very preterm (VPT) (28 to < 32 weeks); moderately preterm (32 to < 35 weeks); and late preterm (MLPT) (35 to < 37 weeks) (see Figure 2). Over 84% of the 15 million PBs each year are MLPT. Only 5% of births are EPT, and the remaining 10% are VPT (Blencowe et al., 2012).

Figure 2

Gestational age classification



Note: Figure created based on data from Portal Clinic, 20 February 2018.

There is currently consensus on how to classify newborns as preterm, term, and post term (> 42 weeks); however, there is no consensus on how to divide certain PBs into subcategories (Engle, 2006). There are many different terms for different GA ranges for MLPT newborns with a reduced risk of neurodevelopmental alterations compared to EPT and VPT individuals. For instance, infants born at between 33 and 37 weeks of gestation are considered to be near-term neonates, while others proposed that births between 32 and 36 weeks can be labeled as marginally preterm (Raju et al., 2006). As a result, together with their lower risk of suffering from an adverse neurodevelopment course and the lack of additional medical follow-up after the newborn period, it is challenging to predict the long-term functioning of MLPTs due to the indiscriminate use of different terms.

2.2.2. Birth weight (BW)

A newborn's BW is the initial weight recorded after birth, ideally during the first hours, before there has been any major postnatal weight reduction. The World Health Organization (2009) defined low birth weight (LBW) as a BW of less than 2500g (up to and including 2499g). Very low birth weight (VLBW, < 1500g) and extremely low birth weight (ELBW, < 1000g) are classifications for LBW.

Furthermore, there is a supplementary classification in which weight is categorized according to specific GA. Firstly, small for gestational age (SGA) is used to define a newborn who is smaller than the usual size based on the number of weeks of pregnancy completed. SGA newborns typically have a BW below the 10th percentile than newborns with the same GA. Meanwhile, newborns may also be defined as large for gestational age (LGA) when their weight is more than the 90th percentile than those with the same GA (see Table 1) (Sysyn, 2004).

Table 1*Birth weight classification*

Infants born preterm may be classified by weight independent of GA		
Low birth weight	LBW	< 2500g
Very low birth weight	VLBW	< 1500g
Extremely low birth weight	ELBW	< 1000g
Infants born preterm may be classified by weight for a specific GA		
Small for gestational age	SGA	Weight < 10th percentile
Appropriate for gestational age	AGA	Weight 10-90th percentile
Large for gestational age	LGA	Weight > 90th percentile

Note: Table created based on WHO Statistical Information Systems (WHOSIS), 2011.

LBW and poor fetal growth continues to be a significant global public health problem that raises a number of adverse neurodevelopmental outcomes, with this being more pronounced in those born preterm than in full-term infants (Vollmer & Edmonds, 2019). For instance, fetuses with intrauterine growth restriction (IUGR) who do not grow to their full potential have been associated with substantial perinatal morbidity and mortality (Suhag & Berghella, 2013).

In 2015, the global LBW prevalence was 14.6%, down from 17.5% in 2000. An estimated 20.5 million live births were LBW, with 91% occurring in low- and middle-income countries, primarily in southern Asia (48%) and Sub-Saharan Africa (24%) (Blencowe et al., 2019). Infants with LBW had newborn death rates 25 times higher than those with a BW of 2500g or greater in 2013 (Mathews et al., 2015). In the population as a whole, the lower the BW the higher the rate of morbidity such as type 2 diabetes and cardiac-related death. BW can then be considered a risk factor for subsequent mortality and morbidity (Class et al., 2014). Nonetheless, data suggests that VLBW and ELBW currently have a higher probability of surviving in the absence of serious neurological disability such as cerebral palsy (CP) (Platt et al., 2007).

2.3. PB clinical manifestations at birth

A variety of organ systems are affected by developmental immaturity. The interaction of PB mechanisms, including inflammation and cytokine damage, have been linked to a number of clinical manifestations in the preterm newborn. The short-term consequences of PB in vulnerable organ systems throughout the prenatal and neonatal periods are summarized in Table 2. According to Behrman and Butler (2007), several of these complications have long-term effects on health, growth, and development.

Table 2

Common clinical manifestations after preterm birth (PB)

Body system	Common clinical manifestations after PB
Respiratory system	Respiratory distress syndrome, bronchopulmonary dysplasia, chronic lung disease or apnea.
Cardiovascular system	Patent ductus arteriosus (PDA), hypotension or bradycardia.
Gastrointestinal system	Necrotizing enterocolitis (NEC), feeding intolerance or gastroesophageal reflux (GER).
Hematologic system	Anemia and newborn jaundice.
Metabolism system	Hypoglycemia.
Immune system	Sepsis or septic shock.
Auditory system	Congenital or perinatal acquired hearing disorders.
Ophthalmic system	Retinopathy of prematurity (ROP).
Temperature regulation system	Hypothermia.
Central nervous system	Germinal matrix injury, intraventricular hemorrhage (IVH), intraparenchymal hemorrhage (IPH) or periventricular leukomalacia (PVL).

Note: Table created based on Behrman & Butler (2007), The National Academies Press.

Focusing on the central nervous system's clinical manifestations, PB can be categorized into two separate divisions: low- and high-risk PB. The influence of PB *per se* on different developmental measures (i.e., cognitive, motor, behavioral and academic outcomes) has been widely studied (Allotey et al., 2018; Arpi et al., 2019;

Bhutta et al., 2002; Brydges et al., 2018; Chan et al., 2016; Dean et al., 2021; McBryde et al., 2020; Mendonça et al., 2019; Rees et al., 2022; Twilhaar et al., 2018; Wong & Edwards, 2013). However, there is a dearth of research that focuses on the neurodevelopmental outcomes in samples that are well-characterized and homogeneous in terms of their clinical manifestations (i.e., high- vs. low-risk preterm samples).

2.3.1. High-risk PB

Preterm newborns are at a higher risk of suffering from brain injury and poor neurologic outcomes due to their brain immaturity and the severe stresses they may have undergone during the perinatal and neonatal periods. Noteworthy progress has been made in the prevention and treatment of many PB complications. For instance, quantitative magnetic resonance imaging (MRI) has exposed discrepancies between the normative developing pathways of the preterm brain at term-equivalent age and infants born at full term, suggesting significant ex utero environmental effects (Counsell et al., 2003). High-risk PB is a term used to describe PB coupled with a newborn brain injury. Research encompassing PB to neonatal brain injury has primarily shown impairments in overall neuropsychological functioning (Anderson, 2014). Encephalopathy of PB, which includes severe brain lesions such as periventricular leukomalacia (PVL) and germinal matrix-intraventricular hemorrhage (GM-IVH), is the most common type of preterm brain injury (Inder et al., 2018). From pages 39 to 42, a further development of both brain injuries will be made.

2.3.1.1. PB neonatal brain injury. Critical biological processes take place during the third trimester of brain development and are necessary for optimum brain growth. When compared to healthy in utero fetuses, brain growth is disturbed after PB even in the absence of structural brain injury (Bouyssi-Kobar et al., 2016). However,

the most frequent type of injury to the preterm brain is cerebral white matter (WM) injury, which is characterized by the loss of premyelinating oligodendrocytes (pre-OLs) and is closely linked to neurodevelopmental dysfunction. The extraordinary sensitivity of WM to the aberrant environment of preterm extrauterine life, in particular ischemia and inflammation, is explained by the distinct cerebrovascular anatomy and physiology of the premature neonate (Khwaja & Volpe, 2008). The cerebral cortex, thalamus, and basal ganglia are all dysmature as a result of cerebral WM injury after PB since these developmental events are initially dependent on normal pre-OL development, which is impaired in this condition (Inder et al., 2021). In contrast, perinatal brain injury in a term newborn will cause neonatal encephalopathy, which most frequently manifests as seizures and decreased reactivity (Hagberg et al., 2016). Therefore, in the term newborn, a dissimilar regional vulnerability is seen leading to two major patterns of injury: a watershed predominant pattern involving the WM, which can extend to the cortical gray matter (GM) when severe; and a basal ganglia/thalamus predominant pattern involving the deep gray nuclei (Miller et al., 2005).

2.3.1.1.1. Germinal matrix-intraventricular hemorrhage (GM-IVH)

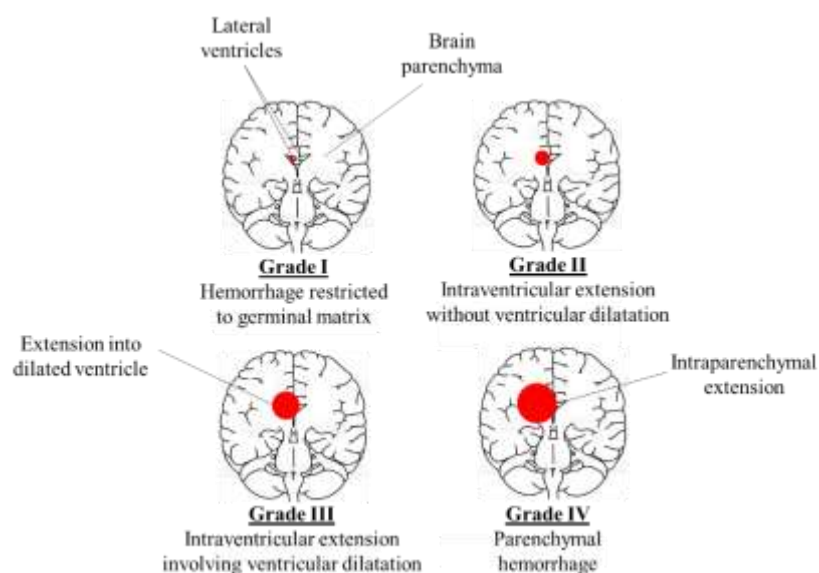
Germinal matrix-intraventricular hemorrhage (GM-IVH) is common in preterm infants and usually occurs within the first week of life (Antoniuk & Da Silva, 2000). The bleeding originates from the small blood vessels in the subependymal germinal matrix, which can rupture the ependymal lining and extend into lateral ventricles (Volpe, 2015). Consequently, GM-IVH significantly increases mortality and morbidity rates (i.e., posthemorrhagic hydrocephalus [PHH], posthemorrhagic ventricular dilatation [PHVD], CP, epilepsy and motor, cognitive, visual and hearing impairments) (Bolisetty et al., 2014; Egesa et al., 2021; Pieper et al., 2003; Rees et al., 2022). All

grades of hemorrhage have been related to poor neurodevelopmental outcomes; however, the worst consequences have been more frequently associated with severe grades of GM-IVH (Futagi et al., 2006; Rees et al., 2022; Sherlock et al., 2005) and the shortest gestation periods (Klebermass-Schrehof et al., 2012). Nevertheless, possible adverse outcomes vary greatly during the course of development (Valdez Sandoval et al., 2019).

Depending on the location and intensity of the bleeding, Papile et al. (1978) created a four-grade classification of GM-IVH using computed tomography scans. Hemorrhage that is restricted to the germinal matrix is classified as grade I, hemorrhage that extends into the lateral ventricles without ventricular dilatation is classified as grade II, ventricular hemorrhage combined with ventricular dilatation is classified as grade III, and parenchymal hemorrhage is classified as grade IV (see Figure 3).

Figure 3

Papile's IVH grade classification



Note: Figure created based on Chari et al., 2021 Child's Nervous System.

Around 25% of all VLBW preterm newborns suffer from this type of brain injury (Inder et al., 2018), meanwhile about 16% of preterm infants with a GA of 24 weeks or less have severe intraventricular hemorrhage (Stoll et al., 2010). Because the incidence of GMH-IVH correlates closely with the degree of immaturity and the survival rate of very small preterm newborns is increasing, it seems that will remain a major problem of concern. In fact, most significant types of preterm brain injury can be categorized as either concurrent lesions or consequences of GMH-IVH (e.g., PVL/PHH and periventricular hemorrhagic infarction [PVI]) (Roland & Hill, 2003). It is for this reason that adverse overall development throughout infancy has been linked to GM-IVH (Egesa et al., 2021; Inder et al., 2018; Leijser & de Vries, 2019; Rees et al., 2022; Roland & Hill, 2003; Whitelaw et al., 2002).

2.3.1.1.2. Periventricular leukomalacia (PVL)

In preterm infants, periventricular leukomalacia (PVL), which is damage to the developing cerebral WM, is the most frequent cause of CP (Bass, 2011; Deng et al., 2008). Perinatal infection, particularly maternal fever and newborn sepsis, and hypotension with inotrope use are major perinatal risk factors for WM abnormalities (Inder et al., 2003). MRI is the most successful technique for detecting PVL in the neonatal period, which can provide prognostic data of both GM atrophy and tract degenerations (Inder et al., 1999; Nagae et al., 2007).

There are two features defining PVL pathologically: diffuse reactive gliosis in the surrounding WM and focal necrosis in the periventricular region. Although they frequently co-occur, it is becoming increasingly understood that the diffuse component can exist independently of the focally necrotic component. Indeed, cystic WM injury (i.e., cystic PVL) has become a rare condition as a result of advancements in neonatal care (Hamrick et al., 2004). Meanwhile, EPT newborns tend to have the non-cystic,

predominantly diffuse form of WM injury (Inder et al., 2003). The diffuse lesion causes a global delay in myelination, while necrotic foci develop into cysts or focal glial scars involving both axons and glial cells. Differences are thought to be caused by the preferential loss of pre-OLs in the immature WM (Haynes et al., 2003; Iida et al., 1995; Kinney et al., 2004). Signs and symptoms of diffuse WM lesions are more extensive and may include cognitive and behavioral impairments seen in preterm survivors, whereas focal necrotic lesions strongly correlate with motor deficits of CP (Folkerth, 2006; Volpe, 2003). However, in general, spastic diplegia, visual, motor, cognitive, and behavioral/attentional impairments are known to be common morbidities of PVL (Ahya & Suryawanshi, 2018).

2.3.2. Low-risk PB

Preterm infants that are thought to have a lower risk for neurodevelopmental problems frequently have GAs between 30 and 36 weeks, mild perinatal problems, and absence of cranial ultrasound (CUS) brain abnormalities (Caravale et al., 2005, 2012; Hart et al., 2008; Soria-Pastor et al., 2009). Given that PB is considered to be a chronic condition (Raju et al., 2017), it is known that even in infants with a GA between 34 to 36 weeks, adverse long-term neurodevelopmental alterations may still develop. However, infants born late preterm, in contrast to those born at 34 weeks, are usually referred to well-newborn maternity units (Escobar et al., 2006). As stated by Mitha et al. (2021), although risks for severe neonatal morbidities are low, late PB still led to a higher risk of adverse outcomes. So, based on these findings, MLPT newborns should not be treated the same as those born at term (Boyle & Boyle, 2013).

Low-risk preterm infant's nervous system immaturity could be responsible for long-term neurodevelopmental problems (Walsh et al., 2014). In the absence of major or significant structural brain injury, third-trimester brain growth is disrupted in

preterm infants compared to healthy in utero fetuses (Bouyssi-Kobar et al., 2016). Due to the timing, they are born during a crucial period for brain development; hence, morbidity and mortality is found to be higher than in their full-term peers (Engle, 2007). Likewise, as mentioned above, these subgroups account for more than 80% of PBs and some of them may underperform academically in a variety of higher- and lower-order subskills (McBryde et al., 2020; Shapiro-Mendoza & Lackritz, 2012). As a result, these preterm newborns are allocated a significant proportion of the financial resources available for PBs as a whole (Behrman & Butler, 2007).

2.4. PB neuropsychological profiles

While neonatal mortality and morbidity rates among preterm newborns have declined significantly in recent decades, these children remain at greater risk of evolving cognitive deficits that must be monitored correctly in the long-term (Anderson, 2014). For instance, mild to severe deficits in a number of central cognitive domains have been found after PB. Deficits in intelligence and executive function, at least, might be associated with GA and/or BW but not with age at evaluation; meaning that (1) as GA and/or BW decrease, the degree of cognitive deficits increases, and that (2) cognitive difficulties exhibited by children born preterm may be deficits instead of delays (Brydges et al., 2018).

The following table (i.e., Table 3) summarizes neuropsychological findings related to PB throughout infancy and childhood, as well as adolescence and adulthood. To facilitate comprehension, the data will be grouped into high- and low-risk preterm samples. Furthermore, the emphasis will be placed on general cognitive functioning and the main cognitive domains affected by PB, such as executive functions, memory, and attention/processing speed.

Table 3*PB neuropsychological profiles*

AUTHOR, YEAR		MAIN FINDINGS
INFANCY & CHILDHOOD		
High-risk preterm		
General cognition	(Arpi et al., 2019; Bhutta et al., 2002; Yaari et al., 2018)	Children born preterm are at higher risk of having poor cognitive scores, and their birth immaturity is closely linked to their mean cognitive functioning at school age. Lower scores in several cognitive domains are commonly displayed in preterm-born infants compared to their full-term peers, which seem to appear early in life and remain long-term.
Executive functions	(Burnett et al., 2018a)	An EPT/ELBW cohort demonstrated poorer executive functions (i.e., working memory, planning, and organization) compared to previous cohorts.
Memory	(Nosarti & Froudish-Walsh, 2016)	Following VPT delivery, because of specific structural brain alterations, episodic memory deficits have been found during childhood.
Attention & processing speed	(Anderson, 2014; Ginnell et al., 2021; Murray et al., 2014)	PB is associated with impairments in processing speed and attention networks, but a robust and detailed articulation of a distinctive preterm attention phenotype cannot be ascertained from the available data.
Low-risk preterm		

General cognition	(Allotey et al., 2018; Ananth et al., 2013; Chan et al., 2016; Chyl et al., 2008; Jin et al., 2020; Martínez-Nadal & Bosch, 2021)	Neuropsychological impairments in low-risk preterm-born individuals have been identified during childhood.
Executive functions	(Arhan et al., 2017; Martínez-Nadal & Bosch, 2021)	Poorer performance in executive functions has been found after low-risk PB compared to full-term controls during childhood
Memory	(Martínez-Nadal & Bosch, 2021; Odd et al., 2012)	Lower scores in short-term verbal memory following low-risk PB have been discovered; meanwhile, MLPT infants achieved memory outcomes comparable with those born at term.
Attention & processing speed	(Arhan et al., 2017; Bogičević et al., 2019; Jin et al., 2020; Martínez-Nadal & Bosch, 2021)	Several authors proposed that low-risk PB exhibit lower scores in attention, but also processing speed during childhood.

ADOLESCENCE & ADULTHOOD

High-risk preterm

General cognition	(Arpi et al., 2019; Burnett et al., 2013; Linsell et al., 2018; O'Reilly et al., 2020; Vollmer & Stålnacke, 2019; Yaari et al., 2018)	Long-lasting cognitive functioning can be predicted with moderate accuracy from evaluations done during childhood; those who do poorly on early childhood assessments are unlikely to catch up.
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Executive functions	(Brydges et al., 2018; Vollmer & Stålnacke, 2019)	Individuals who perform poorly on early childhood age assessments are unlikely to catch up in executive function, despite the fact that the trajectory for this ability is rather uneven.
Memory	(Aanes et al., 2015; Nosarti & Froudust-Walsh, 2016)	Altered memory function persists until adulthood after VPT/VLBW.
Attention & processing speed	(Eryigit Madzwamuse et al., 2015; Vollmer & Stålnacke, 2019)	Following VPT and EPT, adults have displayed problems with attention and processing speed performances.
Low-risk preterm		
General cognition	(Chan et al., 2016; de Jong et al., 2012; Raju et al., 2017)	MLPT subgroups may still be at a higher risk of adverse neurodevelopmental outcomes; leading to a less optimal cognitive functioning from infancy through adulthood.
Executive functions	(Suikkanen et al., 2020)	Adults born late preterm outperformed full-term controls in working memory on average.
Memory	(Dalziel et al., 2007; Heinonen et al., 2015)	Deficits in memory function have been found after late PB; whereas, at 31 years of age, moderately preterm adults have not been related to delayed memory performance.
Attention & processing speed	(Dalziel et al., 2007; Suikkanen et al., 2020)	MLPT adults have outcomes in attention functioning comparable with full-term controls.

2.5. PB emotional-behavioral problems

Due to brain vulnerability identified after PB, increased susceptibility to external stresses during critical periods of development might evolve to behavioral and socioemotional problems in children born preterm (Peralta-Carcelen et al., 2018). Findings back up the notion that children delivered prematurely are more likely to display symptoms of attention deficit/hyperactivity disorder, autism spectrum disorder, and anxiety disorders (Fitzallen et al., 2020). In adulthood, preterm-born individuals have worse educational attainment, employment, independent living, and/or socioeconomic status (SES) (Vollmer & Stålnacke, 2019). Adults born preterm or with LBW are much less likely to have a romantic relationship, engage in sexual activity or become parents, which may raise the risk of poor well-being and non-optimal physical and mental health (Mendonça et al., 2019). For a better understanding, hereinafter, literature will be divided into homogeneous populations of high- and low-risk PB.

2.5.1. High-risk PB

At higher-risk, PB seems to have an impact on social cognitive, adaptive, and behavioral functioning (Marleau et al., 2021). This pattern is known as “preterm behavioral phenotype” that includes difficulties with emotions, attention, and peer relationships. Furthermore, preterm behavioral phenotype has an increased likelihood of internalizing rather than externalizing problems, being more prevalent at youngest GA (Johnson & Marlow, 2011). Nevertheless, children born EPT or ELBW exhibit a variety of qualitatively diverse behavioral outcomes, suggesting a heterogeneous behavioral phenotype. The majority of those children exposed minimal behavioral difficulties (i.e., emotional symptoms, conduct problems, hyperactivity/inattention, and peer problems), and only 20% exhibited a profile in accordance with the preterm behavioral phenotype (Bhutta et al., 2002; Burnett et al., 2019).

In addition, less optimal cognitive and academic performance has been associated with increasing severity of behavioral problems. Indeed, preterm infants' behavioral pattern associates with factors beyond social cognition, including attention, language, and socioeconomic background (Dean et al., 2021). Hence, understanding the heterogeneity in behavioral characteristics might be critical for developing more targeted intervention approaches. Profiles with more severe behavioral difficulties, for instance, reported higher prevalence of neurosensory impairments as well, which could be the result of altered brain development (Burnett et al., 2019). Cognitively stimulating experiences have been linked to lower levels of developmental psychopathology and executive dysfunction congruous with the preterm behavioral phenotype (Vanes et al., 2021). However, among EPT-born adolescents, behavioral problems have not been predominantly observed in those with major neurological disabilities (Samuelsson et al., 2017).

2.5.2. Low-risk PB

Birth at between 32 and 36 weeks of gestation increases the odds for delayed social competence at 2 years of age, which may indicate a higher risk for negative mental health consequences during childhood (Johnson et al., 2015). Male gender, prenatal infection, and maternal smoking are risk factors for behavioral difficulties in MLPTs, whereas multiple birth has been stated as having a protective impact on emotional outcomes (den Haan et al., 2019). On the other hand, children born low-risk preterm do not have higher rates of behavioral disorders (Pérez-Pereira & Baños, 2019). That is to say, clinically relevant behavioral disorders have not been found following low-risk PB. Similarly, Gurka et al., (2010) discovered that infants born late preterm did not exhibit significant shifts from typical behavioral and socioemotional development. Again, the lack of agreement across authors suggests that more research,

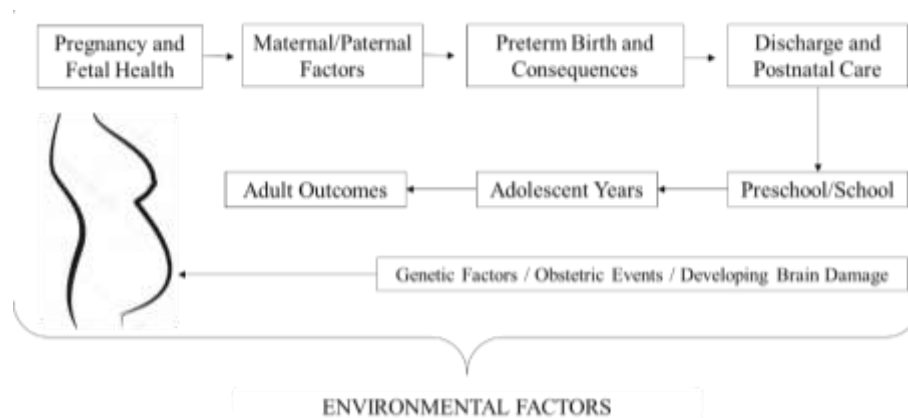
as well as longer follow-up of MLPT children, are needed to establish what effects, if any, are developed later in life.

2.6. Early life environmental factors

PB alters the brain in a wide range of ways, depending on the degree of neonatal immaturity, neurological impairment, environmental influences, and the moment when they occur (Dimitrova et al., 2020; Sansavini et al., 2011). Brain maturation during both prenatal and postnatal periods are considered sensitive periods of development, highly vulnerable to both positive and negative biological and environmental influences (Cheong et al., 2020). Biological factors have an impact on cognition at 22 months of age; however, these effects appear to fade over time (Pérez-Pereira et al., 2020). PB can cause increasing susceptibility to several early life environmental influences given that children born preterm have a higher biological vulnerability (de Jong et al., 2012). Since early environmental exposures can alter preterm infants' long-term neurodevelopment (Cheong et al., 2020), it is crucial to consider the potential impact of specific environmental factors such as noise, developmental care or parental mental health on neurodevelopment following PB, among others (see Figure 4).

Figure 4

Biological and environmental pathways influencing adults' outcomes after PB



Note: Figure created based on Raju et al. (2017), *Acta Paediatrica*.

Certain biological and social factors play a role in influencing cognitive and academic challenges, but these influences differ through development (Burnett et al., 2018b). Early social environment, nurture, and health care could explain more than 1/3 of the heterogeneity in cognition of VPT and VLBW adults (Breeman et al., 2017). For instance, mothers' lower educational level may have an impact on poor cognitive functioning (Linsell et al., 2018). The role of socioeconomic background also seems to call into question the relationship between PB and cognitive deficits throughout childhood (Wong & Edwards, 2013). Furthermore, the quality of the home environment and parenting behaviors have been shown to have certain effects on preterm-born neurobehavioral outcomes (McMahon et al., 2022; Pérez-Pereira et al., 2020). Nonetheless, the extent to which early life environmental influences may affect long-term performance after PB is still unknown. The following three environmental factors will be discussed in more detail below: SES, parental bonding, and adverse childhood experiences (ACEs).

2.6.1. Socioeconomic status (SES)

Parental education and family income are known to impact structural brain regions that are crucial for the development of language, executive functions and memory (Noble et al., 2005; 2015). In preterm populations, there is growing evidence that SES influences the relationship between early-life exposures, brain damage, and neurodevelopmental consequences (Benavente-Fernández et al., 2020). In fact, during preschool age, perinatal biologic risks became less relevant, whereas SES remained increasingly important (Ross & Perlman, 2019). Independent of the degree of immaturity, low parental education has been related to considerably poorer neurocognitive and academic outcomes in heterogeneous preterm samples (Joseph et al., 2018; Sentenac et al., 2021; Stålnacke et al., 2019). In fact, the link between brain damage and adverse cognitive outcomes is

weaker in children born VPT with highly educated mothers (Benavente-Fernández et al., 2019). These strong connections, in both healthy infants and those with clinical conditions, show that the relationship between SES and long-term cognitive functioning is mediated by changes in brain development (Leijser et al., 2018).

According to Wolke (2019), high SES can be regarded as a universal protective factor that leads to better results regardless of whether the child has faced neonatal risk. If, on the other hand, high SES is considered a resiliency factor, those at risk would benefit disproportionately more from growing up in a high SES background. The role of SES on development is still not clear; however, socioeconomic determinants might impact the long-term well-being of EPT and VPT children (Twilhaar et al., 2018). Children exposed to both PB and low SES achieve the worst outcomes in cognitive development (Beauregard et al., 2018). Nevertheless, short- and long-term study findings after low-risk PB are still needed.

2.6.2. Parental bonding

PB has an impact on parent-child bonding (Provasi, 2019); parenting and parental mental health influence an offspring's neurodevelopmental outcomes during the early stages of development, serving as either a protective or aggravating potential factor following VPT deliveries (Montagna & Nosarti, 2016). After PB, optimal brain development can be enabled through responsive care provided by parents (DeMaster et al., 2019). That is to say, positive parenting has predicted the academic catch-up of children born with LBW or VLBW, whereas adverse parenting predicts considerably lower achievement (Jaekel et al., 2015). Hence, healthcare professionals, institutions, and politicians should foster any environment that promotes positive and well-adapted relationships. This includes assisting with decoding and gradually adapting care to

include infant-specific individualities (i.e., PB outcomes) and parental emotional reactions (Provasi, 2019).

Mothers of preterm-born children and mothers of full-term controls displayed comparable sympathetic and receptive measures (Bilgin & Wolke, 2015). However, bonding in parents of preterm infants may be higher than in parents of full-term controls in wealthy countries (Hoffenkamp et al., 2012). Indeed, despite a more protective and supportive parenting style being encouraged by PB (Pyhälä et al., 2011), parents of children born preterm are also more likely to engage in controlling parenting practices (Toscano et al., 2020).

Sensitive parenting (i.e., parents who actively foster academic resilience through cognitive stimulation and attentive parenting) protects against the adverse impact of VPT/VLBW delivery on school outcomes during adolescence (Wolke et al., 2013). Parental demandingness has also been associated with enhanced cognitive functioning, while parental warmth is related to fewer internalizing and externalizing problems during childhood (Neel et al., 2018). The prevalence of adverse behavioral symptoms in children born VPT is susceptible to a cognitively challenging home environment. Disturbed parent-child interactions pose an additional developmental risk for social-emotional problems in VPT samples (Montagna & Nosarti, 2016). Therefore, parental responsiveness may be critical in improving neurodevelopment in preterm newborns (Neel et al., 2018). However, comparable data in low-risk preterm populations is lacking.

2.6.3. Adverse childhood experiences (ACE)

Adversity has been found to influence a child's molecular and genetic constitution, as well as the way neurological, immunological, and endocrine systems develop and function (Boullier & Blair, 2018). The most common types of ACEs faced by children in the United States were economic hardship (22.5%) and parent or guardian divorce or

separation (21.9%) (Crouch et al., 2019). According to Elmore and Crouch (2020), children who had four or more ACEs had a higher risk of suffering anxiety and depression than children who had fewer than four ACEs. Moreover, three or more ACEs have also been linked to certain measures of children's mental and physical health (Turney, 2020). In adulthood, mental health outcomes have also been repeatedly linked to ACE exposure; the impact of these ACEs on adult health status is powerful and cumulative (Chapman et al., 2004; Felitti et al., 2019). Given the evidence of their long-term influence on health, ACEs are a major public health concern (Boullier & Blair, 2018). There is scarce data on these negative experiences following PB; however, ACEs negatively correlated with multiple domains of development in heterogeneous preterm samples (Chung et al., 2020).

2.7. Brain development in PB

The growth of the brain is dependent on a number of complicated and interconnected processes. For instance, GM maturation and functional specialization, as well as the development and myelination of WM connections between different brain regions. Development is the result of interactions between genetic programming, epigenetic variables, and environmental circumstances. Concretely, brain development mainly involves the generation, cutting, and reorganization of neural connections to form brain networks that reflect individuals' experiences and help them adapt to their surroundings. Since the overall structure of the brain is formed prior to term age, brain alterations are more significant during the final weeks of pregnancy and the early postnatal months. Even though the newborn's brain is structured into functional networks from birth, it is not a miniaturized adult brain. Some regions, such as the sensory ones, develop early and fast, whereas associative regions, such as the frontal ones, develop later and slowly up to the end of adolescence. At the same time as this structural evolution of the brain, the child gradually acquires new psychomotor and cognitive skills, although it

is unclear how brain maturation causes the often abrupt changes in behavior seen throughout development (Budday et al., 2015; Cheong et al., 2020; Dubois et al., 2014; Gogtay et al., 2004).

Moreover, cortical development takes place between the ages of 1 and 6 and is characterized by changes in cortical thickness (CTh), surface area, curvature, and GM. Cortical growth trajectories are based on neuroanatomical location, as well as region-specific asymmetries in cortical development (Remer et al., 2017). For instance, age and CTh are shown to have a negative relationship. The highest peak of developmental values of CTh have been reported during childhood in most regions (Frangou et al., 2022).

Altered brain growth after PB, caused by early exposure to the extrauterine environment and aggravated by neuroinflammation, neonatal brain injury, and genetic predisposition, can lead to long-term changes in brain structure and function (Allen et al., 2010; Cheong et al., 2020; Vanes et al., 2022). As previously mentioned, the preterm brain is developed depending on the degree of neonatal immaturity, neurological impairment, environmental factors, and the timing of the child's birth (Sansavini et al., 2011). Deviations from typical brain development following PB have even been related to cognition during child stage (Dimitrova et al., 2020). Therefore, accurate diagnosis of mild or severe neonatal brain abnormalities may mitigate some of the neurodevelopmental concerns of preterm newborns through the implementation of more targeted early intervention programs to improve this population's quality of life (Reubsæet et al., 2017).

The advancement of non-invasive techniques such as MRI has made it possible to link the maturation of cerebral structures to neurodevelopment. Several accessible MRI techniques allow for exploration and tracking of brain development and the plasticity of healthy and at-risk infants over time. MRI is an excellent and risk-free technology for

examining the developing brain. It is non-invasive and non-ionizing, and it allows for significant distinction of regions within the immature brain, demonstrating the rapid development that takes place from 23 to 40 weeks of gestation. Moreover, MRI exhibits the well-known lesions found on CUS while also detecting more subtle abnormalities (Anderson et al., 2015; Counsell et al., 2003; Inder et al., 2021). MRI has been used to define possible abnormalities in cerebral development, since PB impact on cortical micro- and macrostructural maturation and development varies considerably between individual preterm newborns (Dimitrova et al., 2021).

The main neuroimaging measurements studied in this thesis are briefly described below together with their correlations with neuropsychological performance after high- and low-risk PB, respectively.

2.7.1. Structural neuroimaging

2.7.1.1. Volumetric findings. Since there is significant variability in the way that PB impacts brain development (Dimitrova et al., 2020), MRI may correctly detect and quantify GM and WM alterations, which relate to cognitive performance in both high- and low-risk preterm samples (Hadaya & Nosarti, 2020; Luu et al., 2009; Peterson et al., 2000; Soria-Pastor et al., 2009).

PB has been related to regional volume abnormalities at term-equivalent age (Alexander et al., 2019). Even in the absence of focal brain lesions, EPT newborns have an altered global and regional brain growth pattern, involving decreases and increases of brain tissue volumes at term-equivalent age and during childhood (Kvanta et al., 2021; Padilla et al., 2015). Following VPT, altered structural brain development persists in middle age (Kelly et al., 2023; Nosarti et al., 2014).

The preterm brain impacts cognitive functioning during childhood (Vanes et al., 2021); actually, specific brain abnormalities have been associated with a poorer

intelligence quotient (IQ) and executive function across adolescence and adulthood (Hadaya & Nosarti, 2020). After high-risk PB, smaller GM and WM volumes have been linked to GA, which mediated cognitive impairments in a variety of domains in adolescents born VPT (Nosarti et al., 2008). Reductions in thalamus, hippocampus, basal ganglia, amygdala, and cerebellar WM and GM volumes have an indirect effect on VLBW preterm-born adults' IQ (Rimol et al., 2023). More specifically, hippocampal structure appears to be particularly susceptible to adverse pre-perinatal events such as hypoxia/ischemia (Strahle et al., 2019), which are characteristic of high-risk PB.

In low-risk PB, smaller volumes across many subcortical GM and WM structures have been found during childhood (Arhan et al., 2017; Soria-Pastor et al., 2009). Regional cortical GM and WM volumes have been linked to cognitive and language performance in MLPT children at 2 years of age (Kelly et al., 2020). Furthermore, GM reductions in temporal and parietal regions have been proven to be directly correlated with IQ (Soria-Pastor et al., 2009) and anxiety symptoms (Rogers et al., 2014) during childhood. However, long-term brain volumetric findings correlates with neuropsychological performance of adults born low-risk preterm must be explored.

2.7.1.2. Cortical thickness findings. PB leads to atypical cortical development (Kapellou et al., 2006; Nosarti et al., 2011; Phillips et al., 2011), which has been closely linked to general and specific cognitive functioning during infancy (Barnes-Davis et al., 2020; Mürner-Lavanchy et al., 2018; Srzentić et al., 2020). Children born with VPT had thicker CTh in frontal, occipital, and fusiform gyri, and inferior pre-post-central areas, with thinning in the midcingulate cortex (Vandewouw et al., 2020). Furthermore, children and adolescents born preterm without acute brain injury had a considerably thinner temporal and parietal cortex compared to full-term controls (Hasler et al., 2020; Moeskops et al., 2013; Nagy et al., 2011).

In high-risk preterm samples, CTh from mid-adolescence to young adulthood remains altered following VPT (Nam et al., 2015). In adults with VLBW, CTh has been found to be larger in frontal and occipital regions (Rimol et al., 2019). CTh is primarily reduced in the left hemisphere in adults born preterm, which mediates the association between PB and IQ (Schmitz-Koep et al., 2020).

Low-risk preterm children also displayed a thinner cortex in the left postcentral, supramarginal, and caudal middle rostral gyri (Zubiaurre-Elorza et al., 2012). Nevertheless, once again, there is scarce research about CTh in individuals born low-risk preterm.

2.7.1.3. White matter integrity findings. Diffusion tensor imaging (DTI) is a non-invasive MRI method that evaluates water diffusion, characterizing the properties of soft biological tissues on a microstructural scale (Basser & Pierpaoli, 2011). There are four main indexes that are commonly extracted from the DTI. The fractional anisotropy (FA) index is obtained as an estimation of the direction of water molecule motion in each voxel; moreover, mean (MD), axial (AD) and radial diffusivity (RD) expose the average diffusion within a voxel, the amount of diffusion parallel to the diffusion principal axis and the diffusion magnitude perpendicular to the main diffusion direction, respectively. Shifts in water diffusion are an excellent indicator of cellular damage; thus, DTI may also be utilized to detect brain injury or subtle abnormalities before conventional MRI. That is to say, changes in diffusion properties can offer extra evidence of possible focal and diffuse WM injury (Hüppi & Dubois, 2006; Liu et al., 2012).

Preterm neonates have abnormalities in the WM microstructure, including anisotropy decrements and diffusivity increments (Dibble et al., 2021). These lower FA values persist through adolescence and adulthood (Allin et al., 2011; Hadaya & Nosarti, 2020; Meng et al., 2016). Microstructural WM anomalies may strengthen the higher risk

of adverse neurodevelopmental outcomes observed in infants born preterm later in life (Dibble et al., 2021). For instance, GA, BW, reductions in GM, and poor IQ in preterm-born adults have been associated with FA decreases (Allin et al., 2011; Meng et al., 2016).

WM microstructure abnormalities are known to be more pronounced in VPT samples than in MLPT newborns, possibly due to an altered myelination process following high-risk PB (Dibble et al., 2021). However, low-risk PB also leads to a lower FA and higher AD and RD in nearly 70% of the brain's main WM fiber tracts at term-equivalent age (Kelly et al., 2016). An increased AD and RD in the optic radiations, centrum semiovale, and posterior limb of the internal capsule can imply less progressed maturation of the WM after low-risk PB (Leitner et al., 2014). Moreover, increased FA and lower AD, RD, and MD in several WM regions have been related to better cognitive and language performance in MLPT children (Kelly et al., 2020). Nonetheless, little evidence concerning WM microstructural findings in low-risk preterm-born adults remains a gap in knowledge.

2.7.2. Functional neuroimaging

The technique of functional magnetic resonance imaging (fMRI) is well established for the identification and localization of regions of the brain that alter their level of activity in response to particular experimental circumstances. The majority of fMRI investigations employ snapshot imaging techniques such as echo-planar sequences that are responsive to changes in the blood-oxygenation-level-dependent (BOLD) signal, which reflects neural activation (Ogawa et al., 1990). fMRI studies generate activation maps that typically show the average level of involvement of brain regions during the course of a particular task or in reaction to a particular stimulus (Rogers et al., 2007). However, because of minimal subject effort and competency in characterizing functional networks in the pediatric population, the resting state functional magnetic resonance

imaging (rs-fMRI) technique has outperformed other fMRI techniques (Smitha et al., 2017).

2.7.2.1. Resting state functional connectivity (rs-fc). During the third trimester of pregnancy, resting state networks arise (Doria et al., 2010); thus, they emerge prior to the acquisition of cognitive domains in later childhood and continue until young adulthood (Kwon et al., 2016). Signs of altered functional connectivity (FC) have been discovered in the preterm brain even before birth (Thomason et al., 2017). Neonates born VPT have less segregated and integrated resting state networks than full-term controls at term-equivalent age (Bouyssi-Kobar et al., 2019). Even in the absence of significant structural abnormalities, intrinsic brain activity is reduced due to PB (Smyser et al., 2016).

Given that thalamocortical and subcortical-cortical connections emerge during the critical period in the NICU, they seem to be key for posterior preterm neonates' neurocognitive functioning (Brenner et al., 2021; Smyser et al., 2010; Toulmin et al., 2021). In a high-risk preterm population, moderate or severe diffuse WM abnormalities together with very small GA led to decreased rs-fc in executive control and frontoparietal networks, which may be a predisposing factor for cognitive difficulties found during the first years of life (He & Parikh, 2015). However, FC alterations could be present in the absence of major brain structural abnormalities. Children born VPT without evident neurological lesions exhibit FC alterations in important brain networks responsible for motor, language, and executive function soon after birth (Gozdas et al., 2018) and social-emotional outcomes during childhood (Mueller et al. 2022). The latter since the amygdala-prefrontal cortex circuit is impacted by negative experiences (VanTieghem & Tottenham, 2018), prenatal stress after PB also has an impact on the amygdala's FC (Scheinost et al., 2016). From the little that is known in low-risk PB, in late preterm children prefrontal cortical connectivity with posteromedial cortex and lateral parietal

cortex is known to be altered in the absence of neuropsychological deficits (Degnan et al., 2015a; 2015b). The preterm brain has significant variability in FC of higher cognitive networks (Stoecklein et al., 2020), even altering rs-fc in middle age (Bäumel et al., 2015; White et al., 2014). Patterns of altered rs-fc in the occipital and parietal cortices, for example, have been associated with visual short-term memory in preterm-born adults (Finke et al., 2015). Furthermore, preterm individuals without substantial brain injury have altered FC in the cerebellum, which is particularly linked to language performance even in young adulthood (Constable et al., 2013). However, adults born low-risk preterm still need to be adequately studied as regards their brain FC and its correlates.

**III. Rationale, approach to the present work, general
objectives, and hypotheses**

3. Rationale, approach to the present work, general objectives, and hypotheses

Neurological damage, environmental factors, and the time of their occurrence all affect the way PB shapes the brain (Dimitrova et al., 2020; Sansavini et al., 2011). However, there is a dearth of research converging neurodevelopmental outcomes in well-characterized samples in terms of clinical manifestations (high- vs. low-risk preterm samples), which would allow researchers to assess the effect of PB *per se* and brain injury on cognition and brain development respectively. Specifically given that just a small percentage of children born MLPT have a profile of developmental difficulties that is close to the VPT phenotype (Johnson et al., 2018). Moreover, pursuant to the degree of neonatal immaturity, preterm-born children may have a higher biological vulnerability (de Jong et al., 2012). These neurodevelopmental consequences may contribute to lower education, occupational status, and income in this population, leading to decreased well-being and poorer mental and physical health (Kajantie et al., 2019; Winstanley et al., 2015). Even within lower GA there are greater odds of getting a disability pension and /or social benefits (Bilsteen et al., 2018). Nevertheless, aside from the presence or absence of neonatal brain injury, adverse environmental factors may also place preterm born individuals at an even greater developmental risk (Bills et al., 2021).

This thesis is made up of six studies and analyzes high- and low-risk PB, with the first two studies focusing on childhood, the next three covering adolescence and young adulthood, and the sixth study assessing adult stage (see Figure 1). More specifically, it addresses PB impact on the hippocampus and the associations with memory performance during childhood (*study I*); the neuropsychological profiles of MLPT children and the potential role that early life environmental factors play in the cognitive outcomes (*study II*); the long-term neurodevelopmental outcomes of MLPT adults in relation to cognitive

functioning and psychiatric disorders by a systematic review and meta-analysis (*study III*); the neuropsychological profiles of high- and low-risk preterm adolescents and young adults and the possible impact of environmental influences in early life on the cognitive outcomes (*study IV*); the brain structure and cognitive outcomes that can be found after low-risk PB in adolescents and young adults (*study V*); the amygdala structure and function and its link to social-emotional outcomes following low-risk PB during young adulthood (*study VI*).

Figure 1

Developmental stage of the studies included in the thesis



3.1. Study I

“Reduced hippocampal subfield volumes and memory performance in preterm children with and without germinal matrix-intraventricular hemorrhage”

Objectives

- The purpose of this MRI study is to consider the effects that high- and low-risk PB may have on the hippocampus of preterm children and its’ associations with memory performance.

Hypotheses

- High-risk preterm children with GM-IVH will have lower memory scores compared to their low-risk preterm and full-term peers.
- Those suffering from GM-IVH will evidence reduced hippocampal volumes in comparison to low-risk preterm and full-term groups during childhood, which might be related to a lower memory performance.

- Low-risk preterm children without GM-IVH will have decreased hippocampal volumetric values and poorer memory performance in contrast to full-term controls.

3.2. Study II

“Maternal Care and General Cognitive Functioning in Moderate and Late Preterm-Born Children”

Objectives

- To determine the neuropsychological profiles of MLPT children as two independent samples (i.e., moderate and late preterm groups).
- To assess the potential role that early life environmental factors play in the cognitive outcomes of MLPT children.

Hypotheses

- MLPT children will have lower cognitive scores compared to full-term controls.
- Moderate preterm children will have lower cognitive scores in comparison to late preterm and full-term groups.
- Early life environmental factors will moderate childhood cognitive outcomes after MLPT.

3.3. Study III

“Long-term Neurodevelopmental Outcomes after Moderate and Late Preterm Birth: A Systematic Review”

Objectives

- The main objective of this study was to conduct a systematic review and meta-analysis on the neurodevelopmental outcomes of MLPT born adults in relation to cognitive functioning and psychiatric disorders.

- The second objective was to observe the influence of study quality, age at evaluation, GA, and year of publication on the long-term neurodevelopmental outcomes of MLPT born adults.

Hypotheses

- MLPT born adults would have a worse cognitive functioning and greater risk of suffering from psychiatric disorders compared to full-term controls.
- MLPT born adults would have a better cognitive functioning and smaller risk of suffering from psychiatric disorders compared to those born EPT and VPT.
- Study quality, age at evaluation, GA, and year of publication would influence the long-term neurodevelopmental outcomes of MLPT born adults.

3.4. Study IV

“Preterm Birth and Early Life Environmental Factors: Neuropsychological Profiles at Adolescence and Young Adulthood”

Objectives

- To ascertain the neuropsychological profiles of high- and low-risk preterm adolescents and young adults.
- To evaluate retrospectively the potential role that early life environmental factors may play in cognitive outcomes of preterm-born adolescents and young adults.

Hypotheses

- Adolescents and young adults born high- and low-risk preterm will have lower cognitive scores compared to the full-term group.
- Adolescents and young adults born high-risk preterm will have lower cognitive scores compared to low-risk preterm and full-term controls.
- Early life environmental factors will moderate adolescent/young adults’ cognitive outcomes of high- and low-risk PB.

3.5. Study V

“Long-Term Brain Structural and Cognitive Outcomes in a Low-Risk Preterm-Born Sample”

Objectives

- To assess the brain structure and cognitive outcomes that can be found after low-risk PB in adolescents and young adults.

Hypotheses

- Adolescents and young adults born low-risk preterm will have lower scores in different cognitive domains, the general cognitive functioning score and current SES compared to full-term controls.
- Young adults born preterm will have smaller global (left/right) and regional CTh, cortical and subcortical volumetric values, and global mean and regional FA, AD, MD, and RD.

3.6. Study VI

“Amygdala Structure and Function and Its Associations with Social-Emotional Outcomes in a Low-Risk Preterm Sample”

Objectives

- To analyze differences in social-emotional profiles, amygdala volumes and its FC with medial frontal cortex (MedFC) between low-risk preterm and full-term young adults.
- To assess any potential relationships between amygdala volumes or FC (i.e., amygdala - MedFC) and social-emotional outcomes following low-risk PB during young adulthood.

Hypotheses

- Young adults born low-risk preterm would have lower social-emotional scores and reduced amygdala volumes and FC than full-term controls.
- Amygdala volumes and FC (i.e., amygdala - MedFC) will be related to social-emotional outcomes after low-risk PB across young adulthood.

IV. Methods

4. Methods

Methods section will first focus on the empirical studies (*studies I, II, IV and V*) and then the *study III* systematic review and meta-analysis specific methodology will be explained.

Study I, II, IV and V

4.1. Studies' samples

The present thesis comprises subjects born high- and low-risk preterm, as well as full-term controls from different datasets. The recruitment process as well as samples' characteristics will be further and widely explained in the following section.

4.1.1. High- and low-risk preterm subjects

4.1.1.1. Study I. A sample of children born high-risk preterm belonged to a cohort that was followed longitudinally at the Vall d'Hebron University Hospital (Barcelona, Spain). Children born low-risk preterm belonged to a cohort followed at the University of Barcelona (Barcelona, Spain) (see Table 1).

Table 1

Inclusion and exclusion criteria study I

	Inclusion criteria	Exclusion criteria
	PB with a GA <37 weeks.	Having a full-IQ ≤ 70 .
Both preterm groups	Age at time of evaluation of between 6 to 16 years old.	Experiencing any MRI counter-indications. A history of acquired brain injury, CP or other neurological impairment.
High-risk preterm group	Having a neonatal diagnosis of GM-IVH grades II to IV in CUS (Papile et al., 1978).	Being diagnosed with neonatal PVL, any other perinatal cerebral insult, or neurosensory alterations.

Low-risk preterm group	A GA of between 30 to 34 weeks, a BW of under 2500g and an Apgar score at 5 min >7.
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4.1.1.2. Study II. The neonatology department at Cruces University Hospital (Bilbao, Spain) recruited MLPT children considered to be at lower risk of presenting major disabilities. This was reinforced with chain-referral sampling (i.e., a non-probability sampling technique whereby current participants recommend new recruits) in two autonomous regions in Spain (Basque Country and Aragon) (see Table 2).

Table 2

Inclusion and exclusion criteria study II

	Inclusion criteria	Exclusion criteria
Low-risk preterm group	A GA of between 30 to 36 weeks. Age at time of evaluation of between 6 to 15 years old.	A history of acquired brain injury, CP or any other neurological impairment. Substantial neonatal morbidity (i.e., congenital, neurological, cardiac, or digestive malformations, necrotizing enterocolitis, or septic shock).

4.1.1.3. Study IV. A group of adolescents and young adults born high-risk preterm were part of a cohort that was studied longitudinally at the Vall d'Hebron University Hospital in Barcelona, Spain, in collaboration with the University Hospital Clínic (Barcelona, Spain). Preterm adolescents and young adults at lower risk of presenting major disabilities were also recruited at Cruces University Hospital (Bilbao, Spain). Remaining participants were recruited by chain-referral sampling (see Table 3).

Table 3

Inclusion and exclusion criteria study IV

	Inclusion criteria	Exclusion criteria
Both preterm groups	PB with a GA <37 weeks. Ranging in age at evaluation from 15 to 30 years.	
High-risk preterm group	Having a diagnosis of neonatal brain damage by neonatal CUS or MRI.	The concurrence of acquired brain injury, birth trauma, malformation, and infectious or metabolic encephalopathies.
Low-risk preterm group	GA of between 30 to 36 weeks. Absence of brain pathology identified by CUS.	Substantial neonatal morbidity (i.e., congenital malformations, neurologic, cardiac or digestive, necrotizing enterocolitis or septic shock).

4.1.1.4. Study V and VI. A sample of adolescents and young adults born low-risk preterm (i.e., between 16 to 40 years old) was recruited at Cruces University Hospital (Bilbao, Spain) and through chain-referral sampling (see Table 4) for study V. Furthermore, a subset of young adults took part in a neuroimaging analysis for study V and whole analysis for study VI with the same inclusion and exclusion criteria, except for an age range of 20 to 40 years.

Table 4

Inclusion and exclusion criteria studies V and VI

	Inclusion criteria	Exclusion criteria
Low-risk preterm group	A GA of between 30 to 36 weeks.	A history of acquired brain injury, CP or any other neurological impairment. Substantial neonatal morbidity (i.e., congenital, neurological, cardiac, or digestive malformations, necrotizing enterocolitis, or septic shock).

4.1.2. Full-term controls

4.1.2.1. Study I. A sample of children born full-term (GA \geq 37 weeks) with a BW higher than 2500g and age at time of evaluation of between 6 to 16 years old was recruited. The exclusion criteria were the same as those presented in Table 1 for both preterm groups.

4.1.2.2. Study II, IV, V and VI. A group of subjects born full-term (GA \geq 37 weeks) was recruited by chain-referral. However, the ages of assessment differed between studies: a) study II 6 to 15 years; b) study IV 15 to 30 years; c) study V 16 to 40 years; and d) study VI 20 to 40 years. Exclusion criteria for four studies were a history of acquired brain injury, CP, any other neurological impairment, congenital malformations or chromosomal abnormalities.

4.2. Neuropsychological Assessment

Studies I, II, IV, V and VI comprised a thorough neuropsychological assessment to evaluate the sample's cognitive, emotional-behavioral, early life environmental factors, and other measures (i.e., life satisfaction, functionality, resilience, personality data, and current SES). This assessment was conducted by trained neuropsychologists and will be discussed further below. The use of different psychometric tests will be determined by the aim of each study as well as the age of administration. A summary of the neuropsychological assessment is provided in Table 5, which is divided into the evaluated area/domain, study in which was measured, assessment tool, and administration age.

Table 5*Assessment tools for study I, II, IV, V and VI*

AREA/DOMAIN	STUDY	ASSESSMENT TOOL	ADMINISTRATION AGE
COGNITIVE ASSESSMENT			
Analogical reasoning	II, IV, V and VI	Wechsler Intelligence Scale for Children V (WISC-V)	6 – 16 years
		Raven's Advanced Progressive Matrices (RPM)	6 – adulthood
Receptive language	II, IV, V and VI	Peabody Picture Vocabulary Test III (PPVT-III)	2 _{1/2} – 90 years
Working memory	I, II, IV and V	Wechsler Intelligence Scale for Children V (WISC-V)	6 – 16 years
		Wechsler Adult Intelligence Scale IV (WAIS-IV)	16 – 90 years
Phonetic and semantic fluencies	II, IV and V	Verbal fluency test	6 – 90 years
Verbal memory	I and II	Rey Auditory Verbal Learning Test (RAVLT)	8 – 85 years
Processing speed	II, IV and V	Children's Color Trails Test (CCTT) part A	8 – 16 years
		The Trail Making Test (TMT) part A	15 – 70 years
		P and C measures from the Stroop Test	7 – 80 years
Cognitive flexibility	II, IV and V	Children's Color Trails Test (CCTT) part B	8 – 16 years
		The Trail Making Test (TMT) part B	15 – 70 years
		Modified Wisconsin Card Classification Test (M-WCST)	6 -89 years
		PC measure from the Stroop Test	7 – 80 years
Theory of mind	IV, V and VI	Happé's Strange Stories Test	6 – 90 years
Moral competence	IV, V and VI	Moral Judgment Test (MJT)	10 – adulthood
Delayed gratification	IV, V and VI	Delay Discounting Test (DDT)	Adolescence – adulthood

EMOTIONAL-BEHAVIORAL ASSESSMENT			
Internalizing and externalizing problems	I, II, IV, V and VI	Child Behavior Checklist (CBCL)	6 – 18 years
		Adult Self Report (ASR)	18 – 59 years
Behavior problems	II	Conners' Parent Rating Scale (CPRS)	6 – 18 years
Cognitive reappraisal and expressive suppression	VI	Emotion Regulation Questionnaire (ERQ)	18 – Adulthood
EARLY LIFE ENVIRONMENTAL FACTORS			
Parental care and overprotection	II, IV and V	Parental Bonding Instrument	Life span
Familial socioeconomic status (SES)	II, IV, V and VI	Hollingshead Index	Life span
Adverse childhood experiences (ACEs)	II, IV and V	Adverse Childhood Experiences International Questionnaire (ACE-IQ) for children, teens and adults	0 – 12 years
			13 – 19 years
			Adulthood
OTHER MEASURES			
Life satisfaction	II and V	Satisfaction with Life Scale-Child (SWLS-C)	9 – 14 years
		Satisfaction with Life Scale (SWLS)	Adolescence – adulthood
Disability levels	II and V	WHODAS 2.0 parent's report and for adults	Life span
Resilience	II and V	Connor-Davidson Resilience scale (CD-RISC2)	Above 10 years Adolescence
		Connor-Davidson Resilience scale (CD-RISC)	– adulthood
Psychiatric symptomatology	V	NEO FFI	12 – 99 years
Current socioeconomic status (SES)	IV, V and VI	Hollingshead Index	Life span

4.2.1. Cognitive assessment

Analogical reasoning, receptive language, working memory, phonetic and semantic fluencies, verbal memory, processing speed, cognitive flexibility, theory of mind, moral competence, and delayed gratification were measured:

Analogical reasoning. Analogical reasoning was evaluated using a subscale of the Wechsler Intelligence Scale for Children V (WISC-V) (Kaufman et al., 2015) or the Raven's Advanced Progressive Matrices (RPM) test (Raven & Court, 1998) depending on the age of administration. Both test consist of a visual geometric matrices with a missing piece. Depending of the age of administration five to eight possibilities are displayed to fill in the piece.

Receptive language. Receptive language was measured by the Peabody Picture Vocabulary Test III (PPVT-III) (Dunn & Dunn, 1981). The participant must choose which of the four displayed illustrations best represents the meaning of each term.

Working memory. The WISC-V (Kaufman et al., 2015) was used for underage participants by digit span (forward, backward, and increasing) and picture span subscales. The Wechsler Adult Intelligence Scale's IV (WAIS-IV) digit span (forward, backward, and increasing) and arithmetic subscales were administered over 16 years of age instead (Wechsler, 2008).

Phonetic and semantic fluencies. Verbal fluencies were assessed by the Verbal Fluency Test (Lezak et al., 2004), which involves completing phonetic (P, M, R) and semantic fluency (category of animals) tasks with one minute for each trial.

Verbal memory. To assess declarative memory problems, the Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996) was used. Participants were asked to repeat a 15-word list five times (A1-A5), with the following measurements taken: (a)

learning, the sum of the immediate recall of the 15-word list learned across five trials; and (b) delayed recall of the number of words after 20 minutes of interference.

Processing speed. Processing speed was assessed by means of the Stroop Test (i.e. P and C measures) (Stroop, 1992) and the Children's Color Trails Test (CCTT) part A (Williams et al., 1995) or the Trail Making Test (TMT) part A (Reitan, 1958) depending of the age of administration. The P and C measures of the Stroop test consist of reading the words and the color of the X groups, respectively. Moreover, the CCTT part A consists of connecting numbers (1-15) encircled in yellow or pink with a pencil in the shortest amount of time; while TMT part A implies to quickly connect the numbers from the lowest to the highest with lines.

Cognitive flexibility. The CCTT part B (Williams et al., 1995) or the TMT part B (Reitan, 1958), the Modified Wisconsin Card Classification Test (M-WCST) (Schretlen, 2010), and PC and interference measures from the Stroop Test (Stroop, 1992) were used to assess cognitive flexibility. CCTT part B consists of connecting an alternating sequence of numbers (1-15) and colors (yellow/pink) whereas in the TMT part B numbers and letters must be joined with lines in ascending and alphabetical order. Regarding M-WCST, the participant will have to learn new card sorting rules (48 cards in total) while adapting to a new environment that is becoming more and more complex. Lastly, in the Stroop Test PC measure the participant must identify the word and inhibit in the color in which it is written, while the interference measure is a mathematical calculation to know the ability to suppress the interference.

Theory of mind. Theory of mind was measured by using four stories from the Happé's Strange Stories Test (Happé, 1994), by choosing four original stories to reflect a lie, a white lie, a misunderstanding, and a pretense.

Moral competence. Moral competence was tested by means of the Moral Judgment Test (MJT) (Lind, 1978), describing the ability to make ethically upstanding decisions and judgements in two dilemma situations - the "workers' dilemma" and "mercy killing dilemma".

Delayed gratification. The Delay Discounting Test (DDT), also known as the Monetary Choice Questionnaire (Kirby & Maraković, 1996), examined delayed gratification by having participants answer 21 items such as, "Would you rather get €85 in 14 days or €30 now?"

4.2.2. Emotional-behavioral assessment

Internalizing and externalizing problems. The Child Behavior Checklist (CBCL) (Achenbach & Ruffle, 2000) and the Adult Self Report (ASR) (Achenbach et al., 2003) were employed as a measure of emotional-behavioral functioning from the last 6 months. The questionnaire also provides scores for the following scales: anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior and intrusive behavior. CBCL is a parent-report, while the ASR is a self-report.

Behavior problems. The Conners' Parent Rating Scale (CPRS) (Goyette et al., 1978) was used to assess parental reports about the next childhood behavioral problems in: conduct, learning, psychosomatic and impulsive-hyperactive, and anxiety.

Cognitive reappraisal and expressive suppression. Participants' propensity for both was evaluated using the 10-item Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003). On a Likert-type scale, participants rank each item, with 1 representing the strongest disagreement and 7 representing the strongest agreement.

4.2.3. Early life environmental factors

Parental bonding. The Parental Bonding Instrument (Parker et al., 1979) was employed to appraise the participants' parents' independent behavior toward them during childhood. Mother's and father's care and overprotection measures were obtained retrospectively, which means that individuals (over the age of 16) complete it for how they remember their parents during their first 16 years.

Familial SES. The Hollingshead Index (1975) was calculated with the average of parents' ongoing occupation and the level of education. More specifically, to calculate the average, the score in the ongoing occupation was multiplied by a factor of five and the level of education was multiplied by a factor of three and then added up. For underage subjects, data on the occupation and education domains was obtained from a single parent and then merely multiply and summed.

Adverse childhood experiences (ACEs). The WHO (2018) Adverse Childhood Experiences Questionnaire (ACE-IQ) for Children, Teens, and Adults describes childhood trauma. For the current thesis project, 10 different categories were analyzed as they were common to the three versions. Physical abuse, verbal abuse, sexual abuse, physical neglect, and emotional neglect are the five personal categories. A parent who is an alcoholic, a mother who is a victim of domestic violence, a family member in jail, a family member diagnosed with a mental illness, and the disappearance of a parent due to divorce, death, or abandonment are the other five connected with family members.

4.2.4. Other measures

Life satisfaction. The Satisfaction with Life Scale-Child (SWLS-C) (Gadernann et al., 2010) and the Satisfaction with Life Scale (SWLS) (Diener et al., 1985) were used to measure the participants' judgments of satisfaction with their life depending of administration age. In both cases, SWLS-C and SWLS, there are five-item self-reports that assess global life satisfaction.

Disability levels. The WHODAS 2.0 parent and adult reports tools (Üstün et al., 2010) were utilized to construct standardized disability levels and profiles taking into account the following domains: understanding and communicating, getting around, self-care, getting along with people, life activities, and participation in society.

Resilience. The abbreviated version of the Connor-Davidson Resilience scale (CD-RISC2) (Vaishnavi et al., 2007) is a two-item version of original scale intended for children. The Connor-Davidson Resilience scale (CD-RISC) (Connor & Davidson, 2003) comprises of 25 items, each rated on a 5-point scale (0–4). In both versions, higher scores reflect greater resilience score.

Personality data. The NEO Five-Factor Inventory (Costa & McCrae, 2000), a 60-item questionnaire, was used to acquire a precise measure of five domains of personality (i.e., neuroticism, extraversion, openness, agreeableness, and conscientiousness).

Current SES. To consider current SES, the Hollingshead Index (Hollingshead, 1975) was also used. That is, the participants' ongoing occupation and highest level of education were used to construct the total measure. As abovementioned, the score in the ongoing occupation was multiplied by a factor of five and the level of education by a factor of three, before being summed.

4.3. Neuroimaging Acquisition

4.3.1. T1 weighted brain images

For study I, 3-dimensional MRI datasets were obtained for the GM-IVH group at the Unitat de Diagnòstic per la Imatge (Vall d'Hebron University Hospital, Barcelona, Spain) and for the low-risk preterm and full-term groups at the Diagnostic Center for Imaging (Hospital Clínic, Barcelona, Spain). Meanwhile, 3-dimensional MRI datasets for study V were collected from the Magnetic Resonance Imaging Unit "Osatek" at Hospital

Galdakao-Usansolo (Galdakao, Spain). The sequence parameters of each study are displayed in Table 6.

Table 6

Characteristics of T1 acquisition

	Study I	Study V and VI
Model	Siemens 3T TIM TRIO	Philips 3T Achieva dStream
TR	2300 ms	8.1 ms
TE	2.98 ms	3.7 ms
Flip angle	9°	8°
Slices	160	160
Matrix	256 × 256 mm	288 × 248 mm
Voxel size	1 mm isotropic voxel	1 × 1 × 1 mm ³

Note: TR, repetition time; TE, echo time; ms, milliseconds; and mm, millimeters.

4.3.2. T2 brain images

In the study I, to identify GM-IVH lesions in the high-risk preterm sample as well as WM abnormalities in the whole sample, T2-weighted images were also acquired in axial orientation (TR/TE=5150/99ms; 512x307 matrix, flip angle 120°, slice thickness 5 mm with a 1.5 intersection gap), as well as fluid-attenuated inversion recovery images (axial orientation, TR/TE=9040/85ms, TI=2500, 256x156 acquisition matrix, flip angle 150°, slice thickness 5 mm with a 1.5 intersection gap). For low-risk preterm and full-term subjects, T2-weighted images (axial orientation, TR/TE=5533/88ms, 122x122 matrix, flip angle 90°, slice thickness 2 mm, gap=0.6 mm) were also acquired.

4.3.3. Diffusion weighted images

For study V diffusion-weighted MRI images were obtained from a Philips 3T Achieva dStream in an axial orientation with an anterior-to-posterior phase direction

using a multiband and multi-shell EPI sequence with 8 b0 diffusion weighting in 128 uniformly distributed directions (see Table 7).

Table 7

Characteristics of DTI acquisition

Characteristics of study V	
Model	Philips 3T Achieva dStream
TR	3820 ms
TE	81 ms
FOV	224 × 224 × 120
b value2	2000 s/mm ²
Slices	60
Voxel size	2 × 2 × 2 mm ³

Note: TR, repetition time; TE, echo time; FOV, field of view; ms, milliseconds; s/mm², seconds per squared millimeters; and mm³, cubic millimeters.

4.3.4. rs-fMRI images

For study VI rs-fMRI images were acquired also from the Philips 3T Achieva dStream; concretely, 315 whole-brain gradient echo-planar images (see Table 8).

Table 8

Characteristics of fMRI acquisition

Characteristics of study VI	
Model	Philips 3T Achieva dStream
TR	1500 ms
TE	30 ms
FOV	224 × 224 × 132
Slices	44
Voxel size	3 × 3 × 3 mm ³

Note: TR, repetition time; TE, echo time; FOV, field of view; ms, milliseconds; and mm³, cubic millimeters.

4.4. Neuroimaging preprocessing

4.4.1. Preprocessing of T1 images

FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/>) (version v6.0.0) was used to extract cortical and subcortical volumes, as well as global and regional CTh from 3D T1-weighted structural MRI scans for studies I, V, and VI. Several procedures were used to process T1 high-resolution images, including intensity non-uniformity correction, skull stripping, affine transformation to MNI template, intensity normalization, removal of non-brain tissue, linear and nonlinear transformations to a probabilistic brain atlas, and labeling of subcortical/allocortical structures. Priors in spatial localization were employed to choose the appropriate label for each single voxel (Fischl et al., 2002). Furthermore, for studies V and VI, errors in skull stripping, intensity normalization, WM segmentation, and surface extraction were manually rectified as needed. All volumetric quantities are given in cubic millimeters (i.e., mm³).

T1-weighted images were processed for study I using a hippocampus subfield segmentation software, FreeSurfer hippocampal-subfields-T1 command (i.e., utilizing the FreeSurfer hippocampal subfield pipeline) (Iglesias et al., 2015), and left and right hippocampal values were obtained. Moreover, each hemisphere's hippocampus was divided into 12 subfields: hippocampal tail, subiculum, presubiculum, parasubiculum, Cornu Ammonis 1 (CA1), CA2/3, CA4, granule cell layer of dentate gyrus (GC-DG), molecular layer hippocampus, fimbria, hippocampal-amygdalar transition area (HATA), and hippocampal fissure. In accordance with a previous study that employed this form of segmentation in a preterm sample (Aanes et al., 2019), and because our segmentations were based solely on T1-weighted images, and certain hippocampal subfields are

considered less reliable due to their size (Iglesias et al., 2015), three grouped subfield volumes were calculated for each hippocampal hemisphere: CA-field (CA1 + CA2/3 + molecular layer HP + subiculum); Dentate gyrus (GC-DG + CA4); and Subiculum (presubiculum). This redefinition is more in line with Mueller and colleagues' (2018) suggestions and other automatic segmentation approaches (Yushkevich et al., 2015).

For study VI, on the other hand, the amygdala was segmented into the central, lateral, basal, accessory basal, cortical, medial and paralaminar nuclei, as well as into the corticoamygdaloid transition area and anterior amygdaloid area (Saygin et al., 2017).

4.4.2. Preprocessing of DTI images

In study V, the diffusion data was preprocessed and analyzed using the FMRIB Software Library (FSL) version 6.0.3. (Smith et al., 2004). The images of each participant were first concatenated and radiologically oriented. The Brain Extraction Tool (BET) of FSL was then utilized to extract nonbrain tissue (Smith, 2002). Eddy was also used to locate volumes with significant absolute or relative motion and to adjust for distortions and movement. TOPUP was also used because it is a reliable and effective technique for correcting distortions (Andersson et al., 2003). The diffusion gradients were adjusted by rotating them (bvecs). The FA maps were created by fitting a tensor model to the raw diffusion data with FDT (DTIFIT). To analyze group differences in FA, AD, MD, and RD, data was prepared by using tract-based spatial statistic (TBSS) and all FA images were nonlinearly registered into standard space (Smith et al., 2006). The mean FA image was thinned with a threshold of 0.2 to generate a "mean FA skeleton" that represented the centers of all tracts matched by the group. To analyze AD, MD, and RD data, the "TBSS non-FA" script was utilized, which applied the original nonlinear registration to the data and integrated all participants' warped AD, MD, and RD data into a 4D file. This file was projected onto the original mean FA skeleton to create the 4D-projected data.

4.4.3. Preprocessing of rs-fMRI images

The CONN Functional Connectivity Toolbox version 21.a was used to conduct FC analyses (Whitfield-Gabrieli & Nieto-Castanon, 2012). The 315 functional images from each subject were realigned and unwarped, their slice-timing corrected, coregistered with structural data, spatially normalized into standard MNI space (Montreal Neurological Institute, Canada), their outliers detected (ART-based scrubbing), and were smoothed using a Gaussian kernel of 8 mm FWHM. For all preprocessing steps, the volume-based analysis default preprocessing pipeline (to MNI-space) was employed. The structural data was normalized and segmented into GM, WM, and CSF. The anatomical CompCor method was used to reduce noise by extracting the principal components (5 each) from the WM and CSF time series. The estimated motion parameters for each participant, as well as other artificial effects such as BOLD signals in WM and CSF that were added as extra confounds, were subsequently eliminated using a denoising method that used linear regression and band-pass filtering (0.008-0.09 Hz) (Weissenbacher et al., 2009).

4.5. Statistical Analyses

The Kolmogorov-Smirnov test (K-S) was applied to determine the normal distribution of data; tests were performed on mean scores for normally distributed data and on ranked dependent variables for non-normally distributed data. SPSS v.26 and 28 were used to analyze all neuropsychological, sociodemographic, and clinical data.

Missing values for clinical data and environmental factors were imputed using the expectation maximization algorithm (the percentage of missing values for study II was 5.62%, study IV was 0.94%, and study V was 0.61%). Moreover, to generate different cognitive composite scores; all raw scores were transformed into z-values, and a Cronbach's alpha coefficient was obtained for each (see Table 9).

Table 9*Composite scores' characteristics*

COMPOSITE SCORE	STUDY	MEASURES	RELIABILITY
Memory index	I	Learning and delayed recall from RAVLT.	0.85
General cognitive functioning	II	PPVT-III receptive language total scores, M-WCST category and perseverative error scores, RAVLT learning, delayed recall and delayed recognition measures, WISC-V matrices, digit span and picture span, phonetic and semantic fluencies, Stroop Test P, C, PC and interference measures, and CCTT parts A and B.	0.89
General cognitive functioning	IV	RPM's analogical reasoning and PPVT-III's receptive language total scores, M-WCST's category and perseverative error scores, WAIS-IV and WISC-V digit span and working memory index, phonetic and semantic fluencies, Stroop Test's P, C, PC and interference measures, TMT's part A and B, Happé's Strange Stories Test total score, MJT's moral competence final score, and DDT's delay gratification ratio.	0.84

General cognitive functioning	V	RPM's analogical reasoning and PPVT-III's receptive language total scores, M-WCST's category and perseverative error scores, WAIS-IV digit span and working memory index, phonetic and semantic fluencies, Stroop Test's P, C, PC and interference measures, TMT's part A and B, Happé's Strange Stories Test total score, MJT's moral competence final score, and DDT's delay gratification ratio.	0.80
Social-emotional outcomes	VI	Happé's Strange Stories Test total score, MJT's moral competence final score, and DDT's delay gratification ratio, ASR's emotional-behavioral functioning and cognitive reappraisal and expressive suppression from ERQ.	0.78

Note: RAVLT, Rey Auditory Verbal Learning Test; PPVT-III, Peabody Picture Vocabulary Test III; M-WCST, Modified Wisconsin Card Classification Test; WISC-V, Wechsler Intelligence Scale for Children; CCTT, Children's Color Trails Test; RPM, Raven's Advanced Progressive Matrices; WAIS-IV, Wechsler Adult Intelligence Scale IV; TMT, Trail Making Test; MJT, Moral Judgment Test; DDT, Delay Discounting Test; ASR, Adult Self Report; and ERQ, Emotion Regulation Questionnaire.

The effect sizes of outcome measures' comparisons were measured using partial eta squared. To understand this value, .01 represents a small size effect, .06 represents a medium size effect, and greater than .14 represents a large size effect (Cohen, 2013).

The moderating effect of early life environmental factors between the degree of maturity/immaturity at birth and general cognitive functioning score were independently investigated in studies II and IV. Moderation studies were performed to determine the moderation impact using the macro PROCESS 3.5 script for SPSS (published on May 1, 2020) (Hayes, 2017). Outlier analysis was performed prior to moderation analyses and investigated the rupture of linearity, normality, multicollinearity, and homoscedasticity; Mahalanobis and Cook's distances, as well as Leverage parameters, were used to detect potential outliers. A scatterplot and histogram analysis revealed no evidence of outliers in the study sample (no evidence of outliers in the study samples). Further, Johnson-Neyman outcome was assessed to see where early life environmental factors had a significant conditional effect on PB in predicting general cognitive functioning score.

4.5.1. Study I

The Kruskal-Wallis test was performed to investigate differences in clinical data (GA and BW) and age at evaluation. The Chi-squared test was also used to assess differences in the following categorical sociodemographic characteristics: sex, handedness, and parental education. Furthermore, a multivariate analysis of covariance was performed to evaluate neuropsychological performance and neuroanatomical volumetric values in the hippocampus (i.e. left and right hippocampus supplied by FreeSurfer, as well as grouped hippocampal subfields) between the three groups. Analyses were adjusted as follows: (1) age for memory scores; and (2) age, total intracranial volume (eTIV), and the presence or absence of ventriculoperitoneal shunt for hippocampus comparisons.

Additional analyses were performed to regress the effect of sex on memory and hippocampus measurements, as well as to include scanner location as a covariate; nevertheless, both results did not differ after multivariate analyses of covariance. The Bonferroni post-hoc test was applied and the Bonferroni corrected p -value for significance was determined for global bilateral hippocampus volumes and the three bilateral grouped hippocampal subfield volumes ($p=0.05/8=0.006$). Additionally, regression analyses were performed on all memory and hippocampus volumetric factors to determine the extent to which our findings might be explained by neonatal brain damage, GA, or the interaction of both variables.

In both preterm groups independently, as well as in preterm and full-term groups, partial correlations (adjusted for eTIV and age) were performed between the memory index and whole (left/right) as well as regional hippocampal volumes grouped into three subfield volumes for each hemisphere (i.e., CA-field, dentate gyrus, and subiculum). The Bonferroni corrected p -value for significance ($p=0.05/8=0.006$) was also calculated to account for multiple comparisons. Similarly, interaction analyses were performed to see whether memory-hippocampal relationships differed statistically between children born high- and low-risk preterm, as well as between the preterm and full-term groups.

4.5.2. Study II

Differences in non-normally distributed data, such as clinical data (GA and BW), age at evaluation, familial SES, ACEs, emotional-behavioral problems, life satisfaction, functionality, and resilience, were analyzed using the Kruskal-Wallis test. The Chi-squared test was used to analyze differences in two categorical sociodemographic factors (sex and handedness), and univariate analyses of variance were used to compare the scores of maternal and paternal care and overprotection across the three groups. Finally, using age and familial SES as confounders, a multivariate analysis of covariance was

utilized to compare different cognitive test scores and the general cognitive functioning composite score. Bonferroni's post-hoc test was performed and Bonferroni adjusted p -value ($p=0.05/18=0.003$) was used to determine significance in different cognitive tests.

4.5.3. Study IV

Differences in non-normally distributed variables, such as clinical data (GA and BW), age at evaluation, current SES, and emotional-behavioral measures, were analyzed using the Kruskal-Wallis test. This test was also used to examine early life environmental factors (such as familial SES, care measures, and ACEs). The Chi-squared test was also used to evaluate differences in two categorical sociodemographic characteristics: sex and handedness. A univariate analysis of variance was also performed to compare the overprotection measure among the three groups. Moreover, a multivariate covariance analysis was utilized to compare different cognitive domains and the general cognitive functioning score (adjusting for sex and age). Bonferroni's post-hoc test was used and the Bonferroni adjusted p -value for significance was also calculated for each cognitive test ($p=.05/17=0.003$).

4.5.4. Study V

Mann-Whitney U test was employed to assess differences in clinical data (GA and BW), age at time of evaluation, familial SES, care measure, ACEs, emotional-behavioral problems, SWLS, WHODAS, and personality data (except for openness measure). Additionally, the Chi-squared test was used to evaluate differences in sex and handedness, two categorical sociodemographic variables. Student t-tests were also used to compare the levels of overprotection, resilience, and openness measure among both groups. A multivariate covariance analysis was performed to examine different cognitive domains, the general cognitive functioning score, and current SES (age at evaluation as confounder)

in both the whole sample and the neuroimaging sample. For each cognitive test, a Bonferroni corrected p -value for significance was obtained ($p=0.05/17=0.003$).

Furthermore, multivariate analyses of covariance were utilized to evaluate the following data analyzed in SPSS: global (left/right) and regional CTh (adjusted for age at evaluation); cortical and subcortical volumetric regions (adjusted for age at evaluation and eTIV); and global mean FA, AD, MD, and RD (adjusted for age at evaluation). Bonferroni's post-hoc test was employed as well as Bonferroni corrected p -value for significance was computed for left and right regional CTh ($p=0.05/34=0.001$) and subcortical volumetric areas ($p=0.05/23=0.002$).

In order to assess total WM integrity differences in FA, AD, MD, and RD, the "randomize" tool in FSL (5000 permutations) with threshold-free cluster enhancement (TFCE) correction for multiple comparisons, including the - - T2 option, was used. The statistical threshold was set at $p<0.05$ corrected for family wise error (FWE) with an extent threshold of 100 voxels. The maximal coordinates in the clusters and other significant regions were visually evaluated using the MRI Atlas of Human White Matter (Oishi et al., 2010), and structurally labeled applying JHU-ICBMDTI-81 WM Labels and the JHU White-Matter Tractography Atlas implemented in FSL.

4.5.5. Study VI

The Mann-Whitney U test was used to analyze differences in GA, and self- and familial SES. Furthermore, the Chi-squared test was required to assess differences in two qualitative sociodemographic characteristics: gender and handedness. Student's t -tests were also performed to compare BW and age at evaluation between the groups.

A multivariate analysis of covariance was conducted to compare different social-emotional domains (adjusted for age and self-SES), whole amygdala volumes (adjusted for age, self-SES and eTIV), and amygdala subnuclei volumes (adjusted for age, self-SES

and left/right amygdala volume). Moreover, bivariate correlation analyses were performed to assess the relationships between social-emotional outcomes and amygdala volumes (i.e., whole and subnuclei volumetric values).

Regarding FC statistical analysis, between-group differences and correlation analyses (i.e., each group independently) were assessed at the cluster-level inferences by region of interest (ROI)-to-ROI with FWE-corrected $p < 0.05$ Threshold Free Cluster Enhancement (TFCE) (Smith and Nichols 2007). For FC at network level, FDR correction was applied. The ROIs selected based on the Harvard-Oxford Structures Atlas (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>) were: (a) left amygdala, (b) right amygdala, and (c) MedFC. Age and self-SES were used as covariates in the comparison analysis. The correlation between the strength of FC (left and right amygdala – MedFC), expressed by the mean of the normalized correlation coefficient in the cluster, and social-emotional data were studied using the Spearman's rank correlation coefficient in young adults born low-risk preterm and full-term.

4.6. Ethics Statement

This thesis was conducted in accordance with the Declaration of Helsinki. The Ethics Committees of the Vall d'Hebron University Hospital and the University of Barcelona evaluated and approved the project that made it possible to carry out study I. Studies II, IV, V, and VI on the other hand, were evaluated and approved by the Ethics Committee of the University of Deusto [ETK-22/17-18] and the Drug Research Ethics Committee of the Basque Country [CEIm-E, PI2018154]. All participants provided prior written informed consent; in the case of under-aged participants, their consent was required as well as that of their legal tutors at the beginning of the study.

Study III

4.1. Search Strategy

The initial search method was created for use in PubMed; however, Google Scholar and Medline were also among the databases used. The terms to be found in the study's title, abstract, and/or keywords were: (a) premature birth/prematurity; (b) moderate preterm/late preterm/near-term/marginally preterm; (c) cognition/cognitive functioning; (d) psychiatric*/mental health; (e) adult*; and (f) specific long-term outcomes (IQ f1, educational status f2, anxiety f3, depression f4, ADHD f5, autism spectrum disorder f6, and schizophrenia f7). First, a search was conducted for any English-language papers involving adult PB. Following the completion of the search, only studies that included a group of preterm-born adults thought to be at lower risk of presenting neurodevelopmental alterations were chosen (i.e., non-uniform definitions including the terms moderate preterm, late preterm, near-term, and/or marginally preterm). Finally, papers that addressed at least one of the research topics (i.e., cognition, mental health, and/or specific long-term outcomes) were selected. Therefore, searches were made in the databases by using next set of keywords: first (a)+(e); then (a)+(b)+(e) or (a)+(c)+(e) or (a)+(d)+(e) or (a)+(e)+ [f (each f individually)]; and finally, (a)+(b)+(c)+(e) or (a)+(b)+(d)+(e) or (a)+(b)+(e)+[f (each f individually)]. See supplementary Table 1 in the results section of study III for a better understanding of the search approach used.

4.2. Inclusion criteria

Studies involving MLPT adults from January 2000 to February 2021 were included (i.e., they included adults born with a GA between 32+0 to 36+6 weeks) if their primary or secondary goal was to examine at least one of the following domains: cognition and/or mental health.

Findings of the research that met the above-mentioned criteria on the effect of SES were also provided. Similarly, parents' data (e.g., marital status), were deemed significant confounders in the discussion of the data. Further, clinical data, such as being born SGA, were also considered to describe the samples under research. As a result, certain supplemental information was acquired during the research (e.g., SES), whereas data on other variables, such as neonatal information (e.g., BW), were obtained retrospectively by checking health records.

4.3. Eligibility criteria

Two reviewers de-duplicated and screened studies based on title, abstract, and full-text. The same reviewers independently assessed study eligibility for inclusion and extracted full data. A third reviewer, resolved disagreements between the two major reviewers and made the final decision. If further information was required, published data gathered from the selected articles were additionally contacted.

4.4. Study selection and data extraction

A three-step approach was used to acquire reports for this review. Figure 1 in the results section of study III depicts the literature identification process using an adapted flow diagram based on PRISMA guidelines (Page et al., 2021). First, 155 papers were found using a comprehensive database search. Following the removal of duplicates (n=49), 106 reports were acquired using title search, and 44 of them were removed following title screening. Second, the abstracts of 62 articles were evaluated to eliminate those that did not meet the selection criteria. Lastly, the full-text versions of 24 reports were reviewed, and only those that met the inclusion criteria were considered. Eight papers were omitted because they investigated long-term outcomes other than those chosen for the current review (e.g., cortisol profiles, exercise capacity, etc.). As a result, the total number of publications for examination and subsequent analysis was 16 research

papers. Supplementary Table 2 contains research measuring cognitive performance, whereas supplementary Table 3 comprises studies assessing mental health, both in the results section of study III.

4.5. Protocol and registration

The review was carried out in accordance with the "PRISMA 2020 statement: an updated guideline for reporting systematic reviews" standards (Page et al., 2021). This protocol for a systematic review was submitted to PROSPERO, the International Prospective Register of Systematic Reviews (CRD42020153096).

4.6. Risk of bias in individual studies

Using the Newcastle-Ottawa Scale, two reviewers independently rated the quality of the selected studies (Wells et al., 2000). The standards for this scale are divided into three sections: 1) selection, 2) comparability, and 3) outcome. More precisely, each item in the selection and outcome categories might receive a maximum of one star, while the comparability category could receive a maximum of two stars. Studies with six or more stars were called high quality according to the specific acceptance criteria considered for the current study. In order to address the system's consistency, interrater reliability was done, yielding a Cronbach's alpha of 0.94.

4.7. Data synthesis

Hedge's g effect sizes were estimated for quantitative cognitive outcomes to examine the magnitude of the effects identified when comparing group mean differences and in regression analysis. A score of 0.2 indicates a minor effect size, 0.5 suggests a medium effect size, and values greater than 0.8 indicate a large effect size. Because adults' educational attainment was classified qualitatively, the effect magnitude from two studies was omitted (Heinonen et al., 2013; Nomura et al., 2009). Similarly, the impact size from

another study was not found since the data was logarithmically converted (Suikkanen et al., 2020).

The odd ratios (ORs), hazard ratios (HRs), and relative risks (RRs) are supplied by the studies included in this review in order to objectively assess the data from the mental health. The ORs signify the odds of a psychiatric disorder occurring in MLPT adults compared to the odds of a psychiatric disorder occurring in full-term born adults, whereas the HRs and RRs characterize the risk that one MLPT adult out of the total number of MLPT adults under study has to suffer from a psychiatric disorder. Given that none of these ratios were disclosed in one study (Sammallahti et al., 2017), the prevalence data and percentages are provided for this case (see Table 5 in the results section of study III).

Last, the data of those cognitive and psychiatric domains defined in at least three or more studies included in the current review were analyzed using RStudio software (v. 1.2.5001) (Team, 2019). Namely, the meta package was used to run a random-effects model on generic inverse variance (i.e., cognitive data) and binary outcome data (i.e., psychiatric domains). In terms of heterogeneity, Tau-squared (t^2) and I^2 were assessed to determine whether or not heterogeneity was statistically significant, as well as the degree of heterogeneity between studies. An I^2 value of 25%, 50%, or 75% would yield in low, medium, or high heterogeneity, respectively. Forest plots were generated to display the overall effects (i.e., standardized mean difference and OR) obtained from merging the individual studies, and funnel plots were also gotten to measure publication bias. Finally, meta-regression analyses were performed to assess the influence of four moderator variables (i.e., study quality, age at evaluation, GA, and year of publication) on the effect sizes of included studies.

V. Results

5. Results

5.1. Study I

“Reduced hippocampal subfield volumes and memory performance in preterm children with and without germinal matrix-intraventricular hemorrhage”

5.2. Study II

“Maternal care and general cognitive functioning in moderate and late preterm-born children”

5.3. Study III

“Long-term neurodevelopmental outcomes after moderate and late preterm birth: a systematic review”

5.4. Study IV

“Preterm birth and early life environmental factors: neuropsychological profiles at adolescence and young adulthood”

5.5. Study V

“Long-term brain structural and cognitive outcomes in a low-risk preterm-born sample”

5.6. Study VI

“Amygdala Structure and Function and Its Associations with Social-Emotional Outcomes in a Low-Risk Preterm Sample”

Study I



OPEN

Reduced hippocampal subfield volumes and memory performance in preterm children with and without germinal matrix-intraventricular hemorrhage

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Preterm newborns with germinal matrix-intraventricular hemorrhage (GM-IVH) are at a higher risk of evidencing neurodevelopmental alterations. Present study aimed to explore the long-term effects that GM-IVH have on hippocampal subfields, and their correlates with memory. The sample consisted of 58 participants, including 36 preterm-born (16 with GM-IVH and 20 without neonatal brain injury), and 22 full-term children aged between 6 and 15 years old. All participants underwent a cognitive assessment and magnetic resonance imaging study. GM-IVH children evidenced lower scores in Full Intelligence Quotient and memory measures compared to their low-risk preterm and full-term peers. High-risk preterm children with GM-IVH evidenced significantly lower total hippocampal volumes bilaterally and hippocampal subfield volumes compared to both low-risk preterm and full-term groups. Finally, significant positive correlations between memory and hippocampal subfield volumes were only found in preterm participants together; memory and the right CA-field correlation remained significant after Bonferroni correction was applied ($p = .002$). In conclusion, memory alterations and both global and regional volumetric reductions in the hippocampus were found to be specifically related to a preterm sample with GM-IVH. Nevertheless, results also suggest that prematurity per se has a long-lasting impact on the association between the right CA-field volume and memory during childhood.

Preterm birth has been defined as any delivery before 37 completed weeks of gestation. According to its clinical manifestations, prematurity can be classified into two different conditions: low-risk and high-risk prematurity. Preterm newborns considered to be at a lower risk of developing neurodevelopmental alterations commonly evidence a gestational age (GA) of between 30 to 36 weeks, minor perinatal complications, and lack of brain

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abnormalities observed by cranial ultrasound (US)^{1,2}. However, while these children are at a lower risk of presenting developmental complications, their immature nervous system might account for long-term neurodevelopmental alterations³. In contrast, high-risk prematurity commonly refers to preterm birth together with neonatal brain injury, which may cause long-lasting adverse complications. For instance, germinal matrix-intraventricular hemorrhage (GM-IVH) has been related to poorer overall development during infancy⁴.

Early detection of subtle or severe neonatal brain alterations may alleviate some of the neurodevelopmental consequences related to prematurity via the development of more targeted early intervention programs in order to improve the quality of life of this population. For its part, Magnetic Resonance Imaging (MRI) can accurately identify and quantitatively assess gray matter (GM) and white matter (WM) abnormalities⁵, which correlate with cognitive measures in both low- and high-risk preterm samples^{6,7}. Whereas prematurity has been associated with abnormal growth in several brain regions⁸, temporal lobe alteration might occur to a greater extent than in other regions, since reduced GM is often attributed to bilateral temporal lobe damage⁹. Even in low-risk preterm children, abnormalities have been found in the superior temporal sulcus surface¹⁰, as well as neurochemical anomalies in adolescence¹¹. Moreover, smaller hippocampal volumes are often found in high-risk preterm samples¹². This allocortical structure that is localized in the temporal lobe appears to be particularly susceptible to adverse pre-perinatal events such as hypoxia/ischemia, which limit its connections^{13,14}. Overall hippocampal volumetric reductions seem to have an impact on memory performance in prematurity¹⁵; in fact, hippocampal structural alterations may affect episodic memory from childhood to early adulthood¹⁶. Furthermore, based on hippocampal subfield volumes, smaller left dentate gyrus volume has been related to reduced visual working memory in preterm children born between 25 and 34 weeks of gestation without brain pathology¹⁷.

There is a lack of research that focuses on neuropsychological outcomes in well-characterized samples in terms of their clinical manifestations (low- vs. high-risk preterm samples), which allows the effect of low and high-risk prematurity per se on cognition to be researched. Studies conferring neonatal brain damage following preterm birth have mainly observed impairments in global neuropsychological performance by providing a measure such as the intelligence quotient (IQ)¹⁸. For all these reasons, the purpose of this MRI study is to consider the long-term effects that high- and low-risk prematurity may have on the hippocampus of preterm children and their associations with memory performance. Four hypotheses have been proposed. First, high-risk preterm children with GM-IVH will have lower memory scores compared to their low-risk preterm and full-term peers in childhood. Second, those suffering from GM-IVH will evidence reduced hippocampal volumes in comparison to low-risk preterm and full-term groups. Third, hippocampal volumetric reductions might be related to memory performance in high-risk preterm children with GM-IVH. And fourth, the lower the GA, the higher the probability of maturing alterations during development¹⁹, which may result in low-risk preterm children without GM-IVH having decreased hippocampal volumetric values and poorer memory performance in contrast to their full-term peers.

Results

The first analysis showed that a number of variables did not follow a normal distribution: (1) the high-risk preterm sample with GM-IVH: GA (Kolmogorov–Smirnov (K–S) = 0.25 p = 0.009), birth weight (BW) (K–S = 0.22 p = 0.03), A1 (K–S = 0.23 p = 0.03), and right hippocampus (K–S = 0.22 p = 0.03); (2) the low-risk preterm sample without GM-IVH: age (K–S = 0.28 p < 0.001), GA (K–S = 0.22 p = 0.02), internalizing problems (K–S = 0.23 p = 0.006), A1 (K–S = 0.22 p = 0.02), and A4 (K–S = 0.23 p = 0.008); and (3) the full-term sample: age (K–S = 0.29 p < 0.001), GA (K–S = 0.29 p < 0.001), internalizing problems (K–S = 0.22 p = 0.01), A1 (K–S = 0.25 p = 0.002), A3 (K–S = 0.20 p = 0.03), A5 (K–S = 0.22 p = 0.01), delayed recall (K–S = 0.22 p = 0.009), and right dentate gyrus (K–S = 0.23 p = 0.003).

Details of neonatal, clinical and sociodemographic variables are provided in Tables 1 and 2. As expected, there were significant differences between the two preterm groups in neonatal variables (GA and BW) in comparison to the full-term group. Besides, high-risk preterm-born children with GM-IVH showed greater immaturity (lower GA and BW) in both variables in relation to the low-risk preterm group without GM-IVH. No statistically significant differences were found in sex, age, handedness, or parental education among groups. Behavioral results showed no significant differences between groups with regard to internalizing, externalizing and total emotional-behavioral problems.

Regarding cognitive performance, as shown in Table 3, while mean Full Intelligence Quotient (FIQ) was within normal limits in both preterm groups, it was significantly lower compared to full-term children. Similarly, perceptual reasoning and verbal comprehension indexes showed significantly lower scores in both preterm born groups in comparison to their full-term peers. For their part, high-risk preterm children with GM-IVH obtained significantly lower scores in processing speed in relation to the full-term group. Memory performance was established by a composite score (see “Methods” section) with a Cronbach’s alpha coefficient of 0.85. All items from the Rey Auditory Verbal Learning Test, except for A1 and A4, as well as learning, delayed recall and the memory index, significantly differed between high-risk preterm sample with GM-IVH and both low-risk preterm and full-term groups; poorer performance was evidenced by those considered to be high-risk preterm children with GM-IVH. Conversely, A1 and A4 were significantly different among high-risk preterm children with GM-IVH evidencing lower scores in contrast to their full-term peers.

Global bilateral hippocampal volumes and grouped hippocampal subfield volumes (see “Methods” section), as presented in Table 4, were found to be significantly smaller in the high-risk preterm sample with GM-IVH compared to both low-risk preterm and full-term groups after Bonferroni correction for multiple comparisons was applied (p = 0.006). In other words, left and right global hippocampus, bilateral subiculum, bilateral CA-field and right dentate gyrus were found to be smaller in the high-risk preterm sample with GM-IVH. Nonetheless, the left dentate gyrus was only significantly different among high-risk preterm children with GM-IVH and the

	High-risk preterm n = 16	Percentage (%)	Low-risk preterm n = 20	Percentage (%)
Chorioamnionitis ^a	6/7	85.71	2/18	11.11
Antenatal steroids ^a	3/4	75	12/18	66.67
Apgar score < 6 at fifth minute ^a	4/14	28.57	0/18	0
Mechanical ventilation > 14 days ^a	3/13	23.08	0/18	0
Vaginal delivery ^a	8/15	53.33	5/18	27.78
Shunt	3/16	18.75	0/20	0
Seizures ^a	2/9	22.22	0/20	0
IUGR	2/16	12.5	2/20	10
SGA	3/16	18.75	5/20	25
GM-IVH grades				
Grade II	8	50		
Grade III	6	37.5		
Grade IV	2	12.5		

Table 1. Clinical data of high- and low-risk preterm samples. IUGR: intrauterine growth restriction; SGA: small for gestational age; and GM-IVH: germinal matrix-intraventricular hemorrhage. ^aAvailable data for chorioamnionitis: 7 High-risk preterm and 18 Low-risk preterm; antenatal steroids: 4 High-risk preterm and 18 Low-risk preterm; Apgar score < 6 at fifth minute: 14 High-risk preterm and 18 Low-risk preterm; mechanical ventilation > 14 days: 13 High-risk preterm and 18 Low-risk preterm; vaginal delivery: 15 High-risk preterm and 18 Low-risk preterm; and seizures: 9 High-risk preterm and 20 Low-risk preterm.

	High-risk preterm n = 16 Mean ± SD	Low-risk preterm n = 20 Mean ± SD	Full-term n = 22 Mean ± SD	Statistics (<i>p</i>)
Neonatal data				
GA, wk [range]	28.00 ± 2.71 [25–36]	32.50 ± 1.36 [30–34]	39.50 ± 1.01 [38–41]	$H = 47.62 (<.001)^*$
BW, g	1184.50 ± 559.18	1754.25 ± 451.55	3391.55 ± 356.96	$H = 43.40 (<.001)^*$
Sociodemographic data				
Gender, male/female	7/9	11/9	14/8	$X^2 = 1.48 (.48)$
Age, yo [range]	9.56 ± 2.31 [6–14]	9.30 ± 0.66 [8–10]	9.27 ± 0.63 [8–10]	$H = 0.07 (.97)$
Handedness right-handed/left-handed	13/3	18/2	22/0	$X^2 = 4.21 (.12)$
Parental education low/intermediate/high	4/8/4	4/4/12	3/4/15	$X^2 = 8.16 (.09)$
Behavioral variables				
Internalizing problems ^a	6.89 ± 5.35	8.99 ± 6.12	7.81 ± 4.72	$F = 0.77 (.52)$
Externalizing problems ^a	7.16 ± 6.61	9.36 ± 5.97	9.35 ± 5.61	$F = 0.50 (.69)$
Total behavioral problems ^a	22.99 ± 13.06	25.47 ± 14.66	24.70 ± 14.66	$F = 0.24 (.87)$

Table 2. Neonatal, sociodemographic and emotional-behavioral variables. SD: standard deviation; GA: gestational age; wk: weeks; BW: birth weight; g: grams; yo: years; *K*: Kruskal–Wallis test; X^2 : Chi-square test; and *F*: Snedecor's F distribution. *Statistically significant differences between High-risk preterm < Low-risk preterm < Full-term. ^aAvailable data for internalizing problems, externalizing problems and total problems: 16 GM-IVH-preterm, 20 low-risk preterm and 21 term children.

low-risk preterm group without GM-IVH ($p < 0.001$), with the high-risk preterm group with GM-IVH evidencing smaller values. All these results showed large effect sizes.

Attention should be drawn to the fact that the presence of a neonatal brain injury such as GM-IVH explained the variance in memory and neuroimaging variables ($p < 0.05$), while none of them were explained by GA. Furthermore, the interaction of both variables also explained the variance in left hippocampus ($\beta = -3.60$ $p = 0.008$ $\Delta R^2 = 0.09$), left CA-field ($\beta = -3.80$ $p = 0.006$ $\Delta R^2 = 0.10$), and left dentate gyrus ($\beta = -2.99$ $p = 0.04$ $\Delta R^2 = 0.06$).

With reference to correlations in both preterm groups independently, none of the correlations between global and regional hippocampal volumetric measures and memory remained significant after Bonferroni correction for multiple comparisons was applied. As for the correlations in preterm and full-term groups, a significant correlation was observed between the right CA-field and memory performance in preterm-born children (see Fig. 1), remaining significant following Bonferroni correction for multiple comparisons ($r = 0.52$ p -corrected = 0.002). No statistically significant correlations were found in the full-term group.

	High-risk preterm n = 16 Mean ± SD	Low-risk preterm n = 20 Mean ± SD	Full-term n = 22 Mean ± SD	<i>F-Snedecor statistic (p)</i>	η_p^2
Wechsler intelligence scale for children IV					
Verbal Comprehension	106.3 ± 13.29	107.25 ± 15.15	123.73 ± 19.04	7.38 (.001)*	.21
Perceptual Reasoning	94.9 ± 14.52	101.10 ± 13.59	115.64 ± 16.65	9.76 (<.001)*	.26
Working Memory	102.6 ± 13.90	107.60 ± 15.24	108.50 ± 16.25	0.77 (.46)	.03
Processing Speed	98.9 ± 13.02	107.25 ± 14.49	114.50 ± 8.85	7.62 (.001)**	.22
FIQ	99.7 ± 14.55	105.75 ± 13.76	121.91 ± 15.39	12.13 (<.001)*	.31
Rey auditory verbal learning test (covariate according to age)					
A1	4.84 ± 1.26	5.46 ± 1.28	6.02 ± 1.20	3.30 (.027)**	.16
A2	6.92 ± 2.16	8.73 ± 1.98	8.49 ± 1.77	4.38 (.008)***	.20
A3	8.45 ± 3.05	10.69 ± 2.08	10.78 ± 1.75	5.98 (.001)***	.25
A4	10.04 ± 3.47	11.60 ± 2.31	12.11 ± 1.46	5.44 (.002)**	.23
A5	10.79 ± 3.05	12.68 ± 1.69	12.90 ± 1.08	5.39 (.003)***	.23
Learning	41.03 ± 11.22	49.15 ± 7.93	50.30 ± 5.35	7.39 (<.001)***	.29
Delayed Recall	7.99 ± 4.14	10.97 ± 2.09	11.40 ± 1.50	6.00 (.001)***	.25
Memory	-0.75 ± 1.23	0.21 ± 0.76	0.35 ± 0.48	7.67 (<.001)***	.30

Table 3. Full intelligence quotient and learning-memory differences. SD: standard deviation; FIQ: full intelligence quotient; WISC-IV: Wechsler Intelligence Scale for Children IV; RAVLT: Rey Auditory Verbal Learning Test; A1, A2, A3, A4 and A5: RAVLT trials; and η_p^2 : partial eta squared. *Statistically significant differences between High-risk preterm < Full-term and Low-risk preterm < Full-term. **Statistically significant differences between High-risk preterm < Full-term. ***Statistically significant differences between High-risk preterm < Full-term and High-risk preterm < Low-risk preterm.

	High-risk preterm n = 16 Mean ± SD	Low-risk preterm n = 20 Mean ± SD	Full-term n = 22 Mean ± SD	<i>F-Snedecor Statistic (p)</i>	η_p^2
Hippocampus (mm³) (covariate according to eTIV, age and presence of shunt valve)					
Left Hippocampus	2,971.73 ± 579.95	3,459.27 ± 390.23	3,399.56 ± 271.96	13.00 (<.001)*	.56
Right Hippocampus	2,974.33 ± 424.70	3,352.35 ± 382.10	3,402.27 ± 288.50	26.53 (<.001)*	.72
Grouped hippocampal subfields (mm³) (covariate according to eTIV, age and presence of shunt valve)					
Left Subiculum	253.85 ± 62.63	301.99 ± 25.09	325.08 ± 31.07	10.73 (<.001)*	.51
Right Subiculum	241.49 ± 42.45	280.87 ± 29.85	299.92 ± 30.72	14.82 (<.001)*	.59
Left CA-field	1582.24 ± 322.00	1853.45 ± 231.12	1803.92 ± 156.22	12.74 (<.001)*	.55
Right CA-field	1606.23 ± 231.57	1812.39 ± 229.66	1841.89 ± 169.12	21.49 (<.001)*	.67
Left Dentate Gyrus	498.84 ± 86.81	567.66 ± 86.26	547.14 ± 53.92	13.38 (<.001)**	.56
Right Dentate Gyrus	509.74 ± 77.95	545.44 ± 77.38	545.16 ± 69.63	15.27 (<.001)*	.60

Table 4. Left/right hippocampus and grouped hippocampal subfield volumetric differences. SD: standard deviation; mm³: cubic millimeter; and η_p^2 : partial eta squared. *Statistically significant differences between High-risk preterm < Full-term and High-risk preterm < Low-risk preterm. **Statistically significant differences between High-risk preterm < Low-risk preterm. The global bilateral hippocampal volumes and grouped hippocampal subfield volumes shown in bold are those that remained significant after Bonferroni correction was applied for multiple comparisons ($p = .006$).

As far as interaction analyses between high- and low-risk preterm children are concerned, significant differences were only found in the left subiculum correlation coefficients ($F = 4.81$ $p = 0.04$). No statistically significant interactions were found between preterm and full-term groups.

Discussion

By including well-characterized high- and low-risk preterm groups, this study highlights the existence of different cognitive profiles in prematurity during childhood. Reduced hippocampal volumes were found only in those born prematurely, which reaffirms a biological susceptibility in preterm birth, leading to greater vulnerability in the hippocampus due to adverse pre-perinatal factors^{13,14}. Moreover, memory performance was associated with the right CA-field volume only in those born prematurely. This structure-function relation between abnormal hippocampal growth and memory performance has previously been found in very low BW preterm adults with perinatal morbidity²⁰. However, as is already known^{21,22}, memory performance may not always be explained by hippocampal volumetric differences, since this is not the only structure that might be involved.

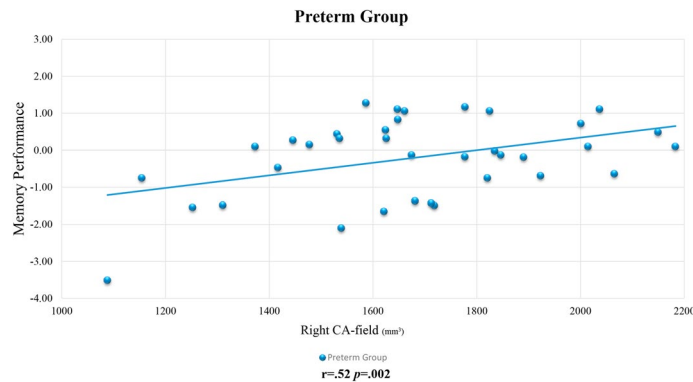


Figure 1. Correlation between the right CA-field and memory performance in preterm-born children. Note: mm³: cubic millimeter. Details of Pearson correlation coefficient (r) and p -corrected value are provided. Significant results were obtained between the right CA-field volume and memory performance after Bonferroni correction for multiple comparisons was applied ($p = .006$). Unstandardized residuals were calculated and used for display purposes (adjusted according to age and eTIV).

Our findings indicated lower scores in FIQ, verbal comprehension, and perceptual reasoning in high- and low-risk preterm-born children. Even though their cognitive performance was within normal range, preterm infants with or without neonatal brain damage continued to fall behind full-term children in several domains associated with intellectual functioning⁷, as well as in academic attainment²³. Research identified lower scores in processing speed only in preterm children with GM-IVH. Processing speed deficits following preterm birth are strong predictors of executive function, inattentive behavior and academic achievement^{24–26}; in fact, this cognitive domain has also been found to be affected in preterm toddlers without neurological abnormalities²⁷. However, in this study, processing speed measurement required the involvement of motor abilities which, after a brain injury such as GM-IVH, is compromised and impacts overall processing speed performance^{28,29}.

Regarding memory, results highlighted the adverse effect of being preterm with GM-IVH on memory skills, which had already been noted in heterogeneous preterm samples³⁰. Furthermore, in this study, the worst learning and delayed recall scores were evidenced in a homogeneous sample of high-risk schooled preterm children with GM-IVH. However, at a different period of development and in the absence of neurologic abnormalities, similar outcomes were also evidenced by preterm toddlers; specifically, deficits in recall, immediate recognition and encoding speed²⁷. Interestingly, in the case of the first immediate recall condition (A1), which might entail less involvement of the hippocampus compared to the following trials due to accumulated memory load, high-risk preterm children with GM-IVH also obtained lower scores than their full-term peers. This result stresses the fact that preterm children with atypical brain development have difficulty in retaining relevant information even over a short time interval, which might go beyond the hippocampal volumetric reductions described in this population, as other authors have suggested in preterm toddlers with subependymal or mild intraventricular hemorrhages³¹, and developmental amnesia³². Nevertheless, there was also found to be differentiation in A4 between high-risk preterm children with GM-IVH and their full-term peers. Finally, low-risk preterm born children without GM-IVH did not obtain lower scores in memory performance compared to full-term children. Therefore, as other authors have also demonstrated, memory may not be influenced by preterm birth in those considered to be at a lower risk of neurological abnormalities in childhood³³, and adulthood³⁴. In fact, although hippocampal growth may be affected due to prematurity, this might not imply memory impairments, as has also been shown in heterogeneous preterm children^{35,36}.

In general, our results are in line with previous MRI analyses that reported reduced hippocampal volumes in heterogeneous preterm samples¹⁶. In fact, smaller hippocampal volumes have been detected in preterm infants with brain injury as well as with several perinatal events at 2 years of age^{12,37}. Similar results were found in this study, since both global and regional hippocampal volumetric reductions were also observed in high-risk prematurity with GM-IVH in childhood. Regarding hippocampal laterality effects, our study found smaller volumes in both left and right hippocampal structures among GM-IVH children, as has already been reported by other authors, with a volumetric reduction of 15.6% in the right and 12.1% in the left hippocampus⁸. The hippocampal abnormalities in this study, apart from being bilateral, were also predominantly right-side; this is the hippocampus side that has been related to memory in young adults with very low BW³⁸. Nevertheless, other studies have found a more symmetrical hippocampus³⁹ and greater left predominance¹⁵, possibly due to altered WM development.

Furthermore, the hippocampal CA-field, which is particularly vulnerable to ischemia⁴⁰, appears to be smaller in those suffering from a neonatal brain injury such as GM-IVH. Indeed, the right CA-field volume proved to be positively related to memory performance in preterm-born children, remaining significant after Bonferroni correction. According to Aanes et al.¹⁷, children with very low BW evidenced a weak correlation between CA-field volumes and number of days on mechanical ventilation. As a consequence, children with very low BW with the most immature lung function may have a greater likelihood of suffering from hypoxia–ischemia in the neonatal period, influencing the development of the CA-field. Nevertheless, among those who spent more than 14 days with mechanical ventilation in our study, there were only 3 children with GM-IVH and none without GM-IVH.

On the other hand, the right dentate gyrus appear to be smaller in those suffering from a neonatal brain injury such as GM-IVH compared to both low-risk preterm and full-term groups; while left dentate gyrus differed from high-risk (GM-IVH) and low-risk preterm children. This structure has been stated as being susceptible to both physical and psychological stress, causing apoptosis and deficient neurogenesis. In fact, stress also impairs the impact of other neurological insults commonly encountered in prematurity such as hypoxia and ischemia⁴¹. Hence, these mechanisms might trigger reduced dentate gyrus volumes seen in the high-risk preterm group with GM-IVH. Finally, being aware that the subiculum is also vulnerable to hypoxic-ischemic episodes⁴², subiculum lower volumetric values were only found in those considered high-risk preterm children with GM-IVH. In fact, correlation coefficient differences were found in the left subiculum between high- and low-risk preterm children. Thus, in line with Aanes et al.¹⁷, the typical growth experienced by this structure might be negatively influenced by particular clinical conditions seen in preterm newborns.

Our results are consistent with the review by Nosarti and Froudust-Walsh¹⁶, which suggested that common brain injuries given after very preterm birth can affect common development of different memory networks. The current study found a robust relationship between the right CA-field volume and memory performance among preterm-born children, even in those without GM-IVH. Preterm hippocampal asymmetry has been evidenced as being smaller than in full-term infants³⁹, and so disproportionate growth of the right hippocampus may give rise to atypical development. Indeed, abnormalities of hippocampal rightward asymmetry displayed in very preterm infants were related to memory alterations³⁹—in other words, a more right lateralized hippocampal activation is a sign of a more mature brain, leading to better memory performance⁴³. However, there would seem to be more severe long-lasting prevailing neurodevelopment alterations in preterm newborns with brain injury, resulting in numerous cognitive and behavioral dysfunctions⁴⁴, even in adulthood⁴⁵. Therefore, abnormalities in the hippocampal structure–function association might be more closely related to preterm birth alongside brain growth, as has already been observed in preterm children and adults with very low BW^{17,38}.

Some limitations of the current study were the total sample size, the sample size of each group and also the wide age range included (6–16 years old), although our analyses were controlled according to age. The small sample size compels us to treat the results deriving from this study with caution. Therefore, further studies are needed in order to provide more evidence regarding hippocampal volumetric values and their association with memory performance in larger preterm samples that are followed longitudinally. Nevertheless, the study has a well-characterized sample since it differentiates between those preterm children with and without brain injury (i.e. with and without GM-IVH), this being deemed necessary when interpreting the possible effects of prematurity according to its clinical manifestations in brain structures and cognitive outcomes. In addition to the limited statistical power, the small sample size is also behind the inability to assess whether hippocampal volume and memory performance may be different when the different grades proposed by Papile et al.⁴⁶ are taken into consideration. Apparently, the more severe the grade, the greater the risk for perinatal morbidities and, specifically, the more negative long-lasting cognitive consequences will be⁴. In fact, despite high-risk preterm children commonly have a lower GA than their low-risk preterm peers without GM-IVH, the present study has proven that GM-IVH better explains memory and hippocampal volumetric differences after preterm birth. Furthermore, MRI images were obtained at different locations, even though the same scanner model and MRI parameters were used. Actually, to our knowledge, this is the first study that has found a structural–functional relationship between memory performance and the right CA-field in a well-characterized preterm sample in terms of their clinical manifestations by using a 3-T scanner with a 1 mm³ isotropic voxel. Furthermore, our study applied rigorous standards to ensure appropriate comparable groups, taking not only neonatal data but also parental education, and emotional-behavioral scores into consideration.

Another disadvantage is that the cross-sectional nature of our study did not make it possible to research into whether neurodevelopmental outcomes in memory due to reduced hippocampal volumes persist, worsen or improve over time. Feasibly, cognitive outcomes over the first few years of life reflect young adults' performance, as displayed in preterm born young adults with very low BW²⁰. In fact, the impact of very preterm birth on hippocampal volume and memory performance continues up to young adulthood and is related to the degree of neonatal brain injury^{47,48}. Likewise, our volumetric analyses were limited to the hippocampus, although further structures may also be affected by neonatal brain injury in prematurity, since they are connected both anatomically and functionally. Finally, as memory can be divided into different subtypes, specific assessments of each one in prematurity such as visual memory may provide future considerations in the development of suitable interventions³².

A noteworthy contribution of our work is that memory function alterations and hippocampal volumetric reductions were shown in a sample of schooled preterm children with GM-IVH. In fact, understanding the scheme in which memory deficits arise in prematurity increases the chances of identifying children considered to be at a higher risk at an early stage. Moreover, despite the fact that hippocampal-memory associations were not found in high- and low-risk preterm children independently, a strong relationship between the right CA-field and memory was found only in preterm-born children (remaining significant after Bonferroni correction). Nevertheless, neuroanatomical substrates linked to memory are certainly complex, and so hippocampal volumetric differences per se may not completely elucidate memory performance³⁶. In fact, according to Tamnes et al.⁴⁹ specific hippocampal subfield volumes and developmental patterns may also be related to general cognition in healthy adolescents. Hence, more research is needed in homogeneous preterm samples in order to gain further insight into possible compensation mechanisms related to everyday cognitive functioning.

Methods

Study participants. A sample of preterm children considered to be at higher risk of developing neurodevelopmental alterations with a history of GM-IVH [henceforth the high-risk preterm group with GM-IVH] was recruited between March and November 2011. This sample belonged to a cohort that was followed longitudinally at the Vall d'Hebron University Hospital (Barcelona, Spain). The inclusion criteria for this study were: (1) preterm birth with a GA < 37 weeks of gestation; (2) having a neonatal diagnosis of GM-IVH grades II to IV in brain ultrasound imaging according to Papile classification⁴⁶; and (3) age at time of evaluation of between 6 to 16 years old. The exclusion criteria involved being diagnosed with neonatal periventricular leukomalacia or any other perinatal cerebral insult, neurosensory alterations, a shunt valve non-compatible with the MRI scanner, or a FIQ ≤ 70. From the initial 107 children that were born at the Vall d'Hebron University Hospital with a neonatal diagnosis of GM-IVH, 24 were excluded due to periventricular leukomalacia (n = 13) or neurosensory alterations (n = 11). Eighty-three participants were initially invited to participate in the study, 50 of whom were not available to complete the assessment, and 6 of whom refused to take part in the study. Therefore, twenty-seven children were evaluated, although 1 of them was excluded since GM-IVH diagnosis could not be confirmed by clinical records, 3 had a GA > 37 weeks, 3 were left out because they had an FIQ score of ≤ 70 according to current evaluation and 1 participant's GA data could not be retrieved from clinical records. Lastly, for the purpose of this study, 3 participants were excluded because T1 weighted images were not obtained (n = 1) or due to movement artifacts (n = 2). The resulting sample consisted of 16 high-risk preterm children with GM-IVH, most of whom were extremely preterm or very preterm children (i.e. eight extremely preterm and six very preterm). No differences were found in sex, age, handedness, FIQ or GM-IVH grades between the high-risk preterm participants included (n = 16) and excluded (n = 11). However, as expected, differences were found in both GA and BW, since three excluded children had a GA > 37 weeks and a BW > 3000 g.

The other two groups belonged to a cohort that had been previously studied at the University of Barcelona (Barcelona, Spain), with their characteristics already having been published elsewhere^{6,10}. Since we were interested in isolating the specific impact of GM-IVH on brain measurements, a group of preterm children considered to be at low risk of evidencing major disabilities was included [known henceforth as the low-risk preterm group without GM-IVH]. The inclusion criteria were: (1) a GA of between 30 to 34 weeks' gestation; (2) no brain pathology as assessed by neonatal cranial US; (3) BW of under 2500 g; (4) Apgar score at 5 min > 7; (5) no substantial neonatal morbidity; and (6) age at time of evaluation of between 6 to 16 years old. Seventy-six preterm children were found to meet these criteria following a search at the Hospital Clinic (Barcelona, Spain). Nevertheless, updated addresses were not available for 36 preterm children, and parents of 19 others declined to take part. Finally, abnormalities in the MRI findings (i.e. giant arachnoid cyst) of one child determined its exclusion. Hence, this low-risk preterm group without GM-IVH comprised 20 children, most of whom were being moderate or late preterm children (i.e. seven moderate preterm and seven late preterm). In addition, a full-term group was included with the following inclusion criteria: (1) GA ≥ 37 weeks; (2) BW higher than 2500 g; and (3) age at time of evaluation of between 6 to 16 years old. Twenty-three full-term children who were mostly classmates of the preterm children assessed were included in the present study. However, due to abnormalities in MRI findings (i.e. venous vascular malformation) one child was excluded, meaning that the full-term group comprised 22 participants. The exclusion criteria for both low-risk preterm and full-term groups were: experiencing any MRI counter-indications, a history of acquired brain injury, cerebral palsy or other neurological impairment, or a FIQ ≤ 70.

Parental education was calculated by the maximum number of years' education completed by the parents, classified into low (primary education or junior secondary vocational education), intermediate (general or senior secondary education) and high (higher vocational education or university)⁵⁰.

Ethical authorization for the study was approved by both the Ethics Committee of the Vall d'Hebron University Hospital and the Ethics Committee of the University of Barcelona. All participants' parents gave written informed consent, and all methods were pursued in accordance with relevant guidelines and regulations.

Neuropsychological assessment. To assess memory performance, all participants were evaluated using the *Rey Auditory Verbal Learning Test*⁵¹, which was chosen because of its recognized sensitivity to declarative memory impairments. Participants were asked to repeat a 15-word list over five trials (A1–A5), with the following measurements being obtained: (a) learning, sum of the immediate recall of the 15-word list learnt over five trials; and (b) delayed recall of the number of words after 20 min of interference.

The *Wechsler Intelligence Scale for Children IV*⁵² was used to measure intellectual ability by assessing the following four indexes: Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed. Furthermore, FIQ was able to be obtained by adding all subtests together.

Emotional-behavioral information was collected via the *Child Behavior Checklist*⁵³, which was used to measure children's emotional-behavioral functioning based on parents' reports. It is made up of eight subscales and some of them were grouped into higher order factors, namely internalizing and externalizing problems. The sum of the above-mentioned eight subscales provided the total score.

MRI images. 3-dimensional MRI datasets were obtained for the GM-IVH group at the *Unitat de Diagnòstic per la Imatge* (Vall d'Hebron University Hospital, Barcelona, Spain) and for the low-risk preterm and full-term groups using the same 3-T scanner and the same sequence parameters at the *Diagnostic Center for Imaging* (Hospital Clinic, Barcelona, Spain). MRI images were obtained from a TIM TRIO 3-T machine (Siemens, Erlangen, Germany), and an MPRAGE sequence was acquired in sagittal orientation (TR/TE = 2300/2.98 ms, TI = 900 ms, 256 × 256 matrix, flip angle 9°, 1 mm³ isotropic voxel). To identify GM-IVH lesions in the high-risk preterm sample, T2-weighted images were also acquired in axial orientation (TR/TE = 5150/99 ms; 512 × 307 matrix,

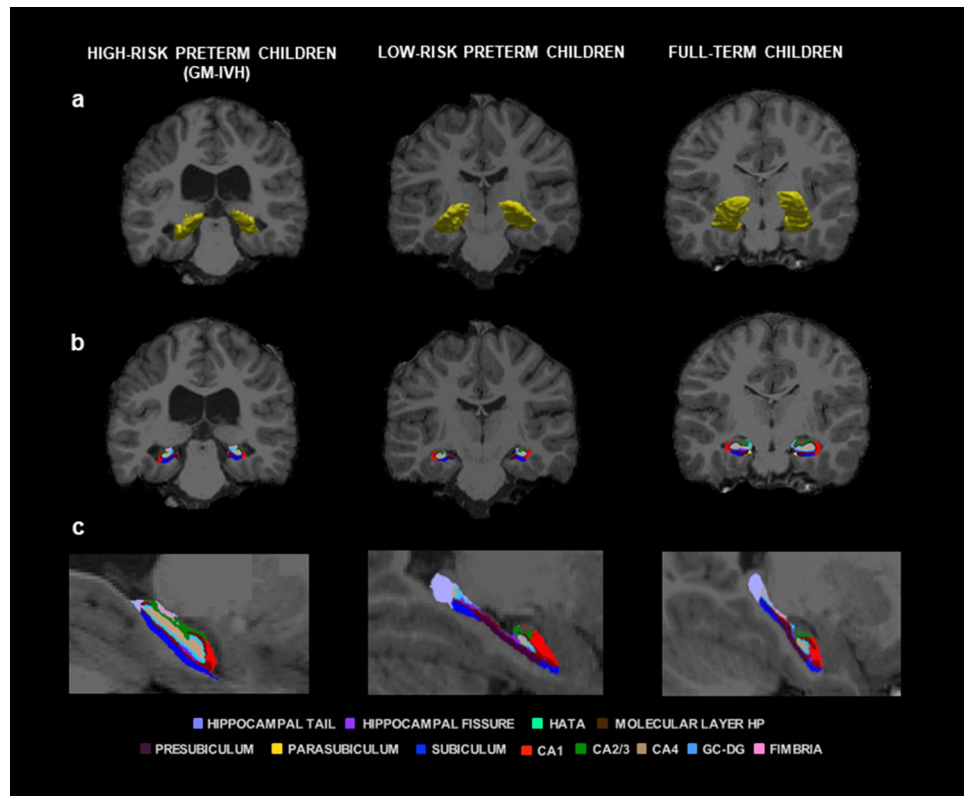


Figure 2. Right and left hippocampus and hippocampal subfield volumes. Coronal (**a,b**) and sagittal (**c**) views showing volumetric segmentation among groups in right and left hippocampus and hippocampal subfields. In accordance with radiological convention, the left side is shown on the right of the image for each view. CA: Cornu Ammonis, GC–DG: granule cell layer of dentate gyrus, HATA: hippocampal–amygdalar transition area; HP: hippocampus; and GM-IVH: germinal matrix-intraventricular hemorrhage. Coronal coordinate (**a,b**): x: -205.43, y: -11.00, z: -127.00; and sagittal coordinate (**c**): x: 2.50, y: 140.00, z: -50.05.

flip angle 120°, slice thickness 5 mm with a 1.5 intersection gap), as well as fluid-attenuated inversion recovery images (axial orientation, TR/TE = 9040/85 ms, TI = 2500, 256 × 156 acquisition matrix, flip angle 150°, slice thickness 5 mm with a 1.5 intersection gap). For low-risk preterm and full-term subjects, T2-weighted images (axial orientation, TR/TE = 5533/88 ms, 122 × 122 matrix, flip angle 90°, slice thickness 2 mm, gap = 0.6 mm) were also acquired. Even though T2-weighted images were obtained using different parameters (GM-IVH group vs. low-risk preterm and full-term groups), these images were merely used for clinical estimation of WM intensities. All MRI data were checked by two pediatric neuroradiologists (E.V. and I.D.) to provide updated GM-IVH information and detect any brain alteration.

Prior to processing, images were also checked for movement and scanner artifacts. T1-weighted images were analyzed using FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/>) (version v6.0.0) in order to obtain hippocampal volumes, and hippocampus segmentations were made of 3D T1-weighted structural MRI scans⁵⁴. Processing of T1 high-resolution images included several procedures: intensity non-uniformity correction, skull stripping, affine transformation to MNI template, intensity normalization, removal of non-brain tissue, linear and non-linear transformations to a probabilistic brain atlas and labelling of subcortical/allocortical structures. Spatial localization priors were used to determine the correct label per each single voxel⁵⁵.

T1-weighted images were processed using a hippocampal subfield segmentation package, FreeSurfer hippocampal-subfields-T1 command (i.e. using the FreeSurfer hippocampal subfield pipeline)⁵⁶, with left and right hippocampal values were obtained. Moreover, the hippocampus was segmented into 12 subfields for each hemisphere: hippocampal tail, subiculum, presubiculum, parasubiculum, Cornu Ammonis 1 (CA1), CA2/3, CA4, granule cell layer of dentate gyrus (GC–DG), molecular layer hippocampus (HP), fimbria, hippocampal–amygdalar transition area (HATA), and hippocampal fissure (see Fig. 2). In line with previous authors who have used this type of segmentation in preterm samples¹⁷, and since our segmentations were based only on T1-weighted images and certain hippocampal subfields are considered less reliable because of their size⁵⁶, three grouped subfield volumes were created for each hippocampal hemisphere: CA-field (CA1 + CA2/3 + molecular layer HP + subiculum); Dentate gyrus (GC–DG + CA4); and Subiculum (presubiculum). This reclassification is more in accordance with proposals put forward by Mueller et al.⁵⁷ and other automated segmentation methods⁵⁸. All hippocampal volumetric values are expressed in mm³.

Statistical analysis. Normal distribution of the data was assessed using the K–S test, with tests being run on raw scores for normally distributed data and on ranked dependent variables for not normally distributed data. A composite score was calculated to create a memory index with learning and delayed recall scores; to do so all raw cognitive scores were converted into z-values, and Cronbach's alpha coefficient was used to determine the internal consistency of this composite score.

The Kruskal–Wallis test was used to analyze differences in neonatal data (GA and BW) and age at time of evaluation. Furthermore, the Chi-squared test was required to assess differences in the following qualitative sociodemographic characteristics: sex, handedness and parental education. Moreover, a multivariate analysis of covariance was used to compare neuropsychological functioning and neuroanatomical volumetric values in the hippocampus (i.e. left and right hippocampus provided by Freesurfer and grouped hippocampal subfields) among the three groups. Covariates were: (1) age for memory scores; and (2) total intracranial volume (eTIV), age and whether or not they had a ventriculoperitoneal shunt for MRI volumetric comparisons. Additional analyses were conducted to regress the effect of sex on memory and hippocampal measures and to add scanner site as covariate; however, both results failed to differ after multivariate analyses of covariance were undertaken among the three groups. Partial eta squared was used to calculate the effect sizes of those comparisons. Bonferroni's post-hoc test was used to assess differences between groups, and Bonferroni corrected *p* value for significance was also calculated for global bilateral hippocampal volumes and the three bilateral grouped hippocampal sub-field volumes ($p = 0.05/8 = 0.006$). Besides, in order to ascertain to what extent our results might be explained by neonatal brain injury, GA or the interaction of both variables, regression analyses were conducted on all memory and hippocampal volumetric variables.

Partial correlations (adjusted for eTIV and age) were performed between the memory index and global (left/right) as well as regional hippocampal volumes grouped into three subfields for each hemisphere (i.e. CA-field, dentate gyrus and subiculum) in both preterm groups independently and also in preterm and full-term groups. In order to correct for multiple comparison purposes, Bonferroni corrected *p* value for significance was calculated ($p = 0.05/8 = 0.006$). Likewise, interaction analyses were conducted to ascertain whether memory-hippocampal associations were statistically different between high- and low-risk preterm children as well as between preterm and full-term groups. For all preceding analyses, the SPSS version 26 was used, and significance level was set at 0.05.

Ethics approval. Ethical authorization for the study was approved by both the Ethics Committee of the Vall d'Hebron University Hospital and the Ethics Committee of the University of Barcelona.

Consent for publication

All participants' parents gave written informed consent to participate and for publication.

Data availability

The data sets and analysis of current study are available from the corresponding author upon reasonable request.

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Author contributions

C.J., E.V., I.D., E.S., S.S.-P., A.M., L.Z.-E and M.A.P. conceived and designed the study, including participant selection, recruitment, and data collection. L.F.G.-O., L.Z.-E and M.A.P. carried out the statistical analysis and interpretation of the data. Along with L.F.G.-O., L.Z.-E., C.J. M.A.P., E.S., and N.O. collaborated in drafting the manuscript and critically revised and edited the initial manuscript. All authors read and approved the final manuscript as submitted.

Competing interests

The authors declare no competing interests.

Additional information

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Maternal care and general cognitive functioning in moderate and late preterm-born children

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ABSTRACT

Aim: To establish the neuropsychological profile in moderate and late preterm (MLPT) samples during childhood, and to assess the potential role of early life environmental factors in cognitive outcomes.

Methods: One hundred-and-six children took part in this study, including 42 moderate preterm ($M_{age}=11.57$ years; $Md_{age}=12$; $SD_{age}=1.77$), 33 late preterm ($M_{age}=12.21$ years; $Md_{age}=12$; $SD_{age}=0.78$) and 31 full-term children ($M_{age}=11.42$ years; $Md_{age}=12$; $SD_{age}=1.84$). All participants underwent an environmental, emotional-behavioural, life satisfaction, functionality, resilience, and cognitive assessment.

Results: Significant differences were found in several cognitive domains among groups. Further, the maternal care measure moderated the relationship between the degree of maturity/immaturity at birth and general cognitive functioning score ($F(4,1014101)=3.72$, $p=0.007$, $R^2=0.13$).

Conclusions: The findings showed different neuropsychological profiles during childhood, with the moderate preterm sample reporting poorer general cognitive functioning. Additionally, the appropriate level of maternal care measure used in this study seems to have had a protective effect on cognitive development.

Prematurity is described as a chronic condition (Raju et al., 2017) which can have adverse long-term neurodevelopmental consequences even for infants born at 32–36 weeks of gestation. Moderate (32–34 weeks' gestational age (GA)) and late (35–36 weeks' GA) preterm (MLPT) neonates are born during a sensitive period for brain development (Walsh et al., 2014), with a commensurate higher risk of neonatal morbidity requiring admission to a neonatal unit when compared to those born at term (Boyle et al., 2015). These subgroups account for more than 80 % of preterm deliveries (Shapiro-Mendoza & Lackritz, 2012), and some may present academic difficulties in a variety of higher- and lower-order subskills (McBryde et al., 2020).

During infancy, lower scores in cognitive performance are commonly displayed in preterm-born infants compared to their full-term peers, which seem to appear early in life and increase over time (Yaari et al., 2018). However, low-risk preterm samples have been far less explored, as have the cognitive differences that may exist between moderate and late preterm newborns. The double burden of

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preterm birth and related factors (i.e., neonatal and environmental factors) are thought to have a strong impact on cognitive functioning across adulthood (Fernández de Gamarra-Oca et al., 2021). Nevertheless, the extent to which these factors may affect early cognition in the MLPT population during childhood still needs to be addressed more thoroughly. While biological factors have a modest effect on cognition at the early stages, they seem to lose their effect over time in low-risk preterm children (Pérez-Pereira et al., 2020). In contrast, environmental factors have been shown to be increasingly important during infancy after preterm delivery (Ross & Perlman, 2019); the quality of the home environment, parenting behaviors and socioeconomic factors appear to challenge the relationship between prematurity and cognitive delays (McMahon et al., 2022; Pérez-Pereira et al., 2020; Wong & Edwards, 2013). Nonetheless, studies carried out to date have largely concentrated on the early years of life, without assessing this potential environmental impact in later years.

As there is wide heterogeneity in the way prematurity shapes the brain (Dimitrova et al., 2020), there may be different factors that influence cognitive functioning during childhood after preterm delivery. This study aims to determine the neuropsychological profiles of MLPT children, given the lack of research on the differences between both preterm samples, as most of the existing studies have focused on extremely and very preterm birth. Furthermore, in view of the biological risk factor of prematurity, contextual factors may put children at an even higher risk of worse functioning (Bills et al., 2021). This study therefore retrospectively assesses the potential role that early life environmental factors play in the cognitive outcomes of MLPT children.

1. Methods

1.1. Participants

A total of 106 children participated in this study, including 42 moderate preterm, 33 late preterm, and 31 full-term children (see Table 1). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Deusto [ETK-22/17-18] and the Drug Research Ethics Committee of the Basque Country [CEIm-E, PI2018154]. All participants provided prior written informed assent and legal tutors' consent was required at the beginning of the study.

A sample of 75 MLPT children born between 2007 and 2011 was recruited by the neonatology department from the Cruces University Hospital (Bilbao, Spain), which was supplemented by chain-referral sampling from two Spanish autonomous regions (Basque Country and Aragon) (see Fig. 1). More specifically, the neonatologist identified 168 potential participants, of whom 56 agreed to take part in the study. Additionally, 32 children were recruited after the research project was publicized; however, 13 of these were excluded (i.e., 10 children had a GA of less than 32 weeks, and three children had intraventricular hemorrhage). Participant inclusion criteria were as follows: (1) absence of brain pathology identified by neonatal cranial ultrasound; (2) lack of substantial neonatal morbidity (i.e., congenital, neurological, cardiac, or digestive malformations, necrotizing enterocolitis, or septic shock); and (3) aged 6–15 at evaluation. In addition, a full-term group of 31 participants was recruited by chain-referral sampling. Inclusion criteria for this group were: (1) GA > 37 weeks; and (2) aged 6–15 at evaluation. The exclusion criteria for the three groups (i.e., moderate preterm, late preterm and full-term children) were a history of acquired brain injury, cerebral palsy or any other neurological impairment, congenital malformations, or chromosomal abnormalities.

1.2. Neuropsychological assessment

Analogical reasoning was evaluated using the matrix reasoning subtest from the Wechsler Intelligence Scale for Children (WISC-V) (Kaufman et al., 2015), whereas *receptive language* was measured by the Peabody Picture Vocabulary Test III (PPVT-III) (Dunn & Dunn, 1981). Verbal fluency was also assessed by the completion of *phonetic* (P, M, R) and *semantic fluency* tasks (category of animals), with a minute being given for each trial (Lezak et al., 2004). The Rey Auditory Verbal Learning Test (RAVLT) was used to assess *memory performance*. The measurements obtained from this test included: learning, delayed recall, and delayed recognition (Baron, 2018). *Working memory* was assessed by the use of the WISC-V (Kaufman et al., 2015); using digit span (forward, backward, and increasing) and picture span subscales. *Cognitive flexibility* was measured using the Children's Color Trails Test (CCTT) part B (Williams et al.,

Table 1
Neonatal and Sociodemographic Data.

	Moderate preterm n = 42 mean ± SD	Late preterm n = 33 mean ± SD	Full-term n = 31 mean ± SD	Statistics (p)
Neonatal data				
GA. wks [range]	33.07 ± 0.81 [32–34]	35.42 ± 0.50 [35,36]	39.29 ± 1.04 [37–41]	$H = 94.289 (<0.001)^*$
BW. g	1874.63 ± 336.14	2133.86 ± 463.11	3160.14 ± 351.44	$H = 62.520 (<0.001)^*$
Sociodemographic data				
Gender. male/female	23/19	17/16	12/19	$X^2 = 1.955 (0.38)$
Age. yrs [range]	11.78 ± 1.50 [7–14]	11.42 ± 1.84 [10–14]	11.42 ± 1.84 [8–14]	$H = 2.329 (0.31)$
Handedness right-handed/left-handed	36/6	31/2	30/1	$X^2 = 3.172 (0.21)$

Note: SD: standard deviation; GA: gestational age; wks: weeks; BW: birth weight; g: grams; yrs: years; H : Kruskal-Wallis test; and X^2 : Chi-square test.
*Statistically significant differences between Moderate preterm < Late preterm, Moderate preterm < Full-term and Late preterm < Full-term.

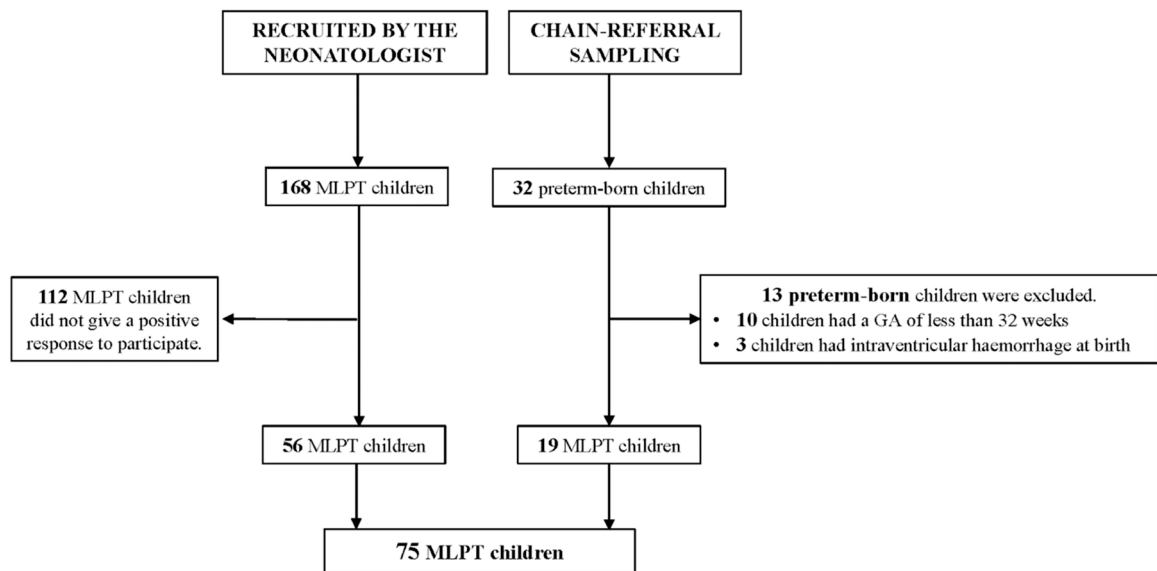


Fig. 1. Flow chart for MLPT children from June 2019 to June 2021, Note: GA: gestational age; and MLPT: moderate and late preterm.

1995), the Modified Wisconsin Card Classification Test (M-WCST) (Schretlen, 2010), and the PC measure from the Stroop Test (Stroop, 1992). Lastly, *processing speed* was assessed by means of the Stroop Test (P and C measures) (Stroop, 1992) and CCTT part A (Williams et al., 1995).

1.3. Emotional-behavioral assessment

The Child Behavior Checklist (CBCL) is a widely used questionnaire used to screen for *emotional-behavioral problems* (Achenbach & Edelbrock, 1983). It measures eight behavioral problem scales that are combined to form broadband scales of both internalizing problems (i.e., anxious/depressed, withdrawn-depressed, and somatic complaints scores) and externalizing problems (i.e., rule-breaking and aggressive behavior). Scores for social, thought, and attention problems obtained from this questionnaire were also taken into account.

The abridged 48-item version of the Conners' Parent Rating Scale (CPRS) (Goyette et al., 1978) provided a picture of children's *emotions and behavior* based on five subscales: conduct problems, learning problems, psychosomatic and impulsive-hyperactive issues, and anxiety.

1.4. Early life environmental factors

Parental care and overprotection measures were obtained using the Parental Bonding Instrument (Parker et al., 1979) to assess the participants' parents' independent behavior toward them. *Familial socioeconomic status (SES)* was measured by means of the Hollingshead Index (Hollingshead, 1975), which considered data from the occupation and education domains from the parent who had signed the informed consent. Lastly, the Adverse Childhood Experiences International Questionnaire (ACE-IQ) (World Health Organization, 2018) was used to assess the *adverse childhood experiences (ACEs)* and the ensuing health consequences.

1.5. Life satisfaction, functionality and resilience

The Satisfaction with Life Scale-Child (SWLS-C) was used to measure the participants' judgements of *satisfaction with their life* (Gadermann et al., 2010), while the WHODAS 2.0 parent's report tool was employed to establish standardized *disability levels and profiles* (Üstün et al., 2010). *Resilience* was assessed by using the 2-item Connor-Davidson Resilience scale (CD-RISC2), with higher scores reflecting greater resilience (Vaishnavi et al., 2007).

All neuropsychological assessments during childhood were conducted at DeustoPsych of the University of Deusto and at the Association of Preterm Infants of Aragon (ARAPREM).

1.6. Statistical analysis

Normal distribution of data was assessed using the Kolmogorov-Smirnov test (K-S). Any missing values (with the exception of cognitive variables) were imputed using the expectation maximization algorithm (5.62 % of the used data). All tests were standardized in order to create a composite score (Cronbach's alpha=0.89), henceforth referred to as the general cognitive functioning score. The

PPVT-III receptive language total scores, M-WCST category and perseverative error scores, RAVLT learning, delayed recall and delayed recognition measures, WISC-V matrices, digit span and picture span, phonetic and semantic fluencies, Stroop Test P, C, PC and interference measures, and CCTT part A and B were used to calculate it.

The Kruskal-Wallis test was used to analyze differences in non-normally distributed data such as neonatal data (GA and BW), age at evaluation, familial SES, ACEs, emotional-behavioral problems, life satisfaction, functionality, and resilience. The Chi-squared test was employed to assess differences in two qualitative sociodemographic characteristics (i.e., sex and handedness), and univariate analyses of variance were run to compare maternal and paternal care and overprotection measures' scores between the three groups. All early life environmental, emotional-behavioral, life satisfaction, functionality, and resilience data are reported in Table 2. Lastly, a multivariate analysis of covariance was used to compare different cognitive test scores and the general cognitive functioning composite score using age and familial SES as covariates (see Table 3). Bonferroni's post-hoc test was employed to assess differences between groups, and a Bonferroni corrected p -value ($p = 0.05/18 = 0.003$) was used in assessing significance in different cognitive tests. Partial eta squared was used to measure the effect sizes of the cognitive comparisons. To interpret this value, around .01 is a small size effect, .06 is medium, and higher than .14 is large (Cohen, 2013).

Finally, the moderating effect of early life environmental factors (i.e., maternal and paternal care, maternal and paternal overprotection, and ACEs) were independently analyzed in the relationship between the degree of maturity/immaturity at birth and general cognitive functioning score. To assess the moderation effect, five moderation analyses (see Fig. 2) were executed using the macro PROCESS 3.5 script for SPSS (released on 1 May 2020) (Hayes, 2017). Outlier analysis assessed rupture of linearity, normality, multicollinearity, and homoscedasticity, and was conducted before carrying out the moderation analyses; Mahalanobis and Cook's distances as well as Leverage parameters were used to detect possible outliers. A scatterplot and histogram check showed no sign of any outliers in the study sample. A Johnson-Neyman output was generated to determine the points at which early life environmental factors had a significant conditional effect on the degree of maturity/immaturity at birth in the prediction of the general cognitive functioning score. For all preceding raw data analyses, IBM SPSS version 26.0 (SPSS Inc., Chicago, USA) was used. Significance level was set at 0.05.

2. Results

As expected, there were significant differences in the neonatal data of the three groups (GA and BW). Greater immaturity levels were found in both preterm groups. There were no statistically significant differences in sex, age, or handedness between groups, as reported in Table 1.

Emotional-behavioral problems showed no significant differences in the present study sample (see Table 2). According to

Table 2
Early Life Environmental, Emotional-Behavioural, Life Satisfaction, Functionality and Resilience Data.

	Moderate preterm n = 42 mean ± SD	Late preterm n = 33 mean ± SD	Full-term n = 31 mean ± SD	Statistics (p)
Early Life Environmental Factors				
Maternal care measure	28.00 ± 5.18	29.49 ± 3.86	29.97 ± 3.53	F=1.890 (0.16)
Paternal care measure	26.90 ± 4.57	28.61 ± 5.88	29.20 ± 4.08	F=2.528 (0.08)
Maternal overprotection measure	15.24 ± 4.57	14.51 ± 5.88	14.96 ± 4.08	F=0.170 (0.84)
Paternal overprotection measure	14.27 ± 4.57	13.88 ± 5.88	13.94 ± 4.08	F=0.076 (0.93)
ACEs	0.36 ± 0.66	0.27 ± 0.52	0.39 ± 0.88	H=0.137 (0.93)
Familial SES	44.10 ± 14.05	36.33 ± 14.56	43.89 ± 11.93	H=6.252 (0.04)*
Emotional-Behavioural Assessment				
Child Behaviour Checklist (CBCL)				
Internalizing problems	8.66 ± 6.10	8.82 ± 7.25	9.84 ± 8.60	H=0.027 (0.99)
Externalizing problems	8.78 ± 8.02	8.04 ± 6.30	7.56 ± 4.62	H=0.226 (0.89)
Attention problems	4.83 ± 4.23	4.67 ± 4.39	3.40 ± 3.42	H=1.833 (0.40)
Thought problems	0.73 ± 0.99	1.01 ± 1.43	0.74 ± 0.81	H=0.186 (0.91)
Social problems	2.17 ± 2.13	2.02 ± 2.64	1.63 ± 1.61	H=1.343 (0.51)
Conners Parent Rating Scale-48 items (CPRS)				
Conduct problems	4.60 ± 3.91	4.25 ± 4.22	3.53 ± 2.48	H=0.841 (0.66)
Learning problems	4.63 ± 3.16	3.03 ± 2.26	3.25 ± 2.34	H=4.273 (0.12)
Psychosomatic complaints	2.34 ± 1.66	1.53 ± 1.39	2.16 ± 1.95	H=5.318 (0.07)
Impulsivity-Hyperactivity	3.86 ± 2.84	3.63 ± 2.65	3.65 ± 2.02	H=0.128 (0.94)
Anxiety	1.77 ± 1.47	1.67 ± 1.31	1.93 ± 1.33	H=0.951 (0.62)
Life satisfaction, Functionality and Resilience				
SWLS	20.05 ± 3.41	18.94 ± 3.78	17.71 ± 3.66	H=7.109 (0.03)*
WHODAS	48.31 ± 13.05	46.23 ± 13.29	45.36 ± 10.50	H=3.296 (0.19)
Resilience	6.00 ± 1.35	5.91 ± 1.44	5.71 ± 1.39	H=1.418 (0.49)

Note: SD: standard deviation; H: Kruskal-Wallis test; F: Snedecor's F distribution; ACEs: adverse childhood experiences; SES: socioeconomic status; SWLS: satisfaction with life scale; and WHODAS: WHO Disability Assessment Schedule.

*Statistically significant differences between Late preterm<Moderate preterm. †Statistically significant differences between Full-term<Moderate preterm.

Table 3
Cognitive Tests Differences and General Cognitive Functioning Score among Three Groups.

	Moderate preterm n = 42 mean ± SD	Late preterm n = 33 mean ± SD	Full-term n = 31 mean ± SD	F-Snedecor Statistic (p)	η_p^2
Matrices (WISC V) [‡]	19.17 ± 3.57	18.64 ± 3.73	20.13 ± 3.83	1.35 (0.27)	.03
PPVT-III	124.16 ± 18.93	127.55 ± 16.45	128.95 ± 21.72	0.89 (0.41)	.02
Phonetic Fluency	25.56 ± 8.12	23.36 ± 7.14	29.67 ± 10.12	4.63 (0.012) [†]	.08
Semantic Fluency	18.26 ± 4.44	18.57 ± 4.66	18.97 ± 4.40	0.23 (0.80)	.00
RAVLT Learning	43.83 ± 9.50	45.92 ± 6.53	45.55 ± 10.24	0.60 (0.55)	.01
RAVLT Delayed Recall	9.71 ± 2.88	10.03 ± 1.92	10.30 ± 2.51	0.50 (0.61)	.01
RAVLT Delayed Recognition	29.03 ± 1.31	29.45 ± 1.00	29.33 ± 0.98	1.38 (0.26)	.03
Digit Span (WISC V)	27.72 ± 5.19	28.00 ± 5.59	28.66 ± 5.22	0.32 (0.73)	.01
Picture Span (WISC V)	31.44 ± 7.56	31.43 ± 8.56	29.71 ± 8.23	0.54 (0.58)	.01
WMI (WISC V)	105.50 ± 14.28	106.19 ± 17.16	105.07 ± 15.34	0.40 (.96)	.00
M-WCST Categories	6.32 ± 0.86	6.21 ± 0.95	6.47 ± 0.77	0.74 (0.48)	.02
M-WCST Perseverative Errors	1.40 ± 1.85	1.13 ± 1.16	0.91 ± 0.88	1.15 (0.32)	.02
Stroop Test (P)	84.85 ± 17.49	84.64 ± 14.30	94.29 ± 15.75	3.79 (0.026) [‡]	.07
Stroop Test (C)	56.93 ± 11.54	53.14 ± 8.65	63.65 ± 14.39	7.63 (<0.0001)[‡]	.13
Stroop Test (PC)	34.73 ± 9.26	33.43 ± 6.98	38.88 ± 10.01	3.77 (0.026) [†]	.07
Stroop Test (Interference)	0.36 ± 7.40	0.82 ± 4.76	1.15 ± 5.00	0.16 (0.85)	.00
CCTT Part A	24.11 ± 13.62	23.43 ± 8.89	20.08 ± 7.69	1.73 (0.18)	.03
CCTT Part B	46.01 ± 17.16	46.44 ± 9.07	37.71 ± 11.76	6.07 (0.003)[‡]	.11
Composite Score					
General Cognitive Functioning Score	-0.07 ± 0.65	-0.05 ± 0.43	0.22 ± 0.64	3.30 (0.041) [‡]	.06

Note: SD: standard deviation; F: Snedecor’s F distribution; PPVT-III: Peabody picture vocabulary test-III; MWCST: Modified Wisconsin Card Sorting Test; RAVLT: Rey Auditory Verbal Learning Test; WISC V: Wechsler Intelligence Scale for Children V; WMI: working memory index; CCTT: Children’s Color Trail Test; and η_p^2 : partial eta squared.

[‡]Available data for Matrices (WISC V): 41 moderate preterm, 33 late preterm and 31 full-term children.

The cognitive domains in bold are those that remained significant after Bonferroni correction was applied for multiple comparisons ($p = 0.003$).

‡Statistically significant differences between Moderate preterm<Full-term and Late preterm<Full-term. [†]Statistically significant differences between Moderate preterm<Full-term. [‡]Statistically significant differences between Late preterm<Full-term.

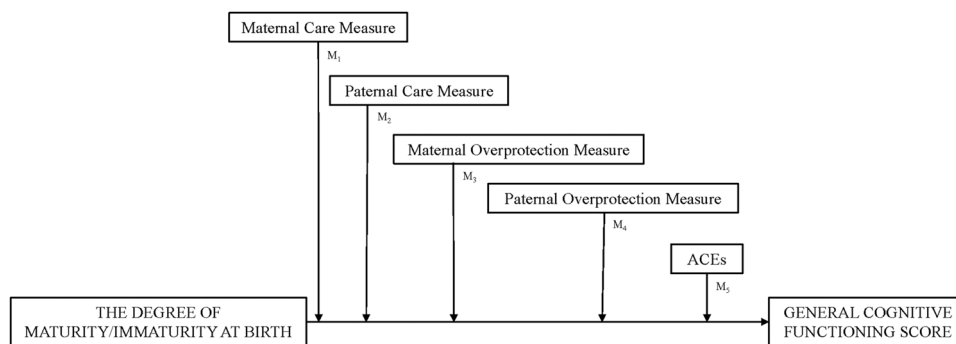


Fig. 2. Moderation Models between the Degree of Maturity/Immaturity at Birth and General Cognitive Functioning Score, Note: ACEs: adverse childhood experiences. M₁: the moderating effect of maternal care measure in the relation between the degree of maturity/immaturity at birth and general cognitive functioning; M₂: the moderating effect of paternal care measure in the relation between the degree of maturity/immaturity at birth and general cognitive functioning; M₃: the moderating effect of maternal overprotection measure in the relation between the degree of maturity/immaturity at birth and general cognitive functioning; M₄: the moderating effect of paternal overprotection measure in the relation between the degree of maturity/immaturity at birth and general cognitive functioning; and M₅: the moderating effect of ACEs in the relation between the degree of maturity/immaturity at birth and general cognitive functioning.

environmental factors, familial SES showed statistically significant differences between both preterm groups, with lower scores being obtained for those born at 35–36 weeks’ GA. Satisfaction with life showed statistically significant differences between moderate preterm-born children and their full-term peers, and higher levels of satisfaction were reported by those born prematurely. Nevertheless, the analysis of the rest of environmental, functionality and resilience variables did not yield any statistically significant differences between the three groups.

Regarding the different cognitive tests, a number of statistically significant differences between the groups remained significant

after a Bonferroni correction was applied for multiple comparisons ($p = 0.003$), as indicated in [Table 3](#). Concretely, lower scores in cognitive flexibility (i.e., CCTT part B), and processing speed (i.e., C Stroop Test measure) were found in the MLPT group compared to full-term children. Moreover, poorer outcomes were observed in processing speed (i.e., P Stroop Test measure) in moderate preterm-born children compared to their full-term peers without surviving Bonferroni correction. Lastly, poorer performance in phonetic fluency, and cognitive flexibility (i.e., PC Stroop Test measure) was found in late preterm children in comparison to the full-term sample without surviving Bonferroni correction. All differences showed medium effect sizes, the largest of which were in the following cognitive domains: Stroop Test C ($\eta_p^2 = .13$), and CCTT part B ($\eta_p^2 = .11$). In addition, no significant differences were found between the groups in receptive language, semantic fluency, M-WCST cognitive flexibility, WISC-V analogical reasoning, digit span, picture span and working memory index, RAVLT verbal memory, and the Stroop Test interference measure. Finally, the general cognitive functioning score showed statistically significant differences, with a medium effect size ($\eta_p^2 = .06$) between moderate preterm and full-term children, with the moderate preterm sample reporting lower values.

Concerning moderation analyses (see [Fig. 2](#)), familial SES could not be analyzed, given the differences in this variable between both preterm groups; therefore, it was used as a covariate in the subsequent analyses. Maternal care was the only early life environmental factor that had a moderating effect, as indicated in [Table 4](#), and 13 % of the variance was explained by the three factors (i.e., the degree of maturity/immaturity at birth, maternal care measure and the interaction of both) in the overall model ($F_{(4,101)} = 3.72, p = 0.007, R^2 = 0.13$). More specifically, for every unit increase in the maternal care measure as a moderator variable there was also an enhancement in the general cognitive functioning score ($\beta = 0.06, t_{(101)} = 2.10, p = 0.03$). Only the low care measure (i.e., low care measure = 25.00) showed a significant relationship between the different degrees of care (see [Figs. 3 & 4](#)). Nevertheless, having either a medium or high level of maternal care (i.e., higher than 28.84) did not further uphold a significant relationship between the degree of maturity/immaturity at birth and cognition across childhood. Additionally, whereas the overall models of all other early life environmental factors (i.e., paternal care, maternal overprotection, paternal overprotection, and ACEs) were significant, the nonsignificant interaction between predictors indicated a lack of moderation effect (see [Table 4](#)).

3. Discussion

The MLPT children who participated in this study obtained similar scores in the emotional-behavioral, life satisfaction, functionality, and resilience variables when compared to their full-term peers. However, different neuropsychological profiles were identified, as moderate preterm-born children had poorer performance in general cognitive functioning. The risk of adverse educational outcomes after being born MLPT has been suggested to rise in primary school and to remain in later years ([Flores et al., 2021](#)). Children born preterm without major neurosensory damage have shown higher levels of learning impairment than the normative population across their final years of primary school ([Bucci et al., 2020](#)). Furthermore, according to our findings, disparities in maternal care moderated the effect of preterm birth on general cognitive functioning during childhood, markedly so in those with greater neonatal immaturity. In other words, high maternal care buffered the impact of greater immaturity levels (i.e., smaller GA) on cognition. Parental responsiveness has been associated with enhanced cognition in preterm-born infants ([Neel et al., 2018](#)); in particular, regarding reduced expression of developmental psychopathology and executive dysfunction after being born with a very small GA ([Vanes et al., 2021](#)).

In general, our results are in line with previous studies that found that preterm children with low risk of having neurodevelopmental deficits achieve poorer cognitive scores than those born at term ([Arhan et al., 2017](#)), even in adulthood ([Fernández de Gamarra-Oca et al., 2021](#)). In a context of low medical and environmental risk, consistently with [Hodel and colleagues \(2017\)](#), MLPT infants displayed subtle alterations in cognitive skills. Specifically, poorer performance in cognitive flexibility, and processing speed was found in MLPT children. Similarly, [Martínez-Nadal and Bosch \(2021\)](#) also showed the presence of mild difficulties in executive functioning, short-term verbal memory, literacy skills, and attention during childhood in a late preterm sample. On the other hand, phonetic fluency was revealed to be a distinguishing feature in the neuropsychological profiles of MLPT children in our study. Late preterm children reported poorer scores in phonetic fluency, on which they are likely to continue to perform poorly at later ages ([Putnick et al., 2017](#)).

Even though cognitive performance was within normal range, some differences were found in this study in general cognitive functioning between those with a smaller GA (i.e., moderate preterm group) and those born at term. In fact, our findings are in

Table 4
Moderation Analyses of Early Life Environmental Factors between the Degree of Maturity/Immaturity at Birth and General Cognitive Functioning Score.

Criterion variable	R	R ²	β	t	p	Predictors
General cognitive functioning score	0.36	0.13	-0.03	-2.01	0.04	Maternal care measure
	0.34	0.11	-0.02	-1.62	0.11	Paternal care measure
	0.30	0.09	0.003	0.19	0.85	Maternal overprotection measure
	0.31	0.10	-0.01	-0.93	0.35	Paternal overprotection measure
	0.32	0.10	0.06	0.65	0.51	ACEs

Note: t: Student's t-test; and ACEs: adverse childhood experiences.

From the general model R and R².

From the interaction model β , t and p.

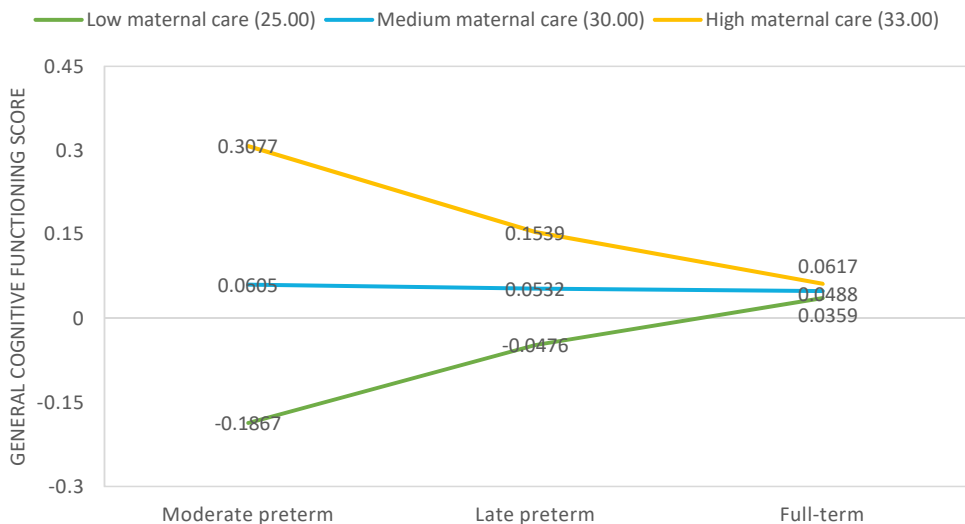


Fig. 3. Moderating Effect of Maternal Care Measure between the Degree of Maturity/Immaturity at Birth and General Cognitive Functioning Score, Note: Low maternal care (green line/bottom line) showed a significant relationship between the degree of maturity/immaturity at birth and cognition across childhood. Nevertheless, either having a medium (blue line/middle line) or high level (yellow line/top line) of maternal care did not further uphold a significant relationship between the degree of maturity/immaturity at birth and cognition across childhood.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

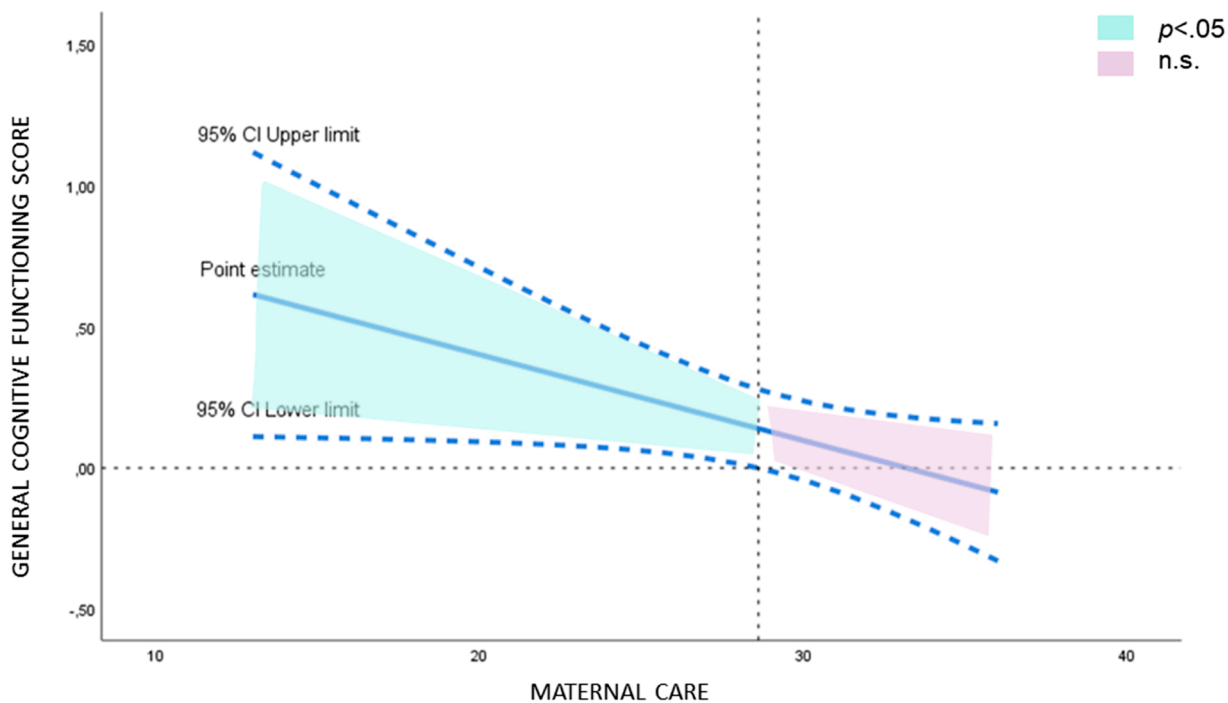


Fig. 4. Johnson-Neyman Moderation Analysis Plot.

agreement with the finding that prematurity in the absence of neonatal brain injury leads to poorer cognition, i.e., preterm birth to any degree affects cognition, resulting in altered neurodevelopment over time (Allotey et al., 2018).

According to Sansavini et al. (2011), preterm birth results in atypical developmental trajectories, which may vary depending on the complex interaction of biological and environmental factors. Long-term cognitive outcomes may be improved by means of factors that go beyond initial neonatal care (i.e., care-related risk factors) in the preterm-born population (Wolke, 2019). For instance, optimal school outcomes in preterm children have been related to greater parental education, child nurturing by both parents, and stability in family composition and geographic residence (Gross et al., 2001). Parent-child attachment has also been associated with brain

development in typically developing children (Hidalgo et al., 2019); even in preterm samples (Treyvaud et al., 2021). Our findings suggest that maternal care moderated the effect of preterm birth on general cognitive functioning. That is, differences in maternal care during childhood might interfere with brain reorganization after prematurity and affect cognitive functioning during childhood, especially in moderate preterm-born children. Nevertheless, maternal responsiveness to nonverbal cues and emotional harmony have been linked to verbal and performance intellectual quotients in both preterm-born and full-term children (Erickson et al., 2018).

The results in this study follow in the footsteps of a previous study that suggested that parents have an important role in shaping the long-term neurodevelopment of high-risk preterm newborns; however, the paternal care measure did not moderate this relationship. Likewise, this study found that a high maternal care measure prevented the impact of prematurity on general cognition during childhood. At the very least, positive parenting has been shown to have long-lasting advantages for preterm-born infants (Cheong et al., 2020). Nonmedical interventions (i.e., Family Nurture Intervention) designed to enhance mother-infant emotional connection have a beneficial impact on preterm-born neurobehavioral functioning at term equivalent age and 18 months (Welch & Myers, 2016). Hence, through these evidence-based interventions, cognition could also be improved. Lastly, our study's findings did not show overprotection measures and ACEs to be moderators of the relationship between the degree of maturity/immaturity at birth and cognition in low-risk preterm children.

4. Limitations

In contrast with previous studies that used heterogeneous preterm samples, this study succeeded to reach comparable groups through their neonatal and sociodemographic data, thus fostering the generalizability of the results. However, differences in familial SES between both preterm groups compels us to treat the results from this study with caution. Another limitation was that there was no longitudinal follow-up from childhood onward in order to assert whether neurodevelopmental outcomes persisted, worsened, or improved over time. Moreover, the sample size was small, and familial SES was only obtained from the parent who completed the questionnaires. Despite no statistically significant differences being shown in which the late preterm group scored lower than moderate preterm-born children did, the mean scores in phonetic fluency and processing speed of late preterm children were lower than those of their preterm-born peers. Since late preterm children exhibited lower values in familial SES, adjustments for the differences have been done. However, caution would be required regarding the outcomes of late preterm birth effects. Furthermore, early life environmental factors were collected retrospectively as well as the theory of attachment on which this study is based has lately been considered to offer an increasingly complex picture of the principles that regulate mother-infant emotional behavior. Future studies should therefore contemplate alternative models such as emotional connection and calming cycle theories (Ludwig & Welch, 2019). Finally, the disparities concerning satisfaction with life were not further explored, although as reported by Gire et al. (2020), the child's overall intellectual ability has been found to be independent of quality of life in cases of extreme prematurity without major neurodevelopmental disability.

5. Conclusions

Our findings show that the participating MLPT children displayed poorer performance in a number of cognitive domains, which might potentially affect their long-lasting academic performance (de Jong et al., 2012). In our opinion, establishing different neuropsychological profiles among children born preterm according to their clinical conditions may support the development of specific intervention programs during childhood if deemed necessary. Moreover, considering preterm-born children's biological vulnerability, parenting quality may be even more significant for developmental consequences (Toscano et al., 2020). In fact, although mothers of preterm children are not less sensitive or responsive than mothers of full-term children (Bilgin & Wolke, 2015), the availability of appropriate resources, mainly for promoting a healthy maternal care, might lead to an improved preterm neuropsychological profile later in life. However, the neurobiological mechanism by which this moderating effect happens remains unknown. Therefore, MRI studies may be necessary to understand whether there are structural or functional alterations that could explain the current findings. More research is needed in MLPT samples to assert the clinical sway of the parent-child care on cognition, since family factors have been stronger predictors of school performance than perinatal complications (Gross et al., 2001).

Ethics approval statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Deusto [ETK-22/17-18] and the Drug Research Ethics Committee of the Basque Country [CEIm-E, PI2018154].

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Data Availability

The datasets generated and/or analysed during this study are available from the corresponding author upon reasonable request.

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Patient consent statement

All participants provided prior written assent and their legal guardians' informed consent was obtained before each subject's participation.

Conflict of interest disclosure

No conflicting financial interests exist.

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Study III

Long-Term Neurodevelopmental Outcomes after Moderate and Late Preterm Birth: A Systematic Review

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Objective To systematically review and perform meta-analyses on the long-term neurodevelopmental outcomes of adults born moderate and late preterm (MLPT) in relation to cognitive functioning and psychiatric disorders.

Study design A search was conducted to identify any studies that involved prematurity in adulthood. From these studies, reports that included a group of MLPT adults and included description of cognitive and/or mental health domains (including specific long-term outcomes) were selected.

Results In total, 155 publications were identified, but only 16 papers met the inclusion criteria. A small effect size ($g = 0.38$) was found in MLPT to demonstrate poorer intellectual performance compared with those born at term. Moreover, MLPT adults exhibited greater odds for any psychiatric (OR 1.14), substance use (OR 1.16), mood (OR 1.06), and psychotic disorders (OR 1.40).

Conclusions Despite inconsistency due to the methodologic differences between the selected studies, MLPT showed minor long-term effects into adulthood. However, more studies are needed, because prematurity seems to confer some vulnerability to biological and environmental factors that enhance susceptibility to adverse neurodevelopment outcomes. (*J Pediatr* 2021; ■:1-10).

Preterm birth is defined as any delivery before 37 completed weeks of gestation. Considering that prematurity is described as a chronic condition,¹ adverse long-term neurodevelopmental consequences are known to occur even in infants born at 34 to 36 weeks of gestation. There are a wide variety of terms (ie, near-term and marginally preterm delivery) to label different gestational age ranges of infants born preterm considered as having a lower risk of neurodevelopmental disorders compared with infants born extremely premature.² Neonates born moderate and late preterm (MLPT), however, are born during a sensitive period for brain development,³ with a commensurate greater risk of morbidity and mortality than their peers born at full term.⁴ These subgroups account for >80% of preterm deliveries,⁵ and some may need early intervention, therapeutic services, and special educational support.^{6,7}

Little is known about whether there are any long-lasting effects of MLPT birth on cognition and mental health in adulthood, although these preterm subgroups might be shown to be at a greater risk of adverse neurodevelopmental outcomes compared with those born at term.¹ The limited evidence gathered among adults in heterogeneous preterm samples of participants whose gestational age was 28-36 weeks indicates that cognitive performance is commonly affected and there is a greater prevalence of behavioral and psychiatric disorders.⁸ However, because previous studies comprised preterm samples with different gestational ages, more studies are needed to specifically assess the neurodevelopmental effects of MLPT birth on adult outcomes.

We focused on the cognitive and mental health characteristics of adults born preterm, who are less likely to present adverse neurodevelopmental outcomes compared with those born extremely or very preterm. Further, in contrast to previous reviews,^{8,9} which focused especially on late prematurity or other gestational ages (ie, early-term birth) and medical/academic outcomes, this review aims to systematically identify empirical studies on the long-term neurodevelopmental outcomes of MLPT adults in relation to cognitive functioning and psychiatric disorders.

Methods

Search Strategy

Databases used included PubMed, Google Scholar, and Medline. The original search strategy was developed for its use in PubMed. The search specified that the terms to be found in the title, abstract and/or key words of the studies

MLPT	Moderate and late preterm
RR	Relative risk
SES	Socioeconomic status
SGA	Small for gestational age

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were: (a) premature birth/prematurity; (b) moderate preterm/late preterm/near-term/marginally preterm; (c) cognition/cognitive functioning; (d) psychiatric*/mental health; (e) adult*; and (f) specific long-term outcomes (IQ f_1 , educational status f_2 , anxiety f_3 , depression f_4 , attention deficit/hyperactivity disorder f_5 , autism spectrum disorder f_6 , and schizophrenia f_7). First, a search was made for any studies written in English that involved prematurity in adulthood. Once the search was completed, only those studies that included a group of adults born preterm who were considered to be at lower risk of presenting neurodevelopmental alterations were selected (ie, non-uniform definitions comprising the following terms: moderate preterm, late preterm, near-term, and/or marginally preterm). Finally, those studies that considered at least 1 of the domains under study (cognition, mental health, and/or specific long-term outcomes) were chosen. Therefore, searches were conducted in the databases using the following set of key words: first (a)+(e); then (a)+(b)+(e) or (a)+(c)+(e) or (a)+(d)+(e) or (a)+(e)+ [f (each f individually)]; and finally, (a)+(b)+(c)+(e) or (a)+(b)+(d)+(e) or (a)+(b)+(e)+[f (each f individually)]. The search strategy is detailed in **Table I** (available at www.jpeds.com).

Inclusion Criteria

Studies from January 2000 to February 2021 were included if they involved MLPT adults (ie, they included adults born with a gestational age between 32^{0/7} and 36^{6/7} weeks); and if their main objective or secondary outcome was to investigate at least 1 of the following domains: cognition and/or mental health.

The results on the effect of the socioeconomic status (SES) included in the studies that fulfilled the aforementioned criteria also were reported. Similarly, some parents' data such as marital status were considered to be important confounders relevant to the interpretation of the results. Additional clinical data also were considered to characterize the samples under study, including having been born small for gestational age (SGA). Hence, some supplementary information was collected when the studies were conducted (eg, SES) and data on other attributes such as neonatal information (eg, birth weight) were retrospectively obtained by consulting medical records.

Eligibility Criteria

Studies were de-duplicated and screened by title, abstract and full-text by 2 reviewers. Study eligibility for inclusion was assessed and full data extraction was conducted independently by the same reviewers. Disagreement between the 2 main reviewers was settled by a third reviewer, who determined the conclusive decision. Published data extracted from the selected publications were also approached for further information if needed.

Study Selection and Data Extraction

Reports for this review were obtained through a 3-step process. **Figure 1** provides an overview of the literature

identification process by means of an adapted flow diagram using PRISMA guidelines.¹⁰ First, 155 articles were retrieved from a systematic database search. After removal of duplicates (n = 49), 106 reports were obtained through title search and 44 studies were excluded after title screening. Second, the abstracts of 62 papers were screened to exclude those papers that did not fulfill the selection criteria. Finally, the full-text versions of 24 reports were assessed, and only those that matched the inclusion criteria were included. Eight articles were excluded because they studied long-term outcomes other than those selected for the present review (eg, cortisol profiles, exercise capacity, etc). Therefore, the final number of publications for review and subsequent analysis consisted of 16 research papers. Studies evaluating cognition and mental health are shown in **Table II** and **Table III**, respectively (available at www.jpeds.com) details those studies based on mental health.

Protocol and Registration

The review was conducted according to the “The PRISMA 2020 statement: an updated guideline for reporting systematic reviews” guidelines.¹⁰ This systematic review protocol was registered with the International Prospective Register of Systematic Reviews, PROSPERO (CRD42020153096).

Risk of Bias in Individual Studies

Two reviewers independently assessed the quality of the selected studies using the Newcastle–Ottawa Scale (**Table IV**).¹¹ This scale's standards are split into 3 sections: (1) selection, (2) comparability, and (3) outcome. Each study was scored for each section. More specifically, a maximum of 1 star could be assigned to each item within the selection and outcome categories, and a maximum of 2 stars could be given to the comparability category. According to the specific acceptability criteria considered for the present review, studies achieving 6 or more stars were considered of high quality. To address the consistency of the system, interrater reliability was performed and a Cronbach alpha of 0.94 was obtained.

Data Synthesis

Regarding quantitative cognitive results, Hedge g effect sizes were calculated to analyze the magnitude of the effects found when comparing group mean differences and in regression analyses. A score of 0.2 shows a small effect size, 0.5 indicates a medium effect size, and values >0.8 reflect a large effect size. The effect size from 2 studies was not included because adults' educational attainment was categorized in a qualitative way.^{12,13} Likewise, the effect size from another study¹⁴ was not obtained, as it provided logarithmically transformed data.

To quantitatively analyze the results from the psychiatric domain, the ORs, hazard ratios, and relative risks (RRs) provided by the studies included in this review are summarized in **Table V**. The ORs represent the odds that a psychiatric disorder will occur in MLPT adults compared with the odds that a full-term born adult would suffer a psychiatric

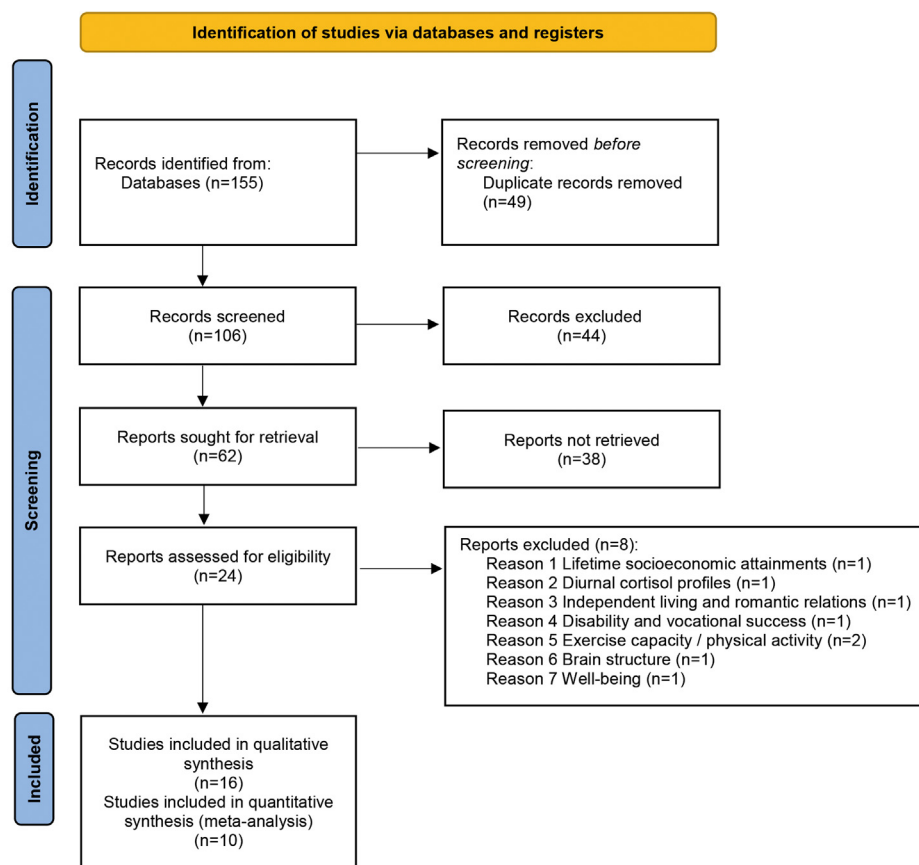


Figure 1. PRISMA 2020 flow diagram for new systematic reviews that included searches of databases and registers only. From Page et al.¹⁰ For more information, visit: <http://www.prisma-statement.org/>.

disorder; hazard ratios and RRs indicate the risk that 1 MLPT adult out of the total number of MLPT adults under study will suffer a psychiatric disorder. Because none of these ratios were described in one of the studies,¹⁵ prevalence data and percentages reported for this case are included in **Table V**.

Finally, RStudio software (version 1.2.5001)¹⁶ was used to analyze the data of those cognitive and psychiatric domains specified in at least 3 or more studies included in the present review. Specifically, the *meta* package was used to analyze generic inverse variance (ie, cognitive data) and binary outcome data (ie, psychiatric domains) through a random-effects model. Regarding heterogeneity, Tau-squared (t^2) and I^2 were calculated to assess whether heterogeneity was statistically significant, and the respective degree of heterogeneity between the studies. An I^2 value of percentages of around 25%, 50%, and 75% would result in low, medium, and high heterogeneity, respectively. Forest plots were used to visualize the overall effects (ie, standardized mean difference and OR) derived from combining the individual studies, and funnel plots were also obtained to assess publication bias. Lastly, meta-regression analyses were conducted to evaluate the impact of four moderator variables (ie, study quality, age at evaluation, gestational age, and year of publication) on the effect sizes of the selected studies.

Results

Study Characteristics

Of the 16 studies, 14 were conducted in 3 European countries—Sweden, Norway, and Finland,^{13-15,17-27} 1 in New Zealand,²⁸ and another 1 in the US (Maryland).¹² All studies were published within the past 13 years. However, they included a substantial range of birth dates (1934-1989) and age at assessment (16-77 years). Ten studies were birth/prospective cohorts,^{12-15,17-21,28} and only 6 were conducted by using national records in a retrospective way.²²⁻²⁷ Sample sizes ranged considerably in studies that included adults born moderately preterm (eg, from $n = 126$ to $n = 1088$),^{27,28} and studies that assessed adults born late preterm (eg, from $n = 47$ to $n = 664$).^{17,20} Three studies were performed on military conscription populations when only male subjects were accepted for this purpose.^{22,24,27} Two publications submitted results relating to both cognition and mental health for the samples under study.^{15,28} Therefore, 10 studies were related to cognition (**Table II**) and 8 to mental health (**Table III**). Finally, all the studies that met the inclusion criteria were rated as being of high quality. In fact, 5 of the selected studies obtained the maximum score from both reviewers (**Table IV**).^{14,17-19,25}

Table IV. Newcastle–Ottawa scale for quality

Quality assessments	Acceptable★	Dalziel et al, 2007 ²⁸	Eide et al, 2007 ²⁴	Ekeus et al, 2010 ²⁷	Heinonen et al, 2013 ¹³	Heinonen et al, 2015 ¹⁷	Heinonen et al, 2016 ¹⁸	Heinonen et al, 2018 ¹⁹	Lahti et al, 2015 ²⁰	Lindström et al, 2009 ²¹	Lundgren et al, 2011 ²²	Moster et al, 2008 ²⁵	Nomura et al, 2009 ¹²	Nosarti et al, 2012 ²³	Sammallahti et al, 2017 ¹⁵	Suikkanen et al, 2020 ¹⁴	Upadhyaya et al, 2020 ²⁶
Selection																	
Representativeness of the exposed cohort?	Near-term, moderate, marginally or late preterm cohort and of both sexes.	★★			★★	★★	★★	★★	★★	★★		★★	★★	★★	★★	★★	★★
Selection of the non-exposed cohort?	Term and/or full-term cohort	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★		★★	★★
Ascertainment of exposure?	Hospital birth records, hospital discharge medical registers, etc.	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★
Demonstration that outcome of interest was not present at start of study?	The absence of intellectual disability and/or psychiatric disorders (ie, congenital malformations, chromosomal abnormality, etc)					★★	★★	★★	★★		★★	★★		★★	★★	★★	★★
Comparability																	
Adjust for sex?	Yes	★★			★★	★★	★★	★★		★★		★★	★★	★★	★★	★★	★
Adjust for any additional factors?	Age, maternal age, BMI before delivery, parity, SES, marital status, subject's maximum attained education, etc.	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★	★★	★★	★★	★★
Outcome																	
Assessment of outcome?	Neuropsychological evaluations, psychometric tests, validated psychiatric manuals, and educational attainment.	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★		★★	★★	★★	★★
Was follow-up long enough for outcome to occur?	Follow-up ≥16 years	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★
Adequacy of follow-up of cohorts?	Complete follow-up, small number lost, or description provided of those lost	★★	★★	★★	★★	★★	★★	★★	★★	★	★★	★★	★★	★	★★	★★	★★
Overall quality score (maximum = 9)	reviewer 1/ reviewer 2	8/8	6/6	6/6	8/8	9/9	9/9	9/9	8/8	8/7	7/7	9/9	7/6	8/9	8/8	9/9	8/9

BMI, body mass index.

Table V. Effect sizes on mental health outcome data in adults who were MLPT

Mental health outcome	Dalziel et al, 2007 ^{28*}	Heinonen et al, 2016 ^{18†}	Lahti et al, 2015 ^{20‡}	Lindström et al, 2009 ^{21§}	Moster et al, 2008 ^{25¶}	Nosarti, 2012 ^{23**}	Sammallahti et al, 2017 ¹⁵	Upadhyaya et al, 2020 ^{26††}
Any psychiatric disorder	RR 0.37 (0.12-1.1) ^{‡‡}	OR 1.08 (0.66-1.80)	HR 1.06 (0.86-1.31)	OR 1.3 (1.2-1.4)			34 (35%)	
Mood disorder		OR 1.08 (0.53-2.21)	HR 0.81 (0.54- 1.23)	OR 1.3 (1.1-1.5)				
Anxiety disorder	RR 0.69 (0.41-1.2)	OR 1.00 (0.40-2.49)	HR 0.89 (0.52-1.52)	OR 1.5 (1.3-1.9)				
Psychotic disorders			HR 1.33 (0.87-2.04)	OR 1.3 (1.1-1.7)	RR 1.3 (1.0-1.7)			
Personality disorders			HR 0.85 (0.43-1.67)					
Organic/neuropsychiatric disorder				OR 2.1 (1.7-2.4)				
Nonaffective psychosis						HR 1.6 (1.1-2.3)		
Depressive disorder	RR 0.56 (0.30-1.0)					HR 1.3 (1.1-1.7)		OR 1.0 (0.81-1.24) OR 0.91 (0.76-1.08) ^{§§}
Bipolar affective disorder						HR 2.7 (1.6-4.5)		
Autism spectrum disorder					RR 0.8 (0.4-1.4)			
Suicides			HR 1.70 (0.91-3.17)	OR 1.2 (1.0-1.4)				
Suicide attempts			HR 0.69 (0.22-2.21)	OR 1.2 (1.0-1.4)				
Substance use and addictive disorders		OR 1.30 (0.73; 2.29)	HR 1.13 (0.85-1.50)	OR 1.2 (1.1-1.3)		HR 1.2 (1.0-1.4)		
Eating disorder						HR 1.4 (0.9; 2.4)		
Alcohol dependency						HR 1.3 (1.1-1.5)		
Discharged from a hospital at least once with a main psychiatric diagnosis				HR 1.16 (1.07; 1.26) (d)				

HR, hazard ratio.

Values are HR, OR, RR (95% CI) or n (%) prevalence (percentage).

*Adjusted for sex, and antenatal betamethasone.

†Adjusted for sex, age and maximum educational level of either parent(s), own educational level, maternal age, and prepregnancy body mass index, multiple pregnancy, parity, SGA, large for gestational age, 5-minute Apgar score, smoking during pregnancy, maternal diabetes, hypertension, and preeclampsia, length of hospitalization after birth, and mother's self-reported mental health.

‡Adjusted for sex and year of birth and adjusted for fetal growth, socioeconomic position in childhood and mothers' marital status at childbirth.

§Adjusted for age, sex, housing, social welfare in 1990, SES, parental psychiatric disorder, low Apgar score, and SGA.

¶Adjusted for sex, year of birth, multiple births, single motherhood, maternal age, mother's level of education, father's level of education, and whether parents were immigrants.

**Adjusted for sex, parity, maternal age at delivery, maternal education, and maternal psychiatric family history.

††Adjusted for parents (age, psychopathology) and just mothers (substance abuse, depression, number of previous births, marital status, SES, smoking during pregnancy and infant's birthplace), and just fathers (immigration status).

‡‡Participants' reported previous psychiatric diagnosis.

§§Boys vs girls.

Summary of Results on Cognition

No differences were found in cognitive functioning between MLPT adults and those born at term (**Table II**).^{14,28} Small effect sizes were found when assessing moderate prematurity for either Full ($g = 0.11$), Verbal ($g = 0.14$), and Performance IQ ($g = 0.06$),²⁸ as well as in late prematurity ($g = 0.20$; $g = 0.13$; $g = 0.20$, respectively).¹⁹ In addition, in Heinonen's¹⁹ regressions, the weight of gestational age groups in adulthood obtained no or small effect sizes for the following cognitive domains: (1) memory $g = -0.28$; (2) verbal fluency $g = -0.03$; (3) sustained attention $g = -0.20$; (4) divided attention $g = -0.34$; and (5) suppression of interference $g = 0.28$ when assessing late preterm birth. In line with the aforementioned results, moderate prematurity was not associated with working memory and attention performance at 31 years of age.²⁸

However, other authors described that those adults who had been born MLPT showed poorer intellectual performance than their peers born at full term.^{17,22,24} Intellectual performance showed the largest effect size ($g = -3.25$) when studying its association with preterm birth in adults born at a gestational age of 33-34 weeks.²⁷ Even though a large effect size related to intellectual performance also was observed in those born at a gestational age of 35-36 weeks, a lower effect size was obtained ($g = -1.25$).²⁷ Studies by both Lundgren et al and Eide et al, in contrast, presented small effect sizes when assessing the association between gestational age and intellectual performance in adults who had been born MLPT ($g = 0.12$; $g = 0.11$).^{22,24} Nonetheless, when the relationship between gestational age and general neurocognitive performance was assessed in late adulthood, medium effect sizes were obtained ($g = -0.46$; $g = -0.78$).¹⁷ Moreover, late preterm birth was related to worse episodic memory and executive functions as well as to a greater risk for mild cognitive impairment in late maturity.¹⁷

Postnatal Growth after MLPT Birth and Long-Term Cognitive Outcomes. SGA was a risk factor for learning and cognitive deficits in childhood, but it was not related to lower educational attainment in adulthood.¹² In connection with this, it was seen that late preterm birth might not enhance the risk of poorer neurocognitive functioning in adulthood, and the double burden of being born late preterm and SGA may increase this risk due to more intrauterine adversities. Namely, those born late preterm and SGA obtained lower scores in Full and Performance IQ compared with those born at term,¹⁹ which indicated long-term cognitive problems in adults born preterm and SGA.¹⁴ Similar conclusions were established in the report by Lundgren et al, in which adults born moderately preterm who were of short stature or had a high body mass index were associated with an even greater risk for poorer cognitive performance.²² In a similar vein, faster growth during the critical early period after late preterm birth was related to better adult neurocognitive performance. Specifically, the effect sizes with respect

to the IQ were larger when the head circumference was taken into account ($g = 0.61$).¹⁵ Likewise, the effect size of executive functioning was larger when weight was considered as a predictor ($g = 0.56$).¹⁵ Hence, faster growth from birth to 5 months in weight and head circumference was associated with a greater IQ and better executive functions during adulthood, and with lower odds of having received special education.¹⁵

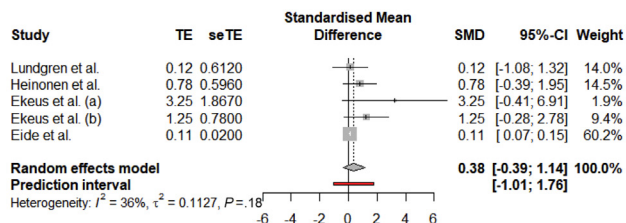
SES Background in MLPT Adults and Long-Term Cognitive Outcomes. Adults born late preterm are more likely to achieve a basic or upper secondary educational level.¹³ However, the negative impact of near-term births on adult educational attainment was approximately 3 times greater in those who lived in poverty conditions during childhood.¹² In the same way, low SES was a stronger determinant of cognitive functioning than moderate prematurity and therefore, low SES augmented the impact of moderately preterm delivery on cognition. The magnitude of the impact of prematurity on intellectual performance was shown to decrease by 26%-33% after adjustment for SES.²⁷

Meta-Analysis Results: Long-Term Cognitive Outcomes in Adults Born MLPT. As a final point, results of the meta-analysis based on the intellectual performance domain showed a small standardized mean difference when considering Hedge g effect sizes ($g = 0.38$, CI -0.39 to 1.14) (**Figure 2**). Moreover, a heterogeneity of 36% was found, which is regarded as small ($t^2 = 0.113$, $P = .18$). The funnel plot displayed the presence of publication bias among the selected studies (**Figure 3**; available at www.jpeds.com). Finally, a meta-regression analysis showed that none of the 4 variables significantly moderated the effect size obtained (ie, study quality $F = 0.12$, $P = .75$; age at evaluation $F = 0.35$, $P = .59$; gestational age $F = 0.01$, $P = .92$; and year of publication $F = 1.99$, $P = .25$).

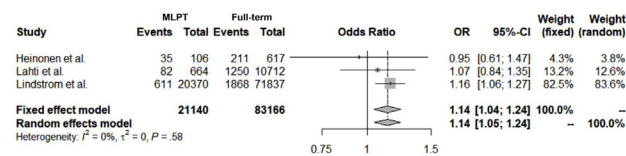
Summary of Results on Mental Health

Some authors have suggested that MLPT does not trigger pervasive impact on mental health and leads to similar^{15,20} or even better²⁸ psychological functioning in adulthood in relation to those who were born at term (**Table III** and **Table V**). More specifically, MLPT has not been found to be related to later symptoms of schizotypy or an increased risk of suffering from mood, anxiety or substance use disorders.^{18,28} Neither has late prematurity (RR 0.8; 0.4-1.4) been associated with an increased risk of autistic spectrum disorders.²⁵ Further, a depression diagnosis has been associated with post-term birth (OR 1.28; 1.07-1.54) in young male adults,²⁶ whereas differences in terms of suffering from depression were only marginally significant (RR 0.56; 0.30-1.0; $P = .06$) among adults who had been born moderately preterm.²⁸ In fact, fewer symptoms of depression have been associated with those born moderately preterm ($P = .02$), and better indexes of general health perception (7; 1-13; $P = .03$) and social functioning (8; 1-15; $P = .04$) have been reported.²⁸ Moreover, adults

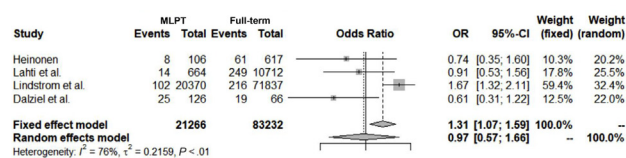
A Intellectual Performance



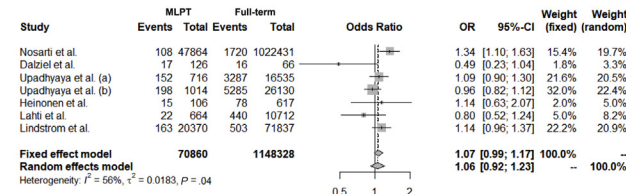
B Any Psychiatric Disorder



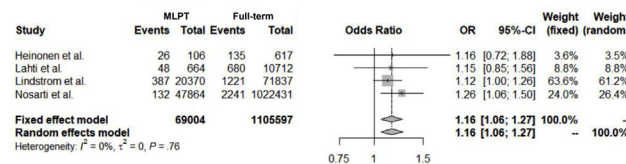
C Anxiety Disorders



D Mood Disorders



E Substance Use Disorders



F Psychotic Disorders

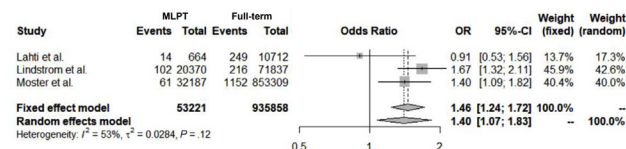


Figure 2. Forest plots of meta-analyses of intellectual performance and psychiatric disorders. *seTE*, standard error; *SMD*, standardized mean difference; *TE*, effect size (Hedges' *g*).

born late preterm have been found to have lower odds of having any common mental disorder (OR 0.37; 0.15-0.94; $P = .04$) and mood disorders (OR 0.27; 0.08-0.92; $P = .04$) than those born early preterm (24 to <34 weeks of gestation). Therefore, within preterm subgroups, the lower the gestational age, the greater the risk to suffer from a psychiatric disorder in adulthood.^{18,25}

Nonetheless, other authors have suggested that adults who are MLPT are at a greater risk of having poorer mental health, as will be outlined herein. Adults born moderately preterm have been found to have a 1.16 greater risk of having a psychiatric disorder.²¹ In this line, consistent with Nosarti et al, adults born moderately preterm have been found to be 60% more likely to have nonaffective psychosis, 34% to have depressive disorder, and more than twice as likely to suffer from a bipolar affective disorder in comparison with adults who were born at term (ie, with a gestational age of 37-41 weeks).²³ Moreover, moderate preterm birth has been associated with a 30% increased risk of alcohol abuse and a 20% increased risk of drug dependency.²³ Hence, the prevalence for substance use disorders decreased as gestational age increased.¹⁸ Finally, only men born late preterm presented an increased suicide risk in adulthood, which means that men born late preterm were found to have a 2.01-fold increased risk of committing suicide in comparison with those men born at term (1.03-3.90; $P = .03$).²⁰

Postnatal Growth after MLPT Birth and Mental Health. The prevalence of mood disorders and comorbidity for

mental disorders increased as the length at birth decreased,¹⁸ and possible complications in the neonatal period such as being SGA had a greater impact on mental health in adulthood. For instance, being SGA accounted for a 1.4-fold increased risk of having a mental disorder (1.07-1.87; $P = .02$), and for a 1.7-fold increased risk of having substance use disorders (1.16-2.41; $P = .01$).²⁰ However, poor fetal growth also has been related to an increased risk of depression with greater gestational ages at birth (ie, full- and post-term birth).²⁶

SES Background in Adults Born MLPT and Mental Health. Susceptibility to being hospitalized due to a psychiatric diagnosis increased as gestational age decreased, and was even greater in preterm-born adults from low SES families.^{21,23} Those born moderately preterm from low SES backgrounds had a 1.44 increased risk of being hospitalized due to a psychiatric disorder ($P = .001$).²¹

Meta-Analysis Results: Mental Health in Adults Born MLPT. In addition, by using a random-effects model, it was found that adults born MLPT are more likely to suffer from any psychiatric (OR 1.14; CI 1.05-1.24), substance use (OR 1.16; CI 1.06-1.27), mood (OR 1.06; CI 0.92-1.23), or psychotic disorders (OR 1.40; CI 1.07-1.83) (Figure 2). Nevertheless, adults born MLPT did not have greater odds of suffering from anxiety disorders (OR 0.97; CI 0.57-0.66). Moreover, the selected studies showed a low heterogeneity regarding any psychiatric ($t^2 = 0$, $P = .58$, $I^2 = 0%$) and substance use disorders ($t^2 = 0$, $P = .76$, $I^2 = 0%$). Mood

and psychotic disorders, in contrast, displayed a moderate heterogeneity ($t^2 = 0.018$, $P = .04$, $I^2 = 56\%$; $t^2 = 0.028$, $P = .12$, $I^2 = 53\%$). Anxiety disorders ($t^2 = 0.216$, $P < .01$, $I^2 = 76\%$) were found to be highly heterogeneous. Funnel plots exhibited publication bias in 2 of the 6 psychiatric domains (ie, mood and anxiety disorders) (Figure 3). In the results from the meta-regression analyses, only the resulting effect size based on studies concerning anxiety disorders was found to be moderated by gestational age (Q-statistic for model fit = 12.36, $P = .002$), and studies related to psychotic disorders were moderated by age at evaluation (Q-statistic for model fit = 4.09, $P = .04$). None of the findings based on the other psychiatric domains were moderated by any of the 4 moderating variables (study quality, age at evaluation, gestational age, and year of publication).

Discussion

Whereas children who were born MLPT have been found to be at a greater risk of more compromised educational outcomes, cognitive deficits, and psychiatric disorders at early school age,^{5,29} findings in adulthood remain controversial. Numerous studies have assessed long-term neurodevelopmental outcomes among those born MLPT during childhood and adolescence,³⁰ but there is still a paucity of scientific research on the adult stage.

Findings in this review suggested that MLPT birth does not increase predisposition to a greater risk of poorer cognitive functioning during adulthood.^{14,19,28} However, 3 studies established the opposite.^{17,22,24} Because preterm birth is considered a chronic condition,¹ there might be an impact on neurocognitive performance in the adult stage through to late adulthood, as has been found in adults born moderately preterm.²² Being born at 33-34 weeks was shown to have a greater impact on intellectual performance than being born at 35-36 weeks²⁷; studies that have regrouped these gestational age ranges together exhibited weaker outcomes with respect to the effect of preterm birth.²² This could be interpreted as a possible difference between newborns born moderately and late preterm during adulthood. Nevertheless, consistent with a meta-analysis study, MLPT had a small impact on intellectual performance during adulthood.

Worse episodic memory, executive functions, and general cognition have been related to late prematurity from 60 years old onwards.¹⁷ Nonetheless, because greater differences have been identified between preterm and full-term births at younger ages,³⁰ maximum attained lifetime education might mitigate aging-related neurocognitive decline¹⁷ as well as the increased risk for having a socioeconomic disadvantage.¹³ Thus, the identification of early preterm-related neurodevelopmental alterations will enable early interventions to mitigate possible cognitive impairment of preterm-born adults in their old age.

Concerning mental health, although MLPT birth did not trigger an extensive impact on the prevalence of psychiatric disorders in adulthood,^{15,20,26,28} the risk of suffering a psychi-

atric disorder and being hospitalized for it was found to increase with younger gestational age.^{21,23,25} However, fewer symptoms of depression and better scores on some variables of quality of life were also found in moderately preterm-born adults.²⁸ Due to the lack of consensus, further research focused on the psychiatric characteristics of preterm birth during adulthood is needed, especially on the greater risk of substance use disorders, as it is also found in adults born very preterm and those with very low birth weight,³¹ and on suicide risk in male subjects.^{18,20,23}

We found that the long-term effects of MLPT per se on cognition and mental health are usually mild, if any, compared with those born extremely or very preterm. However, MLPT together with other clinical and/or sociodemographic variables might carry the risk of long-term adverse outcomes in this population. In fact, the double burden of prematurity and other neonatal factors related to immaturity at birth such as postnatal growth (ie, being SGA) might compromise cognition and mental health in adults born preterm.^{12,14,18-20} For instance, measures such as adult stature and body mass index, as well as growth after birth in weight and head circumference, are related to cognitive performance in MLPT adults.^{15,22} Similarly, because preterm delivery exhibits greater biological vulnerability, MLPT might also lead to greater susceptibility to environmental factors. The impact of SES on preterm cognitive functioning and mental health seems to persist during adulthood, suggestive of the possible impact of MLPT if aggravated by a disadvantaged SES.^{21,23,27} Prematurity seems to confer some vulnerability to biological and environmental factors, which involves greater susceptibility to cognitive alterations and a diagnosis of a psychiatric disorder. Nevertheless, the paucity of studies, together with the variability of the results and the lack of consistency of effect sizes (ie, ranging from small to large) mean that findings are somewhat obscure.

In accordance with the studies of meta-analysis, MLPT adults showed a small likelihood of displaying poorer intellectual performance and greater odds of having any psychiatric, substance use, mood, and psychotic disorders compared with those born at term. The lack of heterogeneity and publication bias in the analyzed studies suggests that our findings could be taken into consideration for future studies. Nonetheless, the moderate heterogeneity in intellectual performance and mood and psychotic disorders, as well as the impact of a moderating variable (ie, age at evaluation) on the results obtained from studies assessing psychotic disorders, suggest that caution would be required regarding the current outcomes in these domains.

Concerning the limitations of this review, there are few studies available concerning cognition and mental health in adults born MLPT, and the different sample selection criteria and assessment tools mean that it is difficult to compare them. For instance, samples were categorized according to different gestational ages, that is, some studies focused on moderate prematurity and others concentrated on late prematurity, and some articles even made a single group containing both. One study¹² recruited its sample by focusing

on the definition of near-term. In addition, some studies used assessment tools that had only been validated in the country of study, or provided little information about their validity, which again made comparability challenging. In addition, although some studies used the same birth cohort,^{13,15,17-19} different clinical data (SGA) and environmental factors (SES) also may have been taken into account as an inclusion criterion. Another limitation of this report is that the reviewed studies assessed Nordic populations who had been treated in prenatal and neonatal care units a long time ago, mostly born before and around the 1980s, when neonatology underwent some major changes, such as the widespread use of antenatal corticosteroid protocols and less-invasive oxygenation strategies. That is, data related to their daily functioning may not be at all accurate for newborns treated with current medical techniques. The generalizability of the current findings to other ethnicities also may be limited. Finally, the impossibility of carrying out studies of meta-analysis with all cognitive and psychiatric domains due to the small number of studies involved in each of them (ie, more than 2 studies per domain) reduces the quality of our results. In fact, in domains such as mood and psychotic disorders, studies based on specific psychiatric disorders such as depression or schizophrenia have been included. Therefore, the procedure (ie, the inclusion criteria) of the present meta-analyses means that the findings related to heterogeneity and publication bias must be treated with due caution.

This review suggests that infants born MLPT have a low risk of developing long-term neurodevelopmental alterations in adulthood compared with those born extremely or very preterm. Despite the relatively lower risk of developmental complications, this review supports that disruptions to the immature nervous system at an early age could contribute to long-term neurodevelopmental alterations that impact cognitive and mental health outcomes in adulthood.^{32,33} Therefore, follow-up care should be re-evaluated to include those low-risk infants born preterm, especially because developmental care programs to date are still inconclusive for cognitive performance and long-term behavioral outcomes.³⁴ Hence, identifying dysfunctional cognitive performance and mental health in low-risk adults born preterm enables specific interventions to be applied to future newborns who are preterm during childhood. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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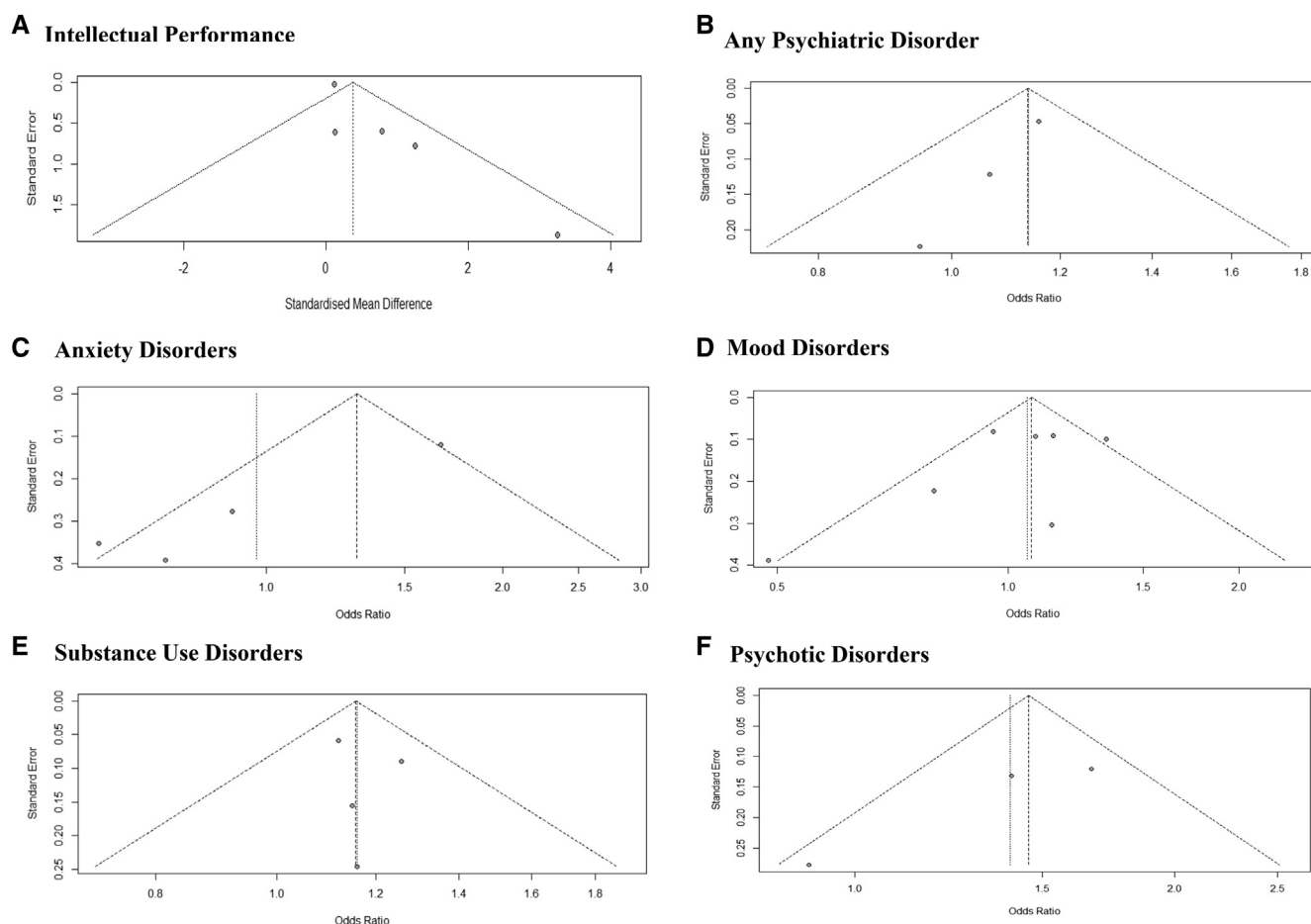


Figure 3. Funnel plots of meta-analyses of intellectual performance and psychiatric disorders.

Table I. Search strategy

Concept 1		Concept 2	
("Premature birth" [MeSH] OR "Prematurity")		AND	(Adult* [MeSH])
Concept 1	Concept 2	Concept 3	
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Moderate preterm" OR "Late preterm" OR "Near-term" OR "Marginally preterm")	
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Cognition" [MeSH] OR "Cognitive functioning")	
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Mental health" [MeSH] OR "Psychiatric*")	
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("IQ" OR "Educational Status" [MeSH] OR "Anxiety" [MeSH] OR "Depression" [MeSH] OR "ADHD" [MeSH] OR "Autism Spectrum Disorder" [MeSH] OR "Schizophrenia" [MeSH])	
Concept 1	Concept 2	Concept 3	Concept 4
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Moderate preterm" OR "Late preterm" OR "Near-term" OR "Marginally preterm")	AND ("Cognition" [MeSH] OR "Cognitive functioning")
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Moderate preterm" OR "Late preterm" OR "Near-term" OR "Marginally preterm")	AND ("Mental health" [MeSH] OR "Psychiatric*")
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Moderate preterm" OR "Late preterm" OR "Near-term" OR "Marginally preterm")	AND ("IQ" OR "Educational Status" [MeSH] OR "Anxiety" [MeSH] OR "Depression" [MeSH] OR "ADHD" [MeSH] OR "Autism Spectrum Disorder" [MeSH] OR "Schizophrenia" [MeSH])

ADHD, attention deficit/hyperactivity disorder; MeSH, Medical Subject Headings.

Using the asterisk at the end of adult* will pick up variations such as adults or adulthood.

Using the asterisk at the end of psychiatric* will pick up variations such as psychiatric disorders or psychiatric diagnoses.

Table II. Summary of the studies assessing cognition in adults who were MLPT

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Dalziel et al, 2007 ²⁸	New Zealand	1969-1974	32.3-35.0 (n = 126) 37.0-40.4 (n = 66)	31.0 ± 0.12 y (mean ± SD)	PC, birth cohort	<ol style="list-style-type: none"> 1. Only included mothers who were expected to deliver between 24 and 36 weeks of gestation. 2. Subjects who lived within Auckland area at 30 years. 	WASI, BVRT, PASAT, and the Brown ADD Scales.	Full-scale IQ Verbal IQ Visual memory Performance IQ	<ol style="list-style-type: none"> 1. No differences were found in IQ scores between adults born moderately preterm and full term. 2. Moderately preterm birth was not associated with later educational attainment, SES, cognitive functioning, working memory, or attention. 	<ol style="list-style-type: none"> 1. Selection bias.
Eide et al, 2007 ²⁴	Norway	1967-1979	26-29 (n = 409) 30-33 (n = 565) 34-36 (n = 10836) 37-38 (n = 37484) 39-41 (n = 209 191) 42-44 (n = 46577)	18 y	RC, national registry	<ol style="list-style-type: none"> 1. Missing data on maternal educational. 2. Missing data on intellectual performance. 	A 53-minute standardized group intelligence test (1953) for the Norwegian draft board and revised in 1962. The test included time-limited subtests covering 3 categories: verbal analogues, number series and geometric figures.	Intellectual performance	Birth weight, birth length, and gestational age are associated with intellectual performance, even after adjustment for social factors and adult body size; however, the associations are weak.	<ol style="list-style-type: none"> 1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, intellectual performance).

(continued)

Table II. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Ekeus et al, 2010 ²⁷	Sweden	1973-1976	24-28 (n = 63) 29-32 (n = 565) 33-34 (n = 1088) 35-36 (n = 3981) 37-38 (n = 19 146) 39-41 (n = 94 821)	18-19 y	RC, national registry	Implausible combinations of birth weight and gestational age	Enlistment Battery 80, with 4 subtests (logical, spatial, verbal, and technical capabilities).	Intellectual performance	<ol style="list-style-type: none"> Low SES is a more powerful determinant of cognitive competence than moderately preterm birth. Low SES enhances the effect of moderately preterm birth on cognitive competence. 	<ol style="list-style-type: none"> Selection bias. Lack of detailed information on exposed cohort (ie, familiar SES).
Heinonen et al, 2013 ¹³	Finland	1934-1944	34-36 (n = 486) 37-41 (n = 8507)	Follow-up: 26-56 y 36-66 y	PC, birth cohort*	<ol style="list-style-type: none"> Gestational age before 34 or after 41 weeks. People born to single mothers. 	SEP in adulthood were obtained based on occupational status, educational attainment, and taxable incomes.	Educational attainment	Adults born late preterm had greater odds of belonging to the manual worker category, to have attained only a basic level of education, and to belong to the lowest income category.	<ol style="list-style-type: none"> Lack of detailed information on exposed cohort (ie, impairments and their severity).

(continued)

Table II. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Heinonen et al, 2015 ¹⁷	Finland	1934-1944	34-36 (n = 47) 37-41 (n = 872)	61.2-77.0 y	PC, birth cohort*	<ol style="list-style-type: none"> Subjects with a history of stroke or other brain injury. Large birth weight for length of gestation. Participants who were born before 34 or after 41 weeks. 	CERAD-NB	Intellectual performance Verbal fluency Memory	<ol style="list-style-type: none"> Late preterm birth is a novel risk factor for neurocognitive impairment in late adulthood. Late preterm birth was associated with lower episodic memory, executive functioning, visual reproduction, and general neurocognition. Late prematurity had a greater risk of MCI. Maximum attained lifetime education may mitigate aging-related neurocognitive impairment, especially among those born late preterm. 	<ol style="list-style-type: none"> Selection bias. Lack of detailed information on exposed cohort (ie, smoking mothers). Lack of generalizability.

(continued)

Table II. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Heinonen et al, 2018 ¹⁹	Finland	1985-1986	34-36 (n = 119) 37-41 (n = 667)	25.4 ± 0.8 y (mean ± SD)	PC, birth cohort [†]	<ol style="list-style-type: none"> 1. Unverified gestational age. 2. Intellectual developmental disability, severe congenital malformations, or chromosomal abnormality. 	WAIS III, TMT, the Stroop Test, verbal fluency, CPT II, and WMS III.	Full-scale IQ Verbal IQ Memory Performance IQ Sustained attention Divided attention Incongruence	<ol style="list-style-type: none"> 1. Late preterm birth did not increase the risk of poorer neurocognitive functioning in adulthood. 2. The double burden of being born late preterm and being SGA did increase this risk. 	<ol style="list-style-type: none"> 1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, SGA was based only on birth weight). 3. Lack of sample representability (ie, late preterm and SGA).
Lundgren et al, 2011 ²²	Sweden	1973-1978	<32 (n = 574) 32-36.9 (n = 9579) 37-42 (n = 210935) >42 (n = 27359)	18-25 y	RC, national registry	<ol style="list-style-type: none"> 1. Birth weight, birth lengths, and head circumferences below 5 SD and above 3 SD. 2. Non-Nordic mothers and multiple births. 3. Congenital malformations. 4. Born SGA. 	Health examination, tests of psychological performance, and general intellectual performance with 4 subtests (logical/inductive, verbal, spatial and theoretical/technical).	Intellectual performance	<ol style="list-style-type: none"> 1. Being born moderately preterm is associated with a greater risk of having poor intellectual performance, as compared to being born at term. 2. Short adult stature or a high body mass index is associated with an even higher risk, indicating the occurrence of common mechanisms underlying growth and cognitive development. 	<ol style="list-style-type: none"> 1. Selection bias.

(continued)

Table II. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Nomura et al, 2009 ¹²	US	1960-1964	33–37 (n = 226) >37 (n = 1393)	Period from 7-8 y to 27-33 y	PC, birth cohort	<ol style="list-style-type: none"> 1. Participants who were born before 33 weeks of gestation. 2. Lack of information on childhood cognitive and learning performance. 3. No information on gestational age. 	<p>During childhood psychological and/or language, hearing, and speech assessment.</p> <p>During adulthood standard questionnaire covering personal characteristics and social and psychological functioning.</p>	Educational attainment	<ol style="list-style-type: none"> 1. Negative consequences of near-terms for their educational success. 2. Negative consequences of near-term birth are stronger when they lived in poverty during childhood. 	<ol style="list-style-type: none"> 1. Lack of detailed information on exposed cohort (ie, raw scores).
Sammallahti et al, 2017 ¹⁵	Finland	1985-1986	34–36 (n = 108)	24-26 y	PC, birth cohort [†]	<ol style="list-style-type: none"> 1. Intellectual developmental disability, congenital malformations, or chromosomal abnormalities. 2. No available data on birth or childhood anthropometry. 3. Not precise gestational age or adult cognitive, school, or psychiatric data. 	<p>WAIS III, WMS III, phonetic and categorical verbal fluency, TMT, and the Bohnen Stroop test.</p>	Full-scale IQ Memory Executive functioning	<ol style="list-style-type: none"> 1. Faster growth during the critical early period after late-preterm birth is associated with better adult neurocognitive functioning. 	<ol style="list-style-type: none"> 1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, rare mental disorders, life-long prevalence of mental disorders, or educational level). 3. Lack of generalizability. 4. Lack of sample representability (ie, late prematurity).

(continued)

Table II. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Suikkanen et al, 2020 ¹⁴	Finland	1985-1986	<34 wk (n = 133) 34-36 (n = 241) >37 (n = 348)	23.3 ± 1.2 y (mean ± SD)	PC, birth cohort	<ol style="list-style-type: none"> Severe mental disability, cerebral palsy, or other severe physical disability. Missing data in all tasks or had outliers in several tasks that indicate poor compliance. 	Cogstate Research a computer-based cognitive test battery (Continuous Paired Associate Learning Test, Detection Test, GML Test, Identification Test, One Card Learning Test, One Back Test, and Social Emotional Cognition Test for the battery).	Executive functioning Attention Memory (working, visual, and spatial)	<ol style="list-style-type: none"> Cognitive weaknesses established in childhood among late prematurity may not persist to adulthood. SGA may be an additional risk factor for cognitive problems in adults born late preterm. 	<ol style="list-style-type: none"> Measure used to collect the data. Lack of detailed information on exposed cohort (ie, previous cognitive testing).

ADD, attention deficit disorder; *BVRT*, Benton Visual Retention Test; *CERAD-NB*, Consortium to Establish a Registry for Alzheimer’s disease Neuropsychological Battery; *CPT*, Conner’s Continuous Performance Test; *GML*, Groton Maze Learning; *MCI*, mild cognitive impairment; *PASAT*, Paced Auditory Serial Addition Test; *PC*, prospective cohort; *RC*, retrospective cohort; *SEP*, socioeconomic position; *TMT*, Trail Making Test; *WAIS*, Wechsler Adult Intelligence Scale; *WASI*, Wechsler Abbreviated Scale of Intelligence; *WMS*, Wechsler Memory Scale.

*Results derived from the same birth cohort.

†Results derived from the same birth cohort.

Table III. Summary of the studies assessing mental health in adults who were MLPT

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Psychiatric outcome	Main findings	Limitations
Dalziel et al, 2007 ²⁸	New Zealand	1969-1974	32.3-35.0 = 126 37.0-40.4 = 66	31.0 ± 0.12 y (mean ± SD)	PC, birth cohort	1. Only included mothers who were expected to deliver between 24 and 36 weeks of gestation. 2. Subjects who lived within Auckland area at 30 years.	BDI-II, STAI, and the Schizotypy Traits Questionnaire, SF-36.	Any psychiatric disorder Anxiety disorder Depressive disorder	1. Moderate preterm birth was not associated with later marital status, symptoms of anxiety, or schizotypy. 2. Moderate preterm birth associated with fewer symptoms of depression and greater levels of satisfaction.	1. Selection bias.
Heinonen et al, Finland 2016 ¹⁸	Finland	1985-1986	24-33 (n = 37) 34-36 (n = 106) 37-41 (n = 617) ≥42 (n = 40)	24.4-27.1 y	PC, birth cohort*	1. Organic mental disorder. 2. Unreliable information on gestational age. 3. Congenital malformations or chromosomal abnormalities.	M-CIDI and ICD-10.	Any psychiatric disorder Mood disorder Anxiety disorder Substance use and addictive disorders	1. Individuals born late preterm born preterm are not at risk for common mental disorders in young adulthood. 2. The prevalence of mood disorders and comorbidity for mental disorders decreased as the length of gestation increased in adults born late preterm. 3. Prevalence for substance use disorders decreased as GA increased in adults born late preterm.	1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, lifetime mental disorder risk). 3. Lack of generalizability. 4. Lack of sample representability (ie, mothers who had smoked more often during pregnancy and parents with a lower level of education).

(continued)

Table III. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Psychiatric outcome	Main findings	Limitations
Lahti et al, 2015 ²⁰	Finland	1934-1944	34-36 (n = 664) 37-41 (n = 10 712) 42-43 (n = 1221)	66-76 y	PC, birth cohort	1. Biologically implausible values for gestational age. 2. Gestational age <34 weeks. 3. Missing or imprecise data from register. 4. Diagnosis of injuries of undetermined intent or of poisonings with no history of psychopathology.	ICD-8 and DSM-3.	Any psychiatric disorder Mood disorder Anxiety disorder Psychotic disorder Personality disorder Suicide Suicide attempts Substance use and addictive disorders	1. Men born late preterm had an increased suicide risk. 2. Late preterm birth did not exert widespread effects on adult psychopathology. 3. The risks of severe mental disorders across adulthood were increased among individuals born SGA and individuals born post-term.	1. Lack of sample representability (ie, anxiety and mood disorders). 2. Lack of detailed information on exposed cohort (ie, hospitalized or died people with mental disorders before 1969).
Lindström et al, 2009 ²¹	Sweden	1973-1979	24-28 (n = 3256) 29-32 (n = 2894) 33-36 (n = 20 370) 37-38 (n = 71 837) 39-41 (n = 450 165)	23-29 y	PC, birth cohort	1. Birth weight less than 3SD and more than 6SD. 2. Improbable measures of length in relation to their recorded weight. 3. Major malformation at birth.	ICD-9.	Any psychiatric disorder Mood disorder Anxiety disorder Psychotic disorder Organic/neuropsychiatric disorder Suicide Suicide attempts Substance use and addictive disorders Discharged from a hospital at least once with a main psychiatric diagnosis Schizophrenia Autism	1. Moderate preterm birth carries some risk for psychiatric disorders requiring hospitalization in young adulthood.	1. Selection bias. 2. Procedure used to collect the data.
Moster et al, 2008 ²⁵	Norway	1967-1983	23-27 (n = 1822) 28-30 (n = 2805) 31-33 (n = 7424) 34-36 (n = 32 945) >37 (n = 858 406)	20-36 y	RC, national registry	1. Sex-specific weight for gestational age that was more than 3 SD. 2. Disability benefits for medical reasons.	ICD.	Schizophrenia Autism	Continuous relationship between decreasing gestational age at birth and a wide range of adverse outcomes.	1. Lack of detailed information on exposed cohort (ie, severity of disabilities or on any functional capacity related to cognitive-social skills). 2. Procedure used to collect the data.

(continued)

Table III. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Psychiatric outcome	Main findings	Limitations
Nosarti et al, 2012 ²³	Sweden	1973-1985	<32 (n = 5125) 32-36 (n = 47 864) 37-41 (n = 1 022 431) ≥42 (n = 221 022)	23.0 ± 4.1 y (mean ± SD)	RC, national registry	1. Participants that had been hospitalized with any psychiatric diagnoses before 16 years	ICD 8th, 9th, and 10th Revisions.	Nonaffective psychosis Depressive disorder Bipolar affective disorder Substance use and addictive disorders Eating disorder Alcohol dependency Any psychiatric disorder	1. Moderate preterm birth was associated with an increased risk of drug and alcohol dependency.	1. Selection bias. 2. Lack of detailed information on exposed cohort (ie estimation of GA based on the mother's last menstrual period).
Sammallahti et al, 2017 ¹⁵	Finland	1985-1986	34-36 = 108	24-26 y	PC, birth cohort*	1. Intellectual developmental disability, congenital malformations or chromosomal abnormalities. 2. No available data on birth or childhood anthropometry. 3. Not precise gestational age or adult cognitive, school, or psychiatric data.	ASEBA ASR.	Any psychiatric disorder	1. Faster growth during the critical early period after late-preterm birth is not associated with better adult mental health outcomes.	1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, rare mental disorders, life-long prevalence of mental disorders, or educational level). 3. Lack of generalizability. 4. Lack of sample representability (ie, late prematurity).
Upadhyaya et al, 2020 ²⁶	Finland	1987-2007	<28 28-31 32-36 37-41 ≥42	19-25 y	RC, national registry	Severe or profound mental disabilities.	ICD-9 and -10.	Depression	Post-term birth was associated with depression diagnosed at adulthood.	1. Selection bias. 2. Procedure used to collect the data. 3. Lack of sample representability (ie, limited age range).

ASEBA, Achenbach System of Empirically Based Assessment; ASR, adult self-report; BDI-II, Beck Depression Inventory II; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; M-CIDI, Munich Composite International Diagnostic Interview; SF-36, Short Form-36 Health Survey; STAI, State-Trait Anxiety Inventory.


*Results derived from the same birth cohort.

Study IV

ARTICLE



Preterm birth and early life environmental factors: neuropsychological profiles at adolescence and young adulthood

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OBJECTIVES: To establish neuropsychological profiles after high- and low-risk preterm birth (i.e., with and without neonatal brain injury) during adolescence and young adulthood and to assess the potential role of early life environmental factors in cognition.

STUDY DESIGN: Participants (N = 177; M_{age} = 20.11 years) of both sexes were evaluated when adolescent or in young adulthood. They were grouped according to their birth status: 30 high-risk preterm, 83 low-risk preterm and 64 born at full term.

RESULTS: Significant differences were found in several cognitive domains between groups. Furthermore, familial socioeconomic status (SES) moderated the relation between the degree of maturity/immaturity at birth and cognition ($F_{(5,171)} = 11.94$, $p < 0.001$, $R^2 = 0.26$).

DISCUSSION: The findings showed different neuropsychological profiles during adolescence and young adulthood, with the high-risk preterm sample evidencing lower cognitive values. In addition, higher scores in the familial SES score in this study seem to have a protective effect on cognition.

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Preterm birth, defined as any birth before 37 weeks of gestation [1], is associated with a higher or lower risk depending on its clinical conditions. High-risk preterm newborns frequently suffer from neonatal brain damage, which can have long-term consequences [2, 3]. The neuropathology of preterm infant brain injury encompasses a variety of pathologies, including periventricular leukomalacia (PVL) with neuronal/axonal abnormalities and severe germinal matrix-intraventricular hemorrhage (GM-IVH), notably with periventricular hemorrhagic infarction [4]. Low-risk prematurity, unassociated with neonatal brain injury, implies a gestational age (GA) of 30–36 weeks, modest neurological abnormalities, and no perinatal comorbidities [5, 6]. However, these children's underdeveloped neural system could account for long-term neurodevelopmental alterations [7].

Preterm-born children frequently exhibit worse cognitive scores than their full-term peers at a preschool age, with similar differences in their intelligence quotient and neuropsychological functions to those observed later in life [8–10]. Preterm delivery can result in neuropsychological problems that last far beyond the first decade of life, implying a clear association between GA and cognition [11, 12]. The limited evidence gathered from preterm

adolescents and young adults born at younger GA's showed structural and functional brain alterations involved in cognitive performance [13], suggesting there had been and would be no improvement over time [14, 15]. Although great advances in neonatal intensive care have been made, prematurity-related consequences (i.e., neuropsychological and behavioral difficulties, hypertensive illnesses and metabolic syndrome) can be expected [16] and will lead to a heavy burden of lifelong neurological morbidity [17].

Apart from the presence or absence of neonatal brain damage, it is important to consider the potential impact of certain environmental factors on neurodevelopment after a preterm delivery. Preterm-born children have a higher biological vulnerability due to greater immaturity at birth, increasing their likelihood of suffering neurological, personality, and behavioral problems [16, 18]. Hence, preterm birth might also lead to a greater susceptibility to early life environmental factors. For instance, an adverse influence from neonatal variables is not sufficient to explain the worsened cognitive performance, but a mother's lower educational level might also influence the outcome [19, 20]. The effect of socioeconomic factors appears

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to influence the relation between prematurity and cognitive delays during childhood [21]. What is more, the quality of the home environment has also been found to have a moderate effect on early cognition in the preterm population [22]. Nevertheless, the extent to which early life environmental factors may affect long-lasting cognition in preterm-born adolescents and young adults is still an area that needs to be determined.

Degrees of neonatal immaturity, neurological damage, environmental factors, and the time of their occurrence all affect the way prematurity shapes the brain [23]. For this reason, the present study aims to ascertain the neuropsychological profiles of high- and low-risk preterm children when they reach adolescence and/or young adulthood. Furthermore, it also seeks to retrospectively evaluate the potential role that early life environmental factors may play in preterm-born adolescents and young adults in so far as their long-term cognitive outcome.

MATERIAL AND METHODS

Participants

A total sample size of 85 participants was estimated according to G*Power tool v.3.1; specifically, a linear multiple regression analysis was conducted with an effect size of 0.15, an error probability of 0.05, and a power of 0.8.

A total of 177 Caucasian participants participated in this study: 113 preterm adolescents and young adults (30 high- and 83 low-risk preterm) and 64 full-term born participants. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Deusto [ETK-22/17-18] and the Drug Research Ethics Committee of the Basque Country [CEIm-E, PI2018154]. All participants provided prior written informed consent; in the case of under-aged participants, their consent was required as well as that of their legal tutors at the beginning of the study.

A sample of 30 preterm adolescents and young adults with a history of neonatal brain damage was recruited (henceforth the high-risk preterm group). Sixteen of these had GM-IVH, and the other 14 subjects presented a diagnosis of PVL. Among the former group, 12 of its participants (GM-IVH) had been included in a cohort that participated in a longitudinal study at the Vall d'Hebron University Hospital (Barcelona, Spain); all of the participants in the latter group (PVL) were also being followed by the Vall d'Hebron University Hospital (Barcelona, Spain) in collaboration with the University Hospital Clinic (Barcelona, Spain). The remaining four participants with GM-IVH were recruited by chain-referral sampling (i.e., a non-probability sampling strategy whereby existing participants refer new individuals for recruitment). The characteristics of both samples over their childhood have already been published elsewhere [24–26]. The established inclusion criteria for the high-risk preterm group were: (1) preterm birth with a GA < 37 weeks of gestation, (2) having a diagnosis of brain damage diagnosed by neonatal cranial ultrasound or magnetic resonance imaging, and (3) ranging in age at the time of evaluation from 15 to 30 years. Exclusion criteria for this group were the concurrence of other brain injuries, birth trauma, malformation, and infectious or metabolic encephalopathies.

Since isolating the specific impact of neonatal brain damage from a preterm birth on cognitive performance was also of interest, a group of preterm adolescents and young adults at lower risk of presenting major disabilities was recruited at Cruces University Hospital (Bilbao, Spain). This group consisted of 83 low-risk preterm subjects and had the following inclusion criteria: (1) GA of between 30 and 36 weeks, (2) absence of brain pathology identified by neonatal cranial ultrasound, (3) lack of substantial neonatal morbidity (i.e., congenital malformations, neurologic, cardiac or digestive, necrotizing enterocolitis or septic shock), and (4) ranging in age at evaluation from 15 to 30 years. A full-term group of 64 participants was included as controls. Inclusion criteria were: (1) GA > 37 weeks, and (2) ranging in age at evaluation from 15 to 30 years. The exclusion criteria for both the low-risk preterm and the full-term group were a history of acquired brain injury, cerebral palsy or any other neurological impairment, congenital malformations and/or chromosomal abnormalities.

Instruments

Neuropsychological assessment. Analogical reasoning was evaluated using Raven's Advanced Progressive Matrices (RPM) test [27], and receptive language was measured with the Peabody Picture Vocabulary Test III

(PPVT-III) [28]. Verbal fluency was assessed in minute-long trials of phonetic (P, M, R) and semantic fluency (category of animals) tests [29].

The *Working memory index* was assessed through the Wechsler Adult Intelligence Scale IV (WAIS-IV) and Wechsler Intelligence Scale for Children (WISC-V), using digit span (forward, backward, and increasing) and arithmetic subscales for those over 16, and digit and picture span subscales for those under that age [30, 31]. *Cognitive flexibility* was measured using The Trail Making Test (TMT) part B [32], the Modified Wisconsin Card Classification Test (M-WCST) [33], and the PC and interference measurements from the Stroop Test [34]. Last, *processing speed* was assessed by means of TMT part A and the Stroop Test (P and C measures) [32, 34].

Cognitive domains driven by motivationally and emotionally significant contexts were also assessed. *Theory of mind* was measured using four stories from Happé's Strange Stories Test [35]. *Moral competence* was evaluated by means of the Moral Judgment Test (MJT) [36], and *delayed gratification* was assessed by the Delay-Discounting Test (DDT), also called the Monetary Choice Questionnaire [37].

Socioeconomic status (SES). The Hollingshead Index was used to consider the occupation and education domains of the participants and their parents independently [38]. Thus, two different measurements were obtained: participants' *current SES* (i.e., participants' highest ongoing occupation and educational level) and *familial SES* (i.e., the average between the highest level of the parents for their occupation and education domains). For under-aged participants, data from the occupation and education domains was determined from a single parent, so *familial SES* was the highest score obtained for either the individual's mother or father.

Emotional-behavioral assessment. The Adult Self Report (ASR) and Child Behavior Checklist (CBCL) were employed to measure emotional-behavioral output; internalizing and externalizing problems were recorded [39, 40].

Early life environmental factors. The *Parental Bond (PB)* was assessed by using the Parental Bonding Instrument to appraise participants' parents' behavior independently (i.e., mother's and father's care and overprotection domains separately) toward them during childhood [41]. *Familial SES* was used as an early life environmental factor [38]. Lastly, *Adverse Childhood Experiences (ACE)* were evaluated by the Adverse Childhood Experiences Questionnaire for Adults and Adverse Childhood Experiences Questionnaire for Teens designed by the WHO [42].

All neuropsychological assessments during adolescence and young adulthood were prospectively conducted in the Deusto University DeustoPsych and Ramon Llull University.

Statistical analysis

The normal distribution of the data was assessed using the Kolmogorov-Smirnov test (K-S). Tests were run on mean scores for the normally distributed data and on the ranked dependent variables for the non-normally distributed data. Missing values for GA (1 low-risk preterm and 12 full-term participants); birth weight (BW) (1 low-risk preterm and 4 full-term participants); familial SES (3 low-risk preterm and 1 full-term participants); care (1 high-risk and 2 low-risk preterm participants); overprotection (1 high-risk and 2 low-risk preterm participants); and ACE variables (1 high-risk preterm, 16 low-risk preterm and 3 full-term participants) were imputed using the expectation maximization algorithm (i.e., the percentage of missing values was of 0.94%). All tests were standardized in order to assess cognitive performance using a composite score (henceforth called general cognitive functioning score) obtained from: RPM analogical reasoning and PPVT-III receptive language total scores, M-WCST category and perseverative error scores, WAIS-IV and WISC-V digit span and working memory index, phonetic and semantic fluencies, Stroop Test P, C, PC and interference measures, TMT parts A and B, Happé's Strange Stories Test total score, MJT moral competence final score and the DDT delay gratification ratio. Cronbach's alpha (reliability) coefficient was 0.84.

The Kruskal-Wallis test was used to analyze differences in non-normally distributed data such as neonatal data (GA and BW), age at evaluation, current SES, and emotional-behavioral measurements. Early life environmental factors (i.e., care measurement, familial SES, and ACEs) were also analyzed using this test. Further, the Chi-squared test was employed to assess differences in two qualitative sociodemographic characteristics: gender and handedness. In addition, a univariate analysis of variance was run to compare the overprotection measurement between the three

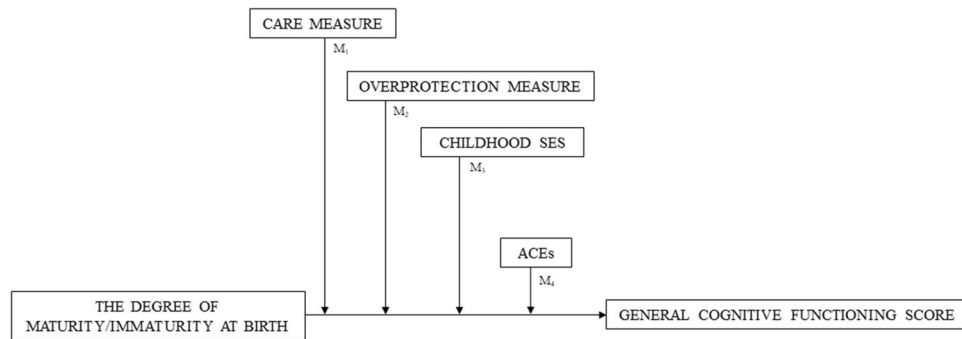


Fig. 1 Moderation Models between the Degree of Maturity/Immaturity at Birth and General Cognitive Functioning Score. Hypothesized moderation models specifying paths between the degree of maturity/immaturity at birth and general cognitive functioning score at adolescence and young adulthood, moderated by care and overprotection measures, familial SES and/or ACEs. An optimal care and overprotection measures can soften the impact of the degree of maturity/immaturity at birth in the long-term general cognitive functioning score (M_1 and M_2). General cognitive functioning score alterations related to the degree of maturity/immaturity at birth during adolescence and young adulthood can also be attenuated through appropriate SES at childhood stage (M_3). Finally, elevated ACEs can exacerbate the negative effect that the degree of maturity/immaturity at birth may have on general cognitive functioning score during adolescence and young adulthood (M_4).

Table 1. Neonatal, sociodemographic, emotional-behavioral variables and early life environmental factors.

	High-risk preterm $n = 30$	Low-risk preterm $n = 83$	Full-term $n = 64$	Statistics
<i>Neonatal data</i>				
GA. wks $\bar{x} \pm IQR$ [range]	29.00 \pm 4 [24–36]	34.00 \pm 2 ^a [30–36]	39.69 \pm 1 ^{ab} [37–41]	$H = 140.25^{**}$
BW. g $\bar{x} \pm IQR$	1300 \pm 608	2030 \pm 440 ^a	3285 \pm 534 ^{ab}	$H = 119.69^{**}$
<i>Sociodemographic data</i>				
Gender. male (%)	16 (53%) ^c	36 (43%)	17 (27%)	$\chi^2 = 7.42^*$
Age. yrs $\bar{x} \pm IQR$ [range]	18.00 \pm 3 [15–27]	21.00 \pm 6 ^a [16–25]	19.00 \pm 5 ^a [16–25]	$H = 8.63^*$
Handedness. right-handed (%)	28 (93%)	75 (90%)	62 (97%)	$\chi^2 = 2.43$
Current SES $\bar{x} \pm IQR$	19.00 \pm 6	21.00 \pm 11	25.00 \pm 8 ^{ab}	$H = 17.80^{**}$
<i>Emotional-Behavioral Assessment^a</i>				
Internalizing problems $\bar{x} \pm IQR$	13.00 \pm 11	12.00 \pm 16	14.00 \pm 10	$H = 1.77$
Externalizing problems $\bar{x} \pm IQR$	6.00 \pm 10	9.00 \pm 10	10.00 \pm 10	$H = 2.20$
<i>Early Life Environmental Factors</i>				
Care measure $\bar{x} \pm IQR$	28.48 \pm 8.72	28.00 \pm 8	28.00 \pm 6.38	$H = 0.29$
Overprotection measure $\bar{x} \pm SD$	12.41 \pm 5.12	13.18 \pm 4.90	13.38 \pm 5.51	$F = 0.37$
Familial SES $\bar{x} \pm IQR$	34.56 \pm 26.75	43.00 \pm 23.50	41.00 \pm 21.63	$H = 3.26$
ACEs $\bar{x} \pm IQR$	2.00 \pm 1.25	3.00 \pm 2	3.42 \pm 2	$H = 4.44$

Alphanumeric superscripts are found in the reference group whose scores are higher than the letter represented, which are a: lower values of the high-risk preterm group; b: lower values of the low-risk preterm group; and c: lower values of the full-term group.

In bold the domains that were significantly different among groups.

GA gestational age, wks weeks, BW birth weight, g grams, yrs years, SES socioeconomic status, ACEs adverse childhood experiences, SD standard deviation, \bar{x} mean, \bar{x} median, IQR interquartile range, H Kruskal–Wallis test, F Snedecor's F distribution, and χ^2 Chi-square test.

* $p < 0.05$; ** $p < 0.001$.

^aAvailable data for emotional-behavioral assessment: 30 high-risk preterm, 79 low-risk preterm and 64 full-term.

Table 2. Cognitive domains' and general cognitive functioning score differences.

	High-risk preterm <i>n</i> = 30 mean ± SD	Low-risk preterm <i>n</i> = 83 mean ± SD	Full-term <i>n</i> = 64 mean ± SD	<i>F</i> -Snedecor Statistic	η_p^2
<i>Neuropsychological Assessment</i> (adjusted for gender and age at evaluation)					
PPVT-III	154.63 ± 17.47	153.93 ± 15.43	159.91 ± 11.39	3.78	0.04
Phonetic Fluency	35.29 ± 12.24	38.91 ± 10.53	44.03 ± 7.87 ^{ab}	8.69	0.09
Semantic Fluency ^a	20.39 ± 6.09	21.54 ± 5.26	23.80 ± 4.26	5.39	0.06
RPM ^b	19.14 ± 6.61	22.70 ± 6.45	23.77 ± 4.73	5.34	0.06
M-WCST Categories	6.03 ± 0.91	6.35 ± 0.86	6.77 ± 0.66 ^{ab}	9.25	0.10
M-WCST Perseverative Errors	0.80 ± 1.02	0.86 ± 1.08	0.74 ± 1.02	0.24	0.00
Stroop Test (P)	95.89 ± 23.65	109.47 ± 13.24 ^a	112.78 ± 13.72 ^a	11.62	0.12
Stroop Test (C)	60.37 ± 17.23	74.47 ± 10.13 ^a	78.02 ± 10.62 ^a	22.71	0.21
Stroop Test (PC)	41.16 ± 14.63	51.05 ± 9.41 ^a	52.47 ± 8.70 ^a	12.87	0.13
Stroop Test (Interference)	4.50 ± 8.59	7.36 ± 8.47	6.52 ± 5.94	1.48	0.02
Digit Span (WAIS-IV, WISC V)	26.84 ± 5.35	30.03 ± 5.69	30.15 ± 5.07	4.27	0.05
WMI (WAIS-IV, WISC V)	97.71 ± 19.13	106.34 ± 16.72 ^a	110.84 ± 12.93 ^a	6.75	0.07
TMT Part A	35.17 ± 19.97	28.64 ± 10.37	27.47 ± 7.96	4.33	0.05
TMT Part B	77.71 ± 45.81	57.54 ± 19.52 ^a	52.19 ± 17.60 ^a	9.94	0.10
Happe's Strange Stories Test	5.86 ± 1.49	6.34 ± 1.33	6.68 ± 0.96	4.28	0.05
MJT ^c	14.37 ± 8.98	16.47 ± 9.23	14.94 ± 9.30	0.75	0.01
Kirby DDT	0.62 ± 0.27	0.59 ± 0.25	0.66 ± 0.27	0.97	0.01
<i>Composite Score</i> (adjusted for gender and age at evaluation)					
General cognitive functioning score	−0.453 ± 0.80	−0.003 ± 0.48 ^a	0.206 ± 0.37 ^{ab}	15.98	0.16

The cognitive domains in bold are those that remained significant after Bonferroni correction was applied for multiple comparisons ($p = 0.003$). Alphanumeric superscripts are found in the reference group whose scores are higher than the letter represented, which are a: lower values of the high-risk preterm group; b: lower values of the low-risk preterm group; and c: lower values of the full-term group.

SD standard deviation, *F* Snedecor's *F* distribution, *PPVT-III* Peabody picture vocabulary test-III, *RPM* Raven's Progressive Matrices, *MWCST* Modified Wisconsin Card Sorting Test, *WMI* working memory index, *WAIS-IV* Wechsler Adult Intelligence Scale IV, *WISC V* Wechsler Intelligence Scale for Children V, *TMT* Trail Making Test, *MJT* Moral Judgement Test, *DDT* Delay-Discounting Task, score; and η_p^2 : partial eta squared.

^aAvailable data for semantic fluency: 30 high-risk preterm, 83 low-risk preterm and 63 full-term adolescents and young adults.

^bAvailable data for RPM: 25 high-risk preterm, 82 low-risk preterm and 64 full-term adolescents and young adults.

^cAvailable data for MJT: 25 high-risk preterm, 80 low-risk preterm and 64 full-term adolescents and young adults.

groups. A multivariate analysis of covariance was also used to compare different cognitive domains and general cognitive functioning score (adjusting for gender and age at evaluation). Bonferroni's post-hoc test was employed to assess differences between groups, and the Bonferroni corrected *p*-value for significance was calculated for the different cognitive tests assessed ($p = 0.05/17 = 0.003$). Partial eta squared was used to calculate the effect sizes of cognitive and general cognitive functioning score comparisons. To interpret this value, around 0.01 is considered a small effect size, 0.06 medium, and higher than 0.14 large.

Last of all, moderation analysis is a type of regression that examines how a third variable influences the connection between the predictor and the outcome variable. In this case, the moderating effect of early life environmental factors (i.e., care measurement, overprotection measurement, familial SES, and ACEs) was independently analyzed in the relation between the degree of maturity/immaturity at birth and the general cognitive functioning score. To assess the moderation effect, four moderation analyses (see Fig. 1) adjusted for gender and age at evaluation were executed using macro PROCESS 3.5 script for SPSS (released 1 May 2020). Before doing the moderation analyses, outlier analyses assessed for rupture of linearity, normality, multicollinearity, and homoscedasticity; the Mahalanobis and Cook distances as well as Leverage parameters were used to detect possible outliers. The scatterplot and histogram check showed no sign of any outliers in the study sample. The Johnson–Neyman outcome was tested to determine the degree to which early life environmental factors had a significant conditional effect on prematurity in the prediction of the general cognitive functioning score.

For all preceding analyses, IBM SPSS version 26.0 (SPSS Inc., Chicago, USA) was used and the significance level was set at 0.05.

RESULTS

Neonatal, sociodemographic, emotional-behavioral variables as well as early life environmental factors are detailed in Table 1. Statistically significant differences were found in gender and age at evaluation between groups; thus, the following comparison and moderation analyses were adjusted for both.

Aim 1: Differences in neuropsychological profiles

Regarding cognitive performance, as shown in Table 2, the following statistically significant differences between groups remained significant after the Bonferroni correction was applied for multiple comparisons ($p = 0.003$): (a) worse performance in phonetic fluency and cognitive flexibility as measured by M-WCST in both preterm groups in comparison with the full-term sample; and (b) worse performance in processing speed as measured by the Stroop Test P and C measurements, cognitive flexibility assessed using TMT Part B and Stroop Test PC measure, and working memory index in high-risk preterm adolescents and young adults compared to the low-risk preterm and full-term groups. All differences showed medium to large effect sizes.

In addition, both preterm groups showed worse performance in the general cognitive functioning score compared to the full-term group with a large effect size (see Table 2). Further, high-risk preterm-born adolescents and young adults showed even worse scores in relation to the low-risk preterm sample.

Aim 2: Moderating effect of early life environmental factors on the general cognitive functioning score

Concerning four moderation analyses (see Table 3), for familial SES as a moderator, 26% of the variance was explained by the three factors (i.e., the degree of maturity/immaturity at birth, familial SES and interaction of both) in the overall model ($F_{(5,171)} = 11.94$, $p < 0.001$, $R^2 = 0.26$). More specifically, for every unit increase in familial SES as a moderator variable there was also an enhancement in the general cognitive functioning score ($\beta = 0.03$, $t_{(171)} = 3.17$, $p = 0.002$), especially in those with a higher degree of neonatal immaturity (i.e., high-risk preterm group). In terms of different backgrounds of familial SES (i.e., low familial SES = 23.00; medium familial SES = 40.50; high familial SES = 57.76), for either low or medium familial SES there was a significant relation between the degree of maturity/immaturity at birth and general cognitive functioning score (see Fig. 2). Nevertheless, having a high familial SES (i.e., higher than 55.31) did not further moderate

the relation between the degree of maturity/immaturity at birth and cognition over adolescence and young adulthood.

In addition, care, overprotection and ACEs early life environmental factors did not moderate the relationship between the degree of maturity/immaturity at birth and the general cognitive functioning score.

DISCUSSION

This study, with high-risk and low-risk preterm groups, established different neuropsychological profiles in preterm-born adolescents and young adults, reporting a greater number of worse cognitive domains in the high-risk preterm sample. Similarly, young adults born with very low BW exhibited worse scores in the intelligence quotient and academic achievement [43]. Furthermore, disparities in SES backgrounds during childhood moderated the effect of prematurity on cognitive performance during adolescence and young adulthood, and more markedly so in those with a greater degree of neonatal immaturity.

Neuropsychological profiles

Our findings indicated a worse performance in phonetic fluency and cognitive flexibility as measured by M-WCST in both preterm

Table 3. Moderating effect of early life environmental factors on general cognitive functioning score.

Criterion variable	R	R ²	β	t	p	Predictors
General Cognitive Functioning Score	0.48	0.23	-0.01	-0.91	0.36	Care measure
	0.48	0.23	0.02	1.92	0.06	Overprotection measure
	0.51	0.26	-0.01	-2.36	0.02	Familial SES
	0.46	0.21	-0.04	-1.09	0.28	ACEs

The significant moderation analysis is in bold.
SES socioeconomic status, ACEs adverse childhood experiences.

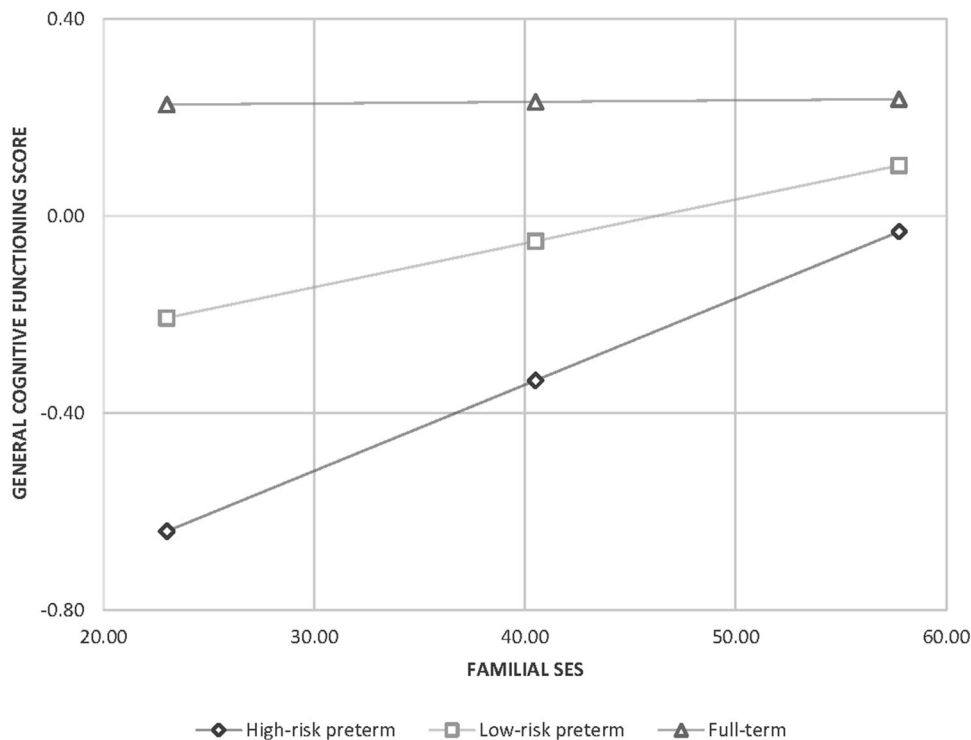


Fig. 2 Moderating Effect of Familial SES between the Degree of Maturity/Immaturity at Birth and General Cognitive Functioning Score. Familial SES familial socioeconomic status.

groups compared to their full-term peers at adolescence and young adulthood. Even though cognitive performance was within the normal range, as was previously reported by Hack [44], our results are also in line with the fact that prematurity in the absence of neonatal brain injury still leads to worse general cognitive functioning in the adolescence and young adult stage. That is, any degree of preterm birth affects cognition resulting in altered neurodevelopment over time [11].

The high-risk preterm-born group, on the other hand, revealed a larger amount of worsened cognitive domains than low-risk preterm adolescents and young adults, reinforcing the concept that the lower the GA, the higher the probability of presenting neurodevelopmental alterations (i.e., increased incidences of brain injury, cerebral palsy, and cognitive deficits) [45]. Processing speed and working memory were the cognitive domains that differentiated the two preterm groups. In addition, cognitive flexibility, regardless of whether it was measured with a motor component or not was also found to differ between high- and low-risk preterm adolescents and young adults. In adolescents who had had younger GAs, white matter microstructure has now been related to both working memory and cognitive flexibility, with reduced microstructure being associated with worse performance [46]. In fact, brain structural alterations, mainly detected after high-risk prematurity, commonly overlap those areas implicated in a worsened cognitive function [13].

Moderating effect of early life environmental factors

According to Sansavini [23], preterm birth results in atypical developmental trajectories, which may vary because of the complex interaction of biological and environmental factors, underlining the non-linear process of development. Despite biological factors having a moderate effect on cognitive development at an early stage, these factors lose their effect over time [22]. On the other hand, environmental factors have been shown to be increasingly important during infancy [47], and their impact on later cognitive development seems to remain [22]. Nevertheless, in the present study, parental bond and ACE did not have a moderating effect on the association between the degree of maturity/immaturity at birth and the general cognitive functioning score.

Consistent with Wolke [48], factors beyond initial neonatal care may improve long-lasting cognitive outcomes for the preterm population. For example, preterm birth and low SES, separately, have been established as risk factors with widespread effects on developmental delay during childhood [49]. Children who were born preterm and also lived in low SES conditions presented worse cognition [50]. Our findings revealed that differences in SES environments during childhood can modulate brain reorganization after central nervous system disorders, thereby affecting cognitive performance during adolescence and young adulthood, markedly in those with neonatal brain damage (i.e., the high-risk preterm group). The current results are consistent with a previous study which suggested that the SES impact on cognition persists until the middle age range [51]. Furthermore, the association of brain injury with worse cognitive performance has been found to be attenuated in children from mothers with higher educational levels [52, 53]. Likewise, in our study, the highest familial SES scores seem to have prevented the impact of prematurity on cognition during adolescence and young adulthood.

Limitations

This study was carried out in homogeneous high- and low-risk preterm samples in order to assess their neuropsychological profiles during adolescence and young adulthood. In other words, unlike prior studies that used heterogeneous preterm samples, this study used very stringent inclusion and exclusion criteria for neonatal data to obtain comparable groups, hence confirming the generalizability of results. In addition, the recruited groups did not

differ in emotional-behavioral and early life environmental measurements. However, there was no longitudinal follow-up from early infancy to young adulthood that could have ascertained whether neurodevelopmental outcomes persisted, worsened or improved over time. Another limitation is sample size, which was not suitable for studying whether there might be different results regarding cognitive domains depending on which neonatal brain injury they had suffered from as well as within the PVL and GM-IVH group classifications as proposed by Flodmark et al. [54] (i.e., radiological classification of PVL) and Papile et al. [55] (i.e., GM-IVH grades detected through cranial ultrasound). Finally, the disparities found in our study concerning current SES have not been further explored; however, preterm birth has already been related to lower educational qualifications and a reduced rate of employment in the adult stage [56]. Indeed, preterm-born children's performance in mathematics is critical for adult educational attainment [57].

CONCLUSIONS

In our opinion, establishing different neuropsychological profiles and SES background impacts after preterm delivery could support the development of specific intervention programs (e.g., in educational and social level), if necessary, during childhood. The supply of appropriate resources to the preterm population, mainly those with a greater degree of neonatal immaturity, might improve their later life neuropsychological profile. Nevertheless, more research is needed in high-risk and low-risk preterm populations in order to understand the implication of SES during childhood and determine their clinical impact on cognitive performance, since interventions may be especially important for low SES preterm children.

DATA AVAILABILITY

The datasets generated during and/or analyzed in the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

LZ-E, BL, OB, CJ, AM, MAP, and NO made substantial contributions to the conception and design of the work. LF-O, LZ-E, AG-G, MM-S, BL, OB, CJ, AM, MAP, and NO played a part in the acquisition, analysis, and interpretation of data for the work. All the authors worked on the draft and revised it critically for important intellectual content. Besides, all of them gave the final approval of the version to be published. Lastly, all authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Study V

**Long-term brain structural and cognitive outcomes in a low-risk preterm-born
sample**

(Research Study under review)

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Abstract

Background: Prematurity has been related to altered brain structure and cognition, so we aimed to describe them after low-risk preterm birth during adolescence and young adulthood.

Methods: The sample consisted of 250 participants, 132 of them low-risk preterm (30 to 36 weeks' gestational age) and 118 full-term individuals (37 to 42 weeks' gestational age), aged between 16 and 38 years old. All participants underwent an extensive neuropsychological assessment. T1- and diffusion-weighted MRI images of 33 low-risk preterm and 31 full-term young adults (20 to 32 years old) were analyzed.

Results: No differences were found in general cognitive functioning score and current socioeconomic status; however, the low-risk preterm group obtained lower scores in phonetic and semantic fluencies, and theory of mind. Significant reductions were identified in the thalamus volume as well as thicker cortex in the inferior temporal gyrus in the low-risk preterm group. Low-risk preterm young adults had greater regional AD and MD compared to the full-term sample.

Conclusions: Our findings suggest that low-risk prematurity results in specific alterations in some brain structural areas and performance outcomes. Being born preterm is associated with poorer performance in various cognitive domains later in life, along with differences in normative structural brain development.

Keywords: Low-risk preterm birth, cognitive functioning, current socioeconomic status, brain macro and microstructure, and adolescence and young adulthood.

Long-term brain structural and cognitive outcomes in a low-risk preterm-born sample

Preterm birth, defined as any birth before 37 completed weeks of gestation, is described as a chronic condition, since it increases the risk of long-term neurological morbidity that can last a lifetime (Raju et al., 2017). In low-risk prematurity [30 to 36 weeks' gestational age (GA)] neuropsychological abnormalities can be detected early in childhood, as well as brain changes that may constitute the basis for adverse long-term neurodevelopment (Caravale et al., 2005; Walsh et al., 2014).

Neuropsychological dysfunctions and worse cognitive scores in preterm newborns are common in early life, showing a significant relationship between GA and cognition (Allotey et al., 2018). Low-risk preterm birth impairs certain domains and overall intellectual performance, which results in poorer cognitive functioning from infancy through to maturity (Arhan et al., 2017; Fernández de Gamarra-Oca et al., 2021; Soria-Pastor et al., 2009). The scant evidence collected among adolescents and young adults has revealed that the general cognition of individuals with very small GA did not catch up over time (O'Reilly et al., 2020).

Atypical cortical development has been shown as an outcome of prematurity in first years of age (Phillips et al., 2011), which has been closely related to general and specific cognitive domains in preterm-born infants (Mürner-Lavanchy et al., 2018). Furthermore, low-risk preterm children have reduced volumes of several subcortical gray matter (GM) and white matter (WM) structures (Arhan et al., 2017; Soria-Pastor et al., 2009), as well as lower fractional anisotropy (FA) values in preterm children and adolescents (Young et al., 2018). For instance, low-risk preterm infants exhibited lower FA and higher axial, mean, and radial diffusivity (AD, MD, and RD, respectively) in approximately 70% of the brain's major WM fiber tracts (Kelly et al., 2016). Very preterm

birth is still strongly linked to altered structural brain anatomy in early adulthood as well as in subcortical areas such as the thalamus, caudate nucleus, and putamen (Nosarti et al., 2014). Additionally, FA reductions have been related to loss in GM as well as to GA, and intelligence quotient (IQ) score in preterm-born adults (Meng et al., 2016); however, more studies are needed that focus on brain development in low-risk preterm-born samples over time.

Pursuant to perinatal brain injury and medical complications a number of structural alterations have been related to a decreased IQ and lower executive functioning scores in adolescence and adulthood following very preterm birth (Hadaya & Nosarti, 2020). For this reason, this study aims to assess the long-term cognitive outcomes and brain structure that can be found after low-risk preterm birth in adolescents and young adults.

Methods

Participants

A total of 250 adolescents and young adults (age range from 16 to 38 years old) partook in this study: 132 low-risk preterm ($M_{\text{age}}=23.23$ years; $M_{\text{age}}=23.50$; $SD_{\text{age}}=4.60$) and 118 full-term ($M_{\text{age}}=23.97$ years; $M_{\text{age}}=24.00$; $SD_{\text{age}}=4.79$) subjects. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Deusto [ETK-22/17-18] and the Drug Research Ethics Committee of the Basque Country [CEIm-E, PI2018154]. All participants provided written informed consent. Underage participants gave written assent and their legal guardians provided informed consent before participation.

A group of preterm adolescents and young adults with a lower risk of presenting major disabilities was recruited at Cruces University Hospital (Barakaldo, Spain) and through chain-referral sampling from September 2018 to April 2021. This group

consisted of 132 low-risk preterm subjects who met the following inclusion criteria: (1) GA of between 30 to 36 weeks (calculated from the last menstrual period and confirmed with the first echography if necessary), (2) absence of brain pathology identified by neonatal cranial ultrasound, (3) lack of substantial neonatal morbidity (i.e., congenital neurological, cardiac, respiratory or digestive malformations, necrotizing enterocolitis, or septic shock), and (4) ranging in age at evaluation from 16 to 40 years. A full-term group of 118 participants was recruited through chain-referral sampling on the same dates. Inclusion criteria were: (1) GA > 37 weeks, and (2) ranging in age at evaluation from 16 to 40 years. The exclusion criteria for both low-risk preterm and full-term groups were a history of acquired brain injury, cerebral palsy or any other neurological impairment, congenital malformations, and chromosomal abnormalities.

In addition, out of the total of 250 adolescents and young adults, 64 participated in a neuroimaging study: 33 low-risk preterm ($M_{\text{age}}=25.33$ years; M_{age} : 26; $SD_{\text{age}}=2.92$) and 31 full-term young adults ($M_{\text{age}}=26.35$ years; M_{age} : 26; $SD_{\text{age}}=2.18$). As above, the same inclusion and exclusion criteria were followed, except for an age ranging from 20 to 40 years.

Instruments

Neuropsychological assessment

Analogical reasoning was evaluated using Raven's Advanced Progressive Matrices (RPM) test, whereas *receptive language* was measured by the Peabody Picture Vocabulary Test III (PPVT-III). Verbal Fluency was also assessed. It involved completing *phonetic* (P, M, R) and *semantic fluency* (category of animals) tasks, (one minute for each trial).

Working memory was assessed on the Wechsler Adult Intelligence Scale IV (WAIS-IV), by using the digit span (forward, backward, and increasing) and arithmetic

subscales. *Cognitive flexibility* was measured using The Trail Making Test (TMT) part B, the Modified Wisconsin Card Classification Test (M-WCST), and PC and interference measures from the Stroop Test. Lastly, *processing speed* was assessed by means of the Stroop Test (i.e. P and C measures) and TMT part A.

Theory of mind was measured by using four stories from the Happé's Strange Stories Test. *Moral competence* was evaluated by means of the Moral Judgment Test (MJT), and the Delay Discounting Test (DDT), also called the Monetary Choice Questionnaire, assessed *delayed gratification*.

With the exception of TMT and M-WCST perseverative errors, a higher score on all tests would imply better performance.

Socioeconomic status (SES)

The Hollingshead Index was used to consider the occupation and education domains of participants and their parents independently. Thus, two different measures were obtained: participants' *current SES* (i.e., participants' ongoing occupation and highest level of education) and *familial SES* (i.e., the average of parents' ongoing occupation and highest level of education). For underage subjects, data on the education and occupation domains was obtained from a single parent, so *familial SES* was the highest score obtained for either the subject's father or mother.

Emotional-behavioral assessment

The Adult Self Report (ASR) and Child Behavior Checklist (CBCL) were employed as a measure of *emotional-behavioral output*; internalizing and externalizing problems were recorded.

Early life environmental factors

The *parental bond* was assessed by using the Parental Bonding Instrument to appraise the participants' parents' independent behavior toward them during childhood

(i.e., mother's and father's care and overprotection domains). *Familial SES* was used as an early life environmental factor. Finally, *adverse childhood experiences (ACEs)* were evaluated by the Adverse Childhood Experiences Questionnaire for Adults and Adverse Childhood Experiences Questionnaire for Teens designed by the WHO.

Life satisfaction, functionality, and resilience

The Satisfaction with Life Scale (SWLS) was used to measure the participants' judgments of *satisfaction with their life*, while the WHODAS 2.0 subjects' report tool was employed to establish standardized *disability levels and profiles*. *Resilience* was assessed on the Connor-Davidson Resilience scale (CD-RISC), with higher scores reflecting greater resilience.

Personality data

NEO Five-Factor Inventory was used to acquire a precise measure of the *five domains of personality* (neuroticism, extraversion, openness, agreeableness, and conscientiousness).

MRI images

3-dimensional MRI datasets were obtained at the Magnetic Resonance Imaging Unit "Osatek", Hospital Galdakao-Usansolo (Galdakao, Spain) for 64 participants, of whom 33 were low-risk preterm and 31 full-term young adults. Diffusion-weighted MRI images were obtained from a Philips 3T Achieva dStream in an axial orientation with an anterior-to-posterior phase direction using a multiband EPI sequence (TR = 3820 ms and TE = 81 ms, matrix size = 128 mm × 112 mm; flip angle = 90°, FOV = 224 x 224 x 120, slice thickness = 2 mm, no gap, 60 slices, acquisition time = 8 min 22.4 sec, voxel size = 1.75 × 1.75 × 2.0) with multi-shell diffusion weighting in 128 uniformly distributed directions ($b = 2,000 \text{ s/mm}^2$) and 8 $b = 0 \text{ s/mm}^2$. T1-weighted images (axial orientation, TR/TE = 8.1/3.7 ms, 288 × 248 matrix, flip angle 8°, slice thickness 1 mm, no gap, 160

slices) were also acquired. Prior to processing, images were checked for movement and scanner artifacts.

FMRIB Software Library (FSL) version 6.0.3 was utilized to preprocess and analyze the diffusion data (Smith et al., 2004). Each subject's pictures were first concatenated and radiologically oriented. FSL's Brain Extraction Tool (BET) was then used to remove nonbrain tissue (Smith, 2002). Eddy was also utilized to spot volumes with a considerable absolute or relative motion, as well as to compensate for distortions and movement. TOPUP was also employed, as it is a robust and effective method that provides more performances in correcting distortions (Andersson et al., 2003). They were rotated to adjust the diffusion gradients (bvecs). FA maps were then constructed by fitting a tensor model to the raw diffusion data using FDT (DTIFIT). To examine group differences in FA, AD, MD, and RD, data was prepared using tract-based spatial statistic (TBSS) in order to perform a nonlinear registration of all FA pictures into standard space (Smith et al., 2006). With a threshold of 0.2, the mean FA image was thinned to form a "mean FA skeleton," which reflected the centers of all tracts shared by the group. The "TBSS non-FA" script was used to evaluate AD, MD, and RD data, applying the original nonlinear registration to the data and integrating all participants' warped AD, MD, and RD data into a 4D file. To construct the 4D-projected data, this file was projected onto the original mean FA skeleton.

Moreover, FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/>) (version v6.0.0) was used in order to obtain cortical and subcortical volumes, and global and regional CTh from 3D T1-weighted structural MRI scans (Fischl, 2012). Processing of T1 high-resolution images included several procedures: intensity nonuniformity correction, skull stripping, affine transformation to MNI template, intensity normalization, removal of nonbrain tissue, linear and nonlinear transformations to a probabilistic brain atlas and

labelling of subcortical/allocortical structures. Spatial localization priors were used to determine the correct label per each single voxel. Skull stripping, intensity normalization, white matter segmentation, and surface extraction errors were all manually corrected if necessary.

Statistical Analysis

Normal distribution of data was assessed using the Kolmogorov-Smirnov test (K-S). Missing values for neonatal data and environmental factors were imputed using the expectation maximization algorithm (i.e., the percentage of missing values was of 0.61%). All tests were standardized in order to assess cognitive performance using a composite score (henceforth named general cognitive functioning score) obtained from: RPM's analogical reasoning and PPVT-III's receptive language total scores, M-WCST's category and perseverative error scores, WAIS-IV digit span and working memory index, phonetic and semantic fluencies, Stroop Test's P, C, PC and interference measures, TMT's part A and B, Happé's Strange Stories Test total score, MJT's moral competence final score, and DDT's delay gratification ratio (reliability analysis of Cronbach's $\alpha=0.80$).

The Mann-Whitney U test was used to analyze differences in neonatal data [GA and birthweight (BW)], age at time of evaluation, familial SES, care measure, ACEs, emotional-behavioral problems, SWLS, WHODAS and personality data, with the exception of the openness measure. Furthermore, the Chi-squared test was required to assess differences in two qualitative sociodemographic characteristics: gender and handedness. Student's t-tests were also performed to compare overprotection, resilience and openness measures between both groups. A multivariate analysis of covariance was conducted to compare different cognitive domains, the general cognitive functioning score and current SES (adjusted for age at evaluation). Bonferroni corrected p -value for

significance was calculated for assessed different cognitive tests ($p=0.05/17=0.003$). Partial eta squared was employed to calculate the effect sizes; around .01 is a small size effect, .06 is medium, and above .14 is considered to be large. For all preceding analyses, the SPSS version 26 was used, and significance level was set at 0.05.

Neuroimaging study

A multivariate analysis of covariance (adjusted for age at evaluation) was used for the differences in cognitive domains, general cognitive functioning score and current SES between groups in the neuroimaging sample.

Based on the analysis of the neuroimaging data, multivariate analyses of covariance were used to compare global (left/right) and regional CTh (adjusted for age at evaluation), cortical and subcortical volumetric areas (adjusted for age at evaluation and eTIV), and global mean FA, AD, MD, and RD (adjusted for age at evaluation). Bonferroni's post-hoc test was employed to assess differences between groups, and the Bonferroni corrected p -value for significance was calculated for left and right regional CTh ($p=0.05/34=0.001$) and subcortical volumetric areas ($p=0.05/23=0.002$).

Regarding DTI analyses, the “randomize” tool in FSL (5000 permutations) with threshold-free cluster enhancement (TFCE) correction for multiple comparisons was employed, including the -- T2 option, to examine total WM integrity differences in FA, AD, MD, and RD. With an extent threshold of 100 voxels, the statistical threshold was set at $p<0.05$, corrected for family wise error (FWE). The maximal coordinates contained in the clusters and other noteworthy regions were visually inspected with the MRI Atlas of Human White Matter (Oishi et al., 2010), and labeled anatomically with JHU-ICBMDTI-81 WM Labels and JHU White-Matter Tractography Atlas implemented in FSL.

Results

Neonatal, sociodemographic, environmental, emotional-behavioral, life satisfaction, functionality, resilience, and personality variables are detailed in Table 1. As expected, there were significant differences in neonatal variables (GA and BW) between both groups. No differences were found in sociodemographic, environmental, emotional-behavioral, life satisfaction, functionality, resilience, and personality variables between both groups, except for the conscientiousness measure, with the full-term sample reporting lower scores. In relation to the neuroimaging sample, significant differences remained only in neonatal data.

In terms of cognitive performance, as shown in Table 2, poorer performance was found in phonetic and semantic fluencies, as well as in theory of mind in low-risk preterm adolescents and young adults compared to their full-term peers. These differences remained significant after the Bonferroni correction was applied for multiple comparisons ($p=0.003$) and they showed small to medium effect sizes. The differences exhibited in the cognitive domains were not maintained in the neuroimaging sample, with the exception of statistically significant differences in phonetic fluency without surviving Bonferroni correction. Moreover, statistically significant differences were found in current SES, with the low-risk preterm sample reporting lower values only in the neuroimaging sample.

Statistically significant differences were not found in global left and right CTh in the neuroimaging study. Moreover, no statistically significant differences were shown in regional CTh among groups. However, increased values in right inferior temporal gyrus were displayed in low-risk preterm young adults compared to the full-term group surviving Bonferroni correction for multiple comparisons ($p=0.001$).

In global volumetric analyses, low-risk preterm young adults did not exhibit differences in cortex, total GM, and cerebral WM volumes compared with the full-term group. Nevertheless, low-risk preterm-born young adults had lower subcortical

volumetric values compared with their full-term peers in the thalamus (see Table 3). These differences did not survive Bonferroni correction (p -value=0.002).

Lastly, as displayed in Figure 1, no statistically significant differences were found in global mean FA, MD, and RD between both groups; while differences were shown in global mean AD ($F=4.24$ $p=0.044$) with the low-risk preterm group reporting greater values. In addition, taking into account group based regional analyses (see Table 4), low-risk preterm young adults showed greater mean AD and MD than their full-term peers (FWE-corrected, $p<0.05$) (see Figure 2). No significant differences were found regionally for mean FA and RD.

Discussion

This study was conducted with both low-risk preterm and full-term groups, and set a number of worse cognitive domains in adolescents and young adults born low-risk preterm. Even while cognitive performance was within normal thresholds, our findings indicate that preterm newborn in the absence of neonatal brain injury present lower cognitive performance during adolescence and young adulthood. Any degree of preterm delivery somewhat has an impact on cognition, resulting in adverse neurodevelopment over time (Allotey et al., 2018). Moreover, even though no global volumetric differences were shown, regionally greater AD and MD have been detected, as in low-risk preterm infants (Kelly et al., 2016), across the frontal part of CC during young adulthood.

Compared with the full-term group, low-risk preterm adolescents and young adults performed worse in phonetic and semantic fluencies, and theory of mind. Although no significant differences in the general cognitive functioning score have been identified in this study, prematurity *per se*, along with neonatal and environmental factors, are thought to have a substantial effect on cognition throughout adulthood (Fernández de Gamarra-Oca et al., 2021). On the other hand, no differences were found in emotional-

behavioral problems, life satisfaction, functionality, resilience, and personality data (with the exception for conscientiousness). However, adults born preterm with very low BW display a higher risk for internalizing problems and socially avoidant personality traits, pointing out BW as a key factor for the presence of these related adverse long-term outcomes (Pyhälä et al., 2017).

Declines described in CTh from 15 to 20 years old follow a similar developmental trajectory in preterm and full-term adolescents (Rimol et al., 2016); which might be in line with current study's results, since no differences were found in bilateral mean CTh values among groups. However, regional CTh increases were found in the right inferior temporal gyrus in the low-risk preterm group; as shown in temporal regions' surface area after very preterm birth during childhood and thought to follow a delayed maturational trajectory (Vandewouw et al., 2020).

GM volume has been shown to be lower after preterm birth at school age, adolescence, and early adulthood, with no signs of catch-up growth; while WM is markedly low during adolescence (Schmitz-Koep et al., 2021). Our findings identified that cortex, GM and WM volumes were not diminished or increased in low-risk preterm young adults. Nevertheless, the low-risk preterm group showed a higher WM mean which is thought to be caused by cortical dysgenesis resulting from the combination of normal brain development processes with perinatal brain lesions (Allin et al., 2004). These lesions are found in the presence of extensive WM microstructural alterations after moderate and late preterm birth at term-equivalent age (Kelly et al., 2016); however, they were excluded from the current study sample. Finally, low-risk preterm-born young adults had lower subcortical volumetric values only in the thalamus; which at term-equivalent age and in the absence of severe WM injury a disrupted development of the thalamocortical system has been observed (Ball et al., 2012). Nonetheless, our results do

not resemble adults born preterm with a wide range of GA (25 to 36 weeks) smaller volumes in putamen, caudate and hippocampus (Meng et al., 2016).

WM microstructure after preterm delivery follows a similar path to that of typically developing newborns from five to seven years of age (Adrian et al., 2022), and during young adulthood, as indicated in the present study, except for global mean AD. Nevertheless, premature exposure to extrauterine environment has been related to WM abnormalities, which are found not only at term equivalent age but also in early maturity (Irzan et al., 2021). In fact, according to our DTI results, low-risk preterm young adults have greater regional AD and MD in widely diverse areas of the brain; a finding that has been previously reported in low-risk preterm-born infants (Kelly et al., 2016). As per Dibble et al. (2021), cellular substrates for these findings may entail altered axonal packing density and water content.

To our knowledge, this is the first study assessing long-term neuropsychological performance with low-risk preterm and full-term groups. In other words, unlike previous studies that used heterogeneous preterm samples, this study employed neonatal and sociodemographic data to reach comparable groups, supporting the generalizability of results. However, there was no longitudinal follow-up from early childhood to young adulthood to determine whether neurodevelopmental outcomes remained, aggravated, or improved over time. Another drawback is the sample size, particularly in the neuroimaging study, which limits the interpretation of these findings. A large age range (16–38 years old) was also represented, even though our analyses were age-controlled. Finally, there were significant differences in conscientiousness and current SES (only in the neuroimaging sample) between both groups, so caution would be required regarding the actual findings.

In conclusion, as discussed in this study, low-risk preterm birth has an impact on phonetic and semantic fluencies, and theory of mind together with deviations from normative structural brain development in the thalamic volume bilaterally, right inferior temporal gyrus and regional AD and MD during young adulthood. Understanding the brain scheme by which long-term performance outcomes arise after low-risk preterm birth increases the chances of identifying children who are at a higher risk early on. In fact, low-risk preterm newborns may be at a social disadvantage compared to those with a lower GA, who are more likely to receive more extensive developmental follow-up and early interventions. Thus, the availability of appropriate resources, mainly for those with an atypical development on areas related to the frontal part of CC, might lead to an improved preterm neuropsychological profile later in life. However, additional research is needed to provide more data concerning structural brain development and its associations with possible adverse future outcomes in larger low-risk preterm samples.

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Tables

Table 1

Neonatal, Sociodemographic, Environmental, Emotional-Behavioral, Life Satisfaction, Functionality, Resilience and Personality Data

	Low-risk preterm n=132 mean ± SD	Full-term n=118 mean ± SD	Statistics (<i>p</i>)
<i>Neonatal data</i>			
GA. wks [range]	34.15±1.65 [30-36]	39.60±0.91 [37-42]	<i>U=15576.00 (<0.001)</i>
BW. g	2085.25±453.49	3303.11±415.65	<i>t=-22.05 (<0.001)</i>
<i>Sociodemographic data</i>			
Gender. male/female	55/77	47/71	<i>X</i> ² = 0.87 (0.77)
Age. yrs [range]	23.23±4.60 [16-38]	23.97±4.79 [16-36]	<i>U</i> =8414.50 (0.27)
Handedness right-handed/left-handed	117/15	111/7	<i>X</i> ² =2.29 (0.13)
<i>Environmental Factors</i>			
Familial SES	39.95±11.58	39.18±14.53	<i>U</i> =7515.50 (0.63)
Care measure	27.33±5.43	27.02±5.10	<i>U</i> =7473.50 (0.58)
Overprotection measure	13.34±5.49	13.81±5.52	<i>t</i> =-0.67 (0.50)
ACEs	3.22±1.64	3.37±1.45	<i>U</i> =8436.50 (0.25)
<i>Emotional-Behavioral Assessment</i>			
Internalizing problems [‡]	15.39±11.08	14.50±8.17	<i>U</i> =7344.50 (0.86)
Externalizing problems [‡]	9.36±7.79	10.42±6.55	<i>U</i> =8278.50 (0.06)
Total behavioural problems [‡]	43.43±27.46	45.78±19.48	<i>U</i> =8166.50 (0.09)
<i>Life satisfaction, Functionality and Resilience</i>			
SWLS [‡]	26.15±5.28	25.62±4.19	<i>U</i> =4704.50 (0.16)
WHODAS [‡]	15.49±4.46	15.53±4.01	<i>U</i> =5278.50 (0.75)
Resilience [‡]	70.60±12.18	72.40±8.74	<i>t</i> =-1.19 (0.23)
<i>Personality Assessment</i>			
Neuroticism [‡]	20.24±8.50	19.33±7.56	<i>U</i> =6987.00 (0.48)
Extraversion [‡]	32.49±7.31	32.37±6.78	<i>U</i> =7252.50 (0.83)
Openness [‡]	29.82±7.72	30.91±7.57	<i>t</i> =-1.12 (0.27)
Agreeableness [‡]	31.97±5.35	32.10±5.43	<i>U</i> =-7241.00 (0.81)
Conscientiousness [‡]	33.05±7.35	31.29±6.25	<i>U=6168.50 (0.03)</i>

Note: SD: standard deviation; GA: gestational age; wks: weeks; BW: birth weight; g: grams; yrs: years; *U*: Mann–Whitney U test; *X*²: Chi-square test; *t*: Student-*t*; SES: socioeconomic status; ACEs: adverse childhood experiences; SWLS: satisfaction with life scale; and WHODAS: WHO Disability Assessment Schedule.

[‡]Available data for emotional-behavioural assessment: 125 low-risk preterm and 116 full-term adolescents and young adults.

[‡]Available data for SWLS: 105 low-risk preterm and 101 full-term adolescents and young adults.

[‡]Available data for WHODAS: 103 low-risk preterm and 100 full-term adolescents and young adults.

[‡]Available data for Resilience: 109 low-risk preterm and 83 full-term adolescents and young adults.

[‡]Available data for personality assessment: 126 low-risk preterm and 117 full-term adolescents and young adults.

Table 2

Differences in Cognitive Domains, General Cognitive Functioning Score and Current SES between Low-Risk Preterm and Full-Term Adolescents and Young Adults

	Low-risk preterm n=132 mean ± SD	Full-term n=118 mean ± SD	<i>F-Snedecor Statistic (p)</i>	η_p^2
<i>Neuropsychological Assessment (adjusted for age at evaluation)</i>				
PPVT-III, receptive language	160.64±15.26	163.82±11.52	4.74 (0.03)	.02
Phonetic Fluency	41.05±11.09	46.00±9.56	14.60 (<0.001)	.06
Semantic Fluency [‡]	22.44±5.12	24.44±4.66	10.39 (0.001)	.04
RPM, analogical reasoning [‡]	22.83±6.24	23.60±4.66	1.18 (0.28)	.01
M-WCST Categories, cognitive flexibility	6.50±0.83	6.77±0.61	8.20 (0.005)	.03
M-WCST Perseverative Errors, cognitive flexibility	0.89±1.08	0.70±0.88	2.12 (0.15)	.01
Stroop Test (P), processing speed	112.35±14.16	114.28±13.26	1.29 (0.26)	.01
Stroop Test (C), processing speed	75.77±10.36	77.50±10.54	1.69 (0.20)	.01
Stroop Test (PC), cognitive flexibility	50.71±9.52	52.63±9.97	2.41 (0.12)	.01
Stroop Test Interference, cognitive flexibility	5.98±8.14	6.58±6.95	0.40 (0.53)	.00
WAIS-IV Digit Span, working memory	30.41±6.25	29.83±5.06	0.63 (0.43)	.00
WAIS-IV WMI, working memory	106.36±17.53	108.08±13.61	0.73 (0.40)	.00
TMT Part A, processing speed	27.64±10.01	26.55±7.62	0.93 (0.34)	.00
TMT Part B, cognitive flexibility	56.61±18.95	52.42±15.83	3.53 (0.06)	.01
Happe's Strange Stories Test, theory of mind	6.30±1.38	6.79±1.09	9.56 (.002)	.04
MJ, moral competence [‡]	15.81±9.03	15.06±9.18	0.41 (.52)	.00
Kirby DDT, delay discounting	0.62±0.27	0.63±0.28	0.05 (.82)	.00
<i>Outcome Data (adjusted for age at evaluation)</i>				
General Cognitive Functioning Score	0.004±0.51	-0.005±0.47	0.02 (.89)	.00
Current SES	33.24±16.48	35.67±16.23	2.54 (0.11)	.01

Note: SD: standard deviation; PPVT-III: Peabody picture vocabulary test-III; RPM: Raven's Progressive Matrices; MWCST: Modified Wisconsin Card Sorting Test; WMI: working memory index; WAIS-IV: Wechsler Adult Intelligence Scale IV; TMT: Trail Making Test; MJT: Moral Judgement Test; DDT: Delay-Discounting Task score; SES: socioeconomic status; and η_p^2 : partial eta squared.

[‡]Available data for semantic fluency: 132 low-risk preterm and 117 full-term adolescents and young adults.

[‡]Available data for RPM: 131 low-risk preterm and 118 full-term adolescents and young adults.

[‡]Available data for MJT: 127 low-risk preterm and 118 full-term adolescents and young adults.

The cognitive domains in bold are those that remained significant after Bonferroni correction was applied for multiple comparisons ($p=0.003$).

Table 3

Differences in Subcortical Volumetric Areas between Low-Risk Preterm and Full-Term Young Adults

	Low-risk preterm	Full-term		
	n=33	n=31		
	mean ± SD	mean ± SD	<i>F-Snedecor</i>	η_p^2
			<i>Statistic (p)</i>	
<i>Subcortical Volumetric Areas mm³ (adjusted for age at evaluation and eTIV)</i>				
Left Cerebellum WM	14137.74± 1745.15	14300.25± 1747.35	019 (0.67)	.00
Left Cerebellum Cortex	54515.94± 6258.88	55189.88± 6548.25	0.24 (0.63)	.00
Left Thalamus Proper	6953.05± 721.37	7286.67± 933.03	4.67 (0.035)	.07
Left Caudate	3481.57± 444.79	3678.39± 588.38	3.45 (0.07)	.05
Left Putamen	5183.92± 683.77	5182.91± 558.32	0.00 (0.99)	.00
Left Pallidum	1765.60± 209.62	1796.11± 249.52	0.45 (0.51)	.01
Left Hippocampus	3849.81± 364.93	3913.21± 457.69	0.53 (0.47)	.01
Left Amygdala	1493.56± 245.35	1473.82± 245.27	0.17 (0.68)	.00
Left Accumbens Area	662.42± 103.23	706.69± 104.11	3.59 (0.06)	.06
Right Cerebellum WM	13553.62± 1663.64	13647.49± 1666.66	0.07 (0.80)	.00
Right Cerebellum Cortex	54859.02± 6604.58	55096.94± 6658.64	0.03 (0.87)	.00
Right Thalamus Proper	6661.04± 662.58	6986.01± 795.72	5.65 (0.021)	.09
Right Caudate	3609.67± 459.49	3789.79± 533.25	3.07 (0.09)	.05
Right Putamen	5116.08± 569.30	5103.83± 522.68	0.01 (0.92)	.00
Right Pallidum	1763.71± 208.14	1833.11± 242.61	2.05 (0.16)	.03
Right Hippocampus	4007.44± 493.00	4008.45± 420.74	0.00 (0.99)	.00
Right Amygdala	1716.93± 237.27	1731.83± 277.35	0.08 (0.78)	.00
Right Accumbens Area	616.19± 95.30	644.13± 97.47	1.49 (0.23)	.02
CC Posterior	906.10± 151.59	936.92± 151.07	0.78 (0.38)	.01
CC Mid Posterior	512.25± 102.21	524.12± 92.44	0.23 (0.64)	.00
CC Central	513.82± 74.24	515.44± 110.05	0.00 (0.95)	.00
CC Mid Anterior	489.80± 76.80	528.24± 146.13	1.78 (0.19)	.03
CC Anterior	896.36± 148.10	879.09± 162.57	0.22 (0.64)	.00

Note: SD: standard deviation; η_p^2 : partial eta squared; mm³: cubic millimeter; eTIV: total intracranial volume; WM: white matter; and CC: corpus callosum.

Table 4

Cluster Characteristics of the White Matter Whole Brain Differences between Low-Risk Preterm and Full-Term Young Adults

	Brain regions	Cluster size (voxels)	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	<i>p</i>
<i>Whole brain differences in mean AD between low-risk preterm and full-term young adults</i>							
Cluster 1	Frontal part of the CC (forceps minor) , inferior fronto-occipital gyrus, middle temporal gyrus, middle frontal gyrus, superior frontal gyrus, anterior corona radiata, anterior and posterior limb of the internal capsule, external capsule, fornix, left cingulum, left transverse temporal gyrus, left cerebral peduncle, right superior longitudinal fasciculus, right gyrus rectus.	33852	103	159	71	3.943	0.002
<i>Whole brain differences in mean MD between low-risk preterm and full-term young adults</i>							
Cluster 1	Optic tract , corticospinal tract, anterior thalamic radiation, CC (forceps major and minor), left gyrus rectus, left medial orbital gyrus, left inferior fronto-occipital fasciculus.	12463	95	130	54	3.134	0.033

Cluster size denotes the extent of the cluster of significant voxels. FMRIB Software Library (FSL) coordinates indicate: *x* increases from left to right; *y* increases from posterior to anterior; and *z* increases from inferior to superior. Regions represent the maximum significant difference coordinate encompassed in the given cluster. AD: axial diffusivity; CC: corpus callosum; and MD: medial diffusivity.

Region in bold represents the maximum coordinate encompassed in the given cluster.

Figures

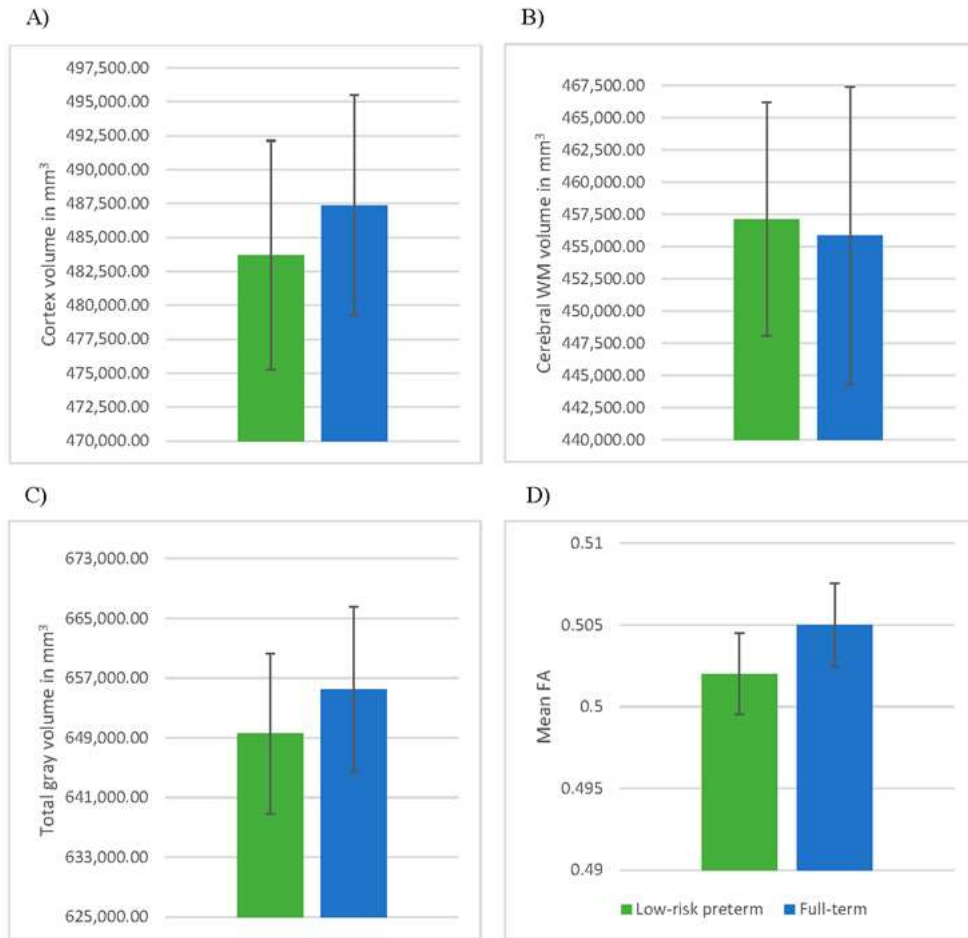
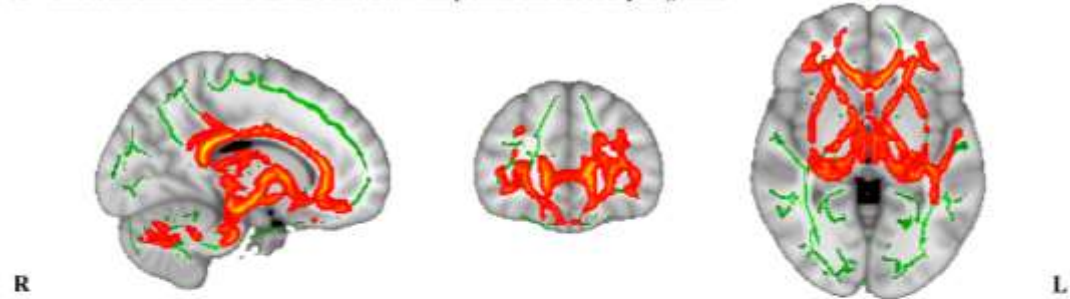


Figure 1. Effects of degree of maturity/immaturity at birth on the global mean FA (A), AD (B), MD (C), and RD (D) in young adults (green, low-risk preterm group; blue, full-term group). * $p < 0.05$; ** $p < 0.01$. FA, fractional anisotropy; AD, axial diffusivity; MD, mean diffusivity; and RD, radial diffusivity.

A. Whole brain differences in mean AD between low-risk preterm and full-term young adults



B. Whole brain differences in mean MD between low-risk preterm and full-term young adults

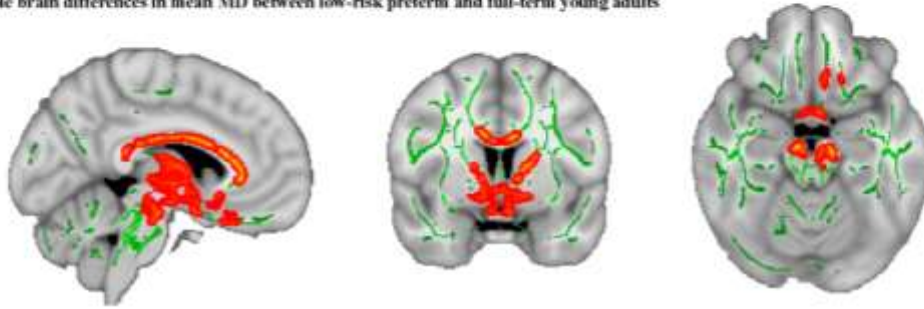


Figure 2. Whole brain AD and MD differences between low-risk preterm and full-term young adults. Differences are significant at $p < 0.05$ corrected for family-wise error (FWE). WM regions in which low-risk preterm young adults showed a higher mean AD and MD compared to their full-term peers are displayed in red-yellow; the WM skeleton is shown in green. R, right; and L, left.

Study VI

**Amygdala Structure and Function and Its Associations with Social-Emotional
Outcomes in a Low-Risk Preterm Sample**

(Research Study under review)

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Abstract

Background: Amygdala atypical volume development and functional connectivity (FC) at small gestational ages (GA) has been found across childhood. This adult-oriented study assess whether altered amygdala structure and function is present after low-risk preterm birth.

Methods: T1-weighted and resting-state functional MRI images of 33 low-risk preterm (30 to 36 weeks' GA) and 29 full-term (37 to 42 weeks' GA) young adults of both sexes, aged between 20 and 32 years old, were analyzed by FreeSurfer (v6.0.0) and Coon Toolbox (v21.a).

Results: No differences were found in social-emotional outcomes or amygdala volumes between the groups. Low-risk preterm young adults showed increased FC between the left amygdala, right amygdala and medial frontal cortex (MedFC) ($F=9.89$, $p\text{-FWE}=0.009$) compared to their full-term peers. Lastly, increased FC at cluster level between the right amygdala and MedFC, and left amygdala and MedFC was related to better social-emotional outcomes only in low-risk preterm young adults ($F=6.60$, $p\text{-FWE}=0.036$).

Conclusions: Low-risk prematurity does not impact on social-emotional outcomes and structural amygdala volumes during young adulthood. However, greater FC between left and right amygdala and MedFC may suggest a brain compensation mechanism for prematurity-related social-emotional functioning.

Keywords: Low-risk preterm birth, functional connectivity, amygdala, social-emotional outcomes, young adulthood.

Amygdala Structure and Function and Its Associations with Social-Emotional Outcomes in a Low-Risk Preterm Sample

Prematurity is defined as any birth before 37 complete weeks of gestation (WHO 1997). Neonates suffering from subtle neurologic abnormalities and perinatal comorbidities who were born low-risk preterm [30 to 36-week gestational age (GA)] make up the majority of preterm deliveries (Caravale et al. 2005; Hart et al. 2008). Moreover, most children born low-risk preterm exhibit a profile of cognitive and behavioral problems shared with children born at term predominantly with socioeconomic risk factors (Johnson et al. 2018). However, brain alterations after low-risk preterm birth may be the cause of their plausibly unfavorable long-term neurodevelopment (Walsh et al. 2014). In line with this, social-emotional functioning appears to be essential for optimal long-term neurodevelopment (Oberle et al. 2014; Peralta-Carcelen et al. 2018). Especially since children and adolescents born moderate and late preterm have a higher risk of emotional and behavioral problems (Cheong and Doyle 2020).

Emotional symptoms have been predicted by different brain volumetric values after very preterm birth (<32-week GA), including amygdala structure (Liverani et al. 2023). The amygdala is highly innervated by glucocorticoid receptors, and the peak of corticotropin-releasing hormone receptor density occurs during the early postnatal weeks, making the newborn stage a time of increased susceptibility to stress (VanTieghem and Tottenham 2018). Following preterm delivery, structural alterations in the amygdala have been found at term equivalent age and childhood (Cismaru et al. 2016; Mueller et al. 2022). Moreover, the presence of altered amygdalar functional connectivity (FC) after very preterm birth suggests that there is a different pattern of associations with social-emotional abilities compared to those born at term, which may point to a reduced degree of functional architecture maturation (Kanel et al. 2022; Rogers et al. 2017; Siffredi et al. 2022). According to a study based on extremely preterm neonates, prenatal stress leads to a significantly reduced connection between the left

amygdala and other areas when compared to those not suffering from such stress (Scheinost et al. 2016).

The amygdala-prefrontal cortex circuit is also impacted by negative experiences and stress (VanTieghem and Tottenham 2018). In the general population, early life stress has been linked to increased negative centromedial amygdala-ventromedial prefrontal cortex connection (Miller et al. 2021). Changes in the function of this circuit seem to have an effect on how emotions are regulated and increase the risk of psychiatric disorders (VanTieghem and Tottenham 2018). For instance, higher exposure to pain-related stress in infants born low-risk preterm has been linked to disrupted developmental scores (Morag et al. 2017).

From a neurodevelopmental perspective, individuals' reactions to emotional events shift significantly from childhood to adulthood (Silvers et al. 2017). The amygdala-prefrontal brain circuit continues developing until early adulthood despite the fact that amygdala reactivity diminishes during aging (VanTieghem and Tottenham 2018). However, in preterm populations, although decreased amygdala volume and altered FC have been described, only social functioning correlates with altered amygdala-posterior cingulate FC with no structural associations shown during adulthood (Johns et al. 2019; Schmitz-Koep et al. 2021a). In fact, due to functional changes in key emotion processing brain networks, including suboptimal amygdala modulation, adults born very preterm continue to exhibit subtle abnormalities in emotion recognition (Papini et al. 2016). Nevertheless, there is still no data available concerning low-risk preterm samples.

The risk of social-emotional problems in those born preterm has a substantial influence on their quality of life and on the burden of healthcare in society (Linsell et al. 2019; Raju et al. 2017). Furthermore, atypical development of the amygdala subnuclei volumes together with its altered FC have been related to social-emotional outcomes in children born very preterm (Mueller et al. 2022). For this reason, and given the lack of studies focused on those considered

to be at lower risk of presenting neurodevelopmental alterations following preterm birth, this study aims to assess the different social-emotional profiles between young adults born low-risk preterm and their full-term counterparts. Besides, it aims to analyze amygdala structure and its FC with medial frontal cortex (MedFC) in young adults born low-risk preterm. Finally, the study seeks to evaluate the possible associations during young adulthood between social-emotional outcomes and amygdala volumes and FC (i.e., amygdala – MedFC) after low-risk preterm birth. It was hypothesized that, based on the literature (Cheong and Doyle 2020; Cismaru et al. 2016; Mueller et al. 2022), young adults born low-risk preterm would have reduced amygdala volumes and FC, as well as lower social-emotional scores, than the full-term controls.

Methods

Participants

A total of 62 young adults (aged between 20 and 32 years) took part in this study: 33 low-risk preterm ($M_{age}=25.33$ years; $SD_{age}=2.92$) and 29 full-term ($M_{age}=26.41$ years; $SD_{age}=2.24$) subjects. A group of young preterm adults with a lower risk of presenting major disabilities was recruited at Cruces University Hospital (Barakaldo, Spain) by chain-referral sampling from September 2018 to April 2021. This group consisted of 33 low-risk preterm subjects who met the following inclusion criteria: (1) 30 to 36-week gestational age (GA), (2) absence of brain pathology identified by neonatal cranial ultrasound, (3) lack of substantial neonatal morbidity (i.e., congenital neurological, cardiac, respiratory or digestive malformations, necrotizing enterocolitis, or septic shock), and (4) ranging in age at evaluation from 20 to 40 years. A full-term group of 29 subjects was recruited; the inclusion criteria for these participants were as follows: (1) > 37-week GA, and (2) ranging in age at evaluation from 20 to 40 years. The exclusion criteria for both low-risk preterm and full-term groups were a

history of acquired brain injury, cerebral palsy or any other neurological impairment, congenital malformations and chromosomal abnormalities.

Measures

Social-Emotional Assessment

Social-emotional functioning was measured according to the following domains. The instruments used to measure each domain are described below. A composite score (henceforth called social-emotional outcomes) was then created to assess general social-emotional functioning by standardizing all the tests. Cronbach's alpha (reliability) coefficient was 0.78.

Theory of mind was measured using the Happé's Strange Stories Test (Happé 1994); by selecting four of the original stories to represent lie, white lie, misunderstanding, and pretense.

Moral competence was evaluated by means of the Moral Judgment Test (MJT) (Lind 1978), characterizing the ability to make morally upstanding decisions and judgments in two dilemma situations – the “workers' dilemma” and “mercy killing dilemma”.

The Delay Discounting Test (DDT) (Kirby and Maraković 1996), also called the Monetary Choice Questionnaire, assessed *delayed gratification* by participants answering 21 questions, such as the following: “Would you rather have €85 in 14 days or €30 now?”

The Adult Self Report (ASR) was employed as a measure of *emotional-behavioral functioning* (Achenbach et al. 2003). The questionnaire provides scores for the following scales: anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior and intrusive behavior. Internalizing and externalizing problems were also obtained from the sum of these scales.

The 10-item Emotion Regulation Questionnaire (ERQ) measures participant predisposition for both *cognitive reappraisal* and *expressive suppression* of their emotions (Gross and John 2003). Participants respond to each item on a Likert-type scale, ranging from 1 (strongly disagree) to 7 (strongly agree).

General Cognitive Assessment

The Raven's Advanced Progressive Matrices (RPM) test was used to assess *analogical reasoning* as general non-verbal cognition (Raven and Court 1998), while the Peabody Picture Vocabulary Test III (PPVT-III) was employed to measure *receptive language* since it characterizes general verbal cognitive performance (Dunn and Dunn 1981). Additional findings on cognitive data have been published elsewhere (Fernández de Gamarra-Oca et al., *under review*).

Socioeconomic status (SES)

The occupation and educational domains of participants and their parents were taken into account separately using the Hollingshead Index (Hollingshead 2011). The participants' *self-SES* (i.e., participants' ongoing occupation and highest level of education) and *familial SES* (i.e., the average of parents' retrospective occupation and highest level of education) were thus two distinct measures that were obtained.

Image Acquisition

3-dimensional MRI datasets were obtained at the Magnetic Resonance Imaging Unit OSATEK, Hospital of Galdakao (Galdakao, Spain) for 64 participants; however, two were eventually excluded due to difficulties in acquisition process. Hence, there was a final sample of 33 low-risk preterm and 29 full-term young adults. A single session was used to acquire both sequences. T1-weighted images were obtained from a Philips 3T Achieva dStream (axial orientation, 3 min 58.9 sec session, 160 slices, TR/TE = 8.1/3.7 ms, 288×248 matrix, 8° flip angle, 1 mm slice thickness, no gap). Resting-state functional MRI (rs-fMRI) was also acquired: 8 min session, 315 whole-brain gradient echo-planar images, 44 axial slices, TR/TE = 1500/30 ms, FOV= $240 \times 240 \times 132$ mm², voxel size = $3 \times 3 \times 3$ mm³.

Before acquiring rs-fMRI, the participant's head was restrained from movement and protected from scanner noise using foam padding and earplugs. Subjects were told not to

perform any specific cognitive or physical tasks, keep their eyes closed, and avoid falling asleep. After scanning, participants completed the Amsterdam Resting-State Questionnaire (ARSQ) (Alexander Diaz et al. 2013). ARSQ is a 27-item self-report survey covering seven dimensions of *resting-state cognition* (i.e., discontinuity of mind, theory of mind, self, planning, sleepiness, comfort and somatic awareness).

Image Preprocessing

Whole and subnuclei amygdala volumes

FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/>) (version v6.0.0) was used in order to obtain whole and subnuclei amygdala volumes from 3-dimensional T1-weighted MRI scans (Fischl 2012). T1-weighted image processing included several procedures: intensity nonuniformity correction, skull stripping, affine transformation to an MNI template, intensity normalization, removal of nonbrain tissue, linear and nonlinear transformations to a probabilistic brain atlas and the labeling of subcortical/allocortical structures. Spatial localization priors were used to determine the correct label voxel-per-voxel. Skull stripping, intensity normalization, white matter segmentation and surface extraction errors were all manually corrected where necessary, and the global structural results have been published elsewhere (Fernández de Gamarra-Oca et al., *under review*). Subsequently, the amygdala was segmented into the central, lateral, basal, accessory basal, cortical, medial and paralaminar nuclei, as well as into the corticoamygdaloid transition area and anterior amygdaloid area (Saygin et al. 2017).

Resting-state functional connectivity (FC)

FC analyses were carried out using the CONN Functional Connectivity Toolbox version 21.a (Whitfield-Gabrieli and Nieto-Castanon 2012). Each subject's 315 functional images were realigned and unwarped, their slice-timing corrected, coregistered with structural data, spatially normalized into standard MNI space (Montreal Neurological Institute, Canada),

their outliers detected (ART-based scrubbing), and were smoothed using an Gaussian kernel of 8 mm FWHM. The default preprocessing pipeline for volume-based analysis (to MNI-space) was used for all preprocessing steps. The structural data was normalized and segmented into GM, WM, and CSF. The anatomical CompCor method was used to reduce noise by extracting the principal components (5 each) from the WM and CSF time series. The subject's estimated motion parameters and other artificial effects, such as BOLD signals in WM and CSF, which were included as additional confounds, were then removed by a denoising process that was implemented using linear regression and band-pass filtering (0.008–0.09 Hz) (Weissenbacher et al. 2009).

Statistical and Imaging Analysis

Normal distribution of data was assessed using the Kolmogorov-Smirnov test (K-S). The Mann-Whitney U test was used to analyze differences in GA, and self- and familial SES. Furthermore, the Chi-squared test was required to assess differences in two qualitative sociodemographic characteristics: gender and handedness. Student's t-tests were also performed to compare birthweight (BW) and age at evaluation between the groups.

A multivariate analysis of covariance was conducted to compare different social-emotional domains (adjusted for age and self-SES), whole amygdala volumes (adjusted for age, self-SES and eTIV), and amygdala subnuclei volumes (adjusted for age, self-SES and left/right amygdala volume). Partial eta squared was employed to calculate effect sizes; around .01 is a small size effect, .06 medium, and above .14 is considered large. Moreover, bivariate correlation analyses were performed to assess the relationships between social-emotional outcomes and amygdala volumes (i.e., whole and subnuclei volumetric values). For all preceding analyses, the SPSS version 28 was used, and significance level set at 0.05.

Regarding FC statistical analysis, between-group differences and correlation analyses (i.e., each group independently) were assessed at the cluster-level inferences by region of

interest (ROI)-to-ROI with FWE-corrected $p < 0.05$ Threshold Free Cluster Enhancement (TFCE) (Smith and Nichols 2007). For FC at network level, FDR correction was applied. The ROIs selected based on the Harvard-Oxford Structures Atlas (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>) were: (a) left amygdala, (b) right amygdala, and (c) MedFC. Age and self-SES were used as covariates in the comparison analysis. The correlation between the strength of FC (left and right amygdala – MedFC), expressed by the mean of the normalized correlation coefficient in the cluster, and social-emotional data were studied using the Spearman's rank correlation coefficient in young adults born low-risk preterm and full-term.

Results

As expected, there were significant differences in neonatal variables (GA and BW) between the groups. No differences were found in sociodemographic and general cognitive measures (i.e., receptive language and analogical reasoning) between the groups, except for the self-SES, with the low-risk preterm sample reporting lower scores (see Table 1). The following analyses will therefore be adjusted for self-SES together with specific covariates (see methods section, statistical analysis).

Aim 1: Differences in Social-Emotional Outcomes

In terms of social-emotional functioning, as shown in Table 2, no differences were shown between young adults born low-risk preterm and full-term. No differences were found between the groups in the composite score and social-emotional domains.

Aim 2: Differences in Whole and Subnuclei Amygdala Volumes and Resting-State Functional Connectivity (FC)

No significant differences were displayed in relation to the whole left and right amygdala volumes and amygdala subnuclei volumes between young adults born low-risk preterm and full-term controls (see Table 3).

No significant differences in the total score ($F=0.97$, $p=0.33$) and seven individual dimensions of resting-state cognition ($F_{DoM}=0.11$, $p=0.74$; $F_{ToM}=1.89$, $p=0.17$; $F_{Self}=2.62$, $p=0.11$; $F_{Plan}=0.49$, $p=0.49$; $F_{Sleep}=0.04$, $p=0.85$; $F_{Comfort}=0.01$, $p=0.91$; $F_{SomA}=0.04$, $p=0.83$) were found between the groups in the ARSQ.

Low-risk preterm young adults showed left and right amygdala – MedFC FC differences at cluster level ($F=9.89$, $p\text{-FWE}=0.009$) compared to the full-term group (see Figure 1). Specifically, young adults born low-risk preterm presented: a) increased FC between the left amygdala and MedFC ($T(58)=2.93$, $p\text{-FDR}=0.014$); and b) increased FC between the right amygdala and MedFC ($T(58)=2.25$, $p\text{-FDR}=0.028$) in comparison with their full-term peers. Nevertheless, no significant FC differences between the left amygdala and right amygdala ($T(58)=1.69$, $p\text{-FDR}=0.096$) were observed between the groups.

Aim 3: Correlation Analysis

No significant correlations were found in the low-risk preterm group and full-term group between social-emotional outcomes and amygdala volumetric values (i.e., whole and subnuclei volumes).

Positive correlations ($F=6.60$, $p\text{-FWE}=0.036$) were found at cluster level between the strength of left and right amygdala – MedFC and social-emotional outcomes only in young adults born low-risk preterm. Specifically, right amygdala – MedFC strength was positively related to social-emotional outcomes ($T(31)=2.64$, $p\text{-FDR}=0.038$) in low-risk preterm young adults, but not in the full-term group. That is, right amygdala – MedFC increased FC was associated with better social-emotional outcomes in young adults born low-risk preterm (see Figure 2). However, specific to the low-risk preterm group, left amygdala – MedFC strength did not correlate with social-emotional outcomes ($T(31)=1.91$, $p\text{-FDR}=0.064$). Moreover, no significant correlations were found between left and right amygdala FC strength and social-emotional outcomes in either group.

Discussion

To our knowledge, this is the first study assessing amygdala volume and its FC in young adults born preterm who are considered to be at lower risk of presenting neurodevelopmental alterations. Although low-risk preterm delivery has no effect on social-emotional outcomes and whole and subnuclei amygdala volumes during young adulthood, increased FC strength between left and right amygdala and MedFC was found. According to Kennedy and Adolphs (2012), the best approach to understand the social brain, including its dysfunction and recovery, is through large-scale networks rather than discrete structures. So, our results may suggest that the low-risk preterm brain may have established a compensation mechanism to make up for early-stage social-emotional deficits (Cheong and Doyle 2020). In fact, similarly, children and adolescents born very preterm also have enhanced FC in and between networks involved in higher-order cognitive performance (Wehrle et al. 2018).

Prematurity has been deemed an independent risk factor with regard to psychiatric disorders; social-emotional problems are particularly prevalent in samples of individuals who were born very preterm (Montagna and Nosarti 2016). For instance, Gilchrist and colleagues (2022) identified a different biological basis for externalizing problems in adolescents born very preterm. Equally, a higher risk of delayed social competence in the first two years of life has been associated with births between 32 and 36 weeks GA (Cheong et al. 2017; Johnson et al. 2015). However, according to this study covering young adulthood, there is a lack of social-emotional impairment due to prematurity *per se* rather than other neonatal comorbidities excluded in the sample characterization. Comparable to our results, up to the age of 5 years, no specific preterm social phenotypes have been established. However, deficits in social attention in the first year of life evidence poorer social cognition in forthcoming years (Dean et al. 2021).

Even while amygdala volume is lastingly reduced in heterogeneous preterm samples during both childhood and adulthood (Chau et al. 2019; Schmitz-Koep et al. 2021a), our results

displayed no differences in amygdala volumetric values after low-risk preterm birth. These findings are in line with Rogers' study targeting children born late preterm (Rogers et al. 2014). Moreover, after very preterm birth, smaller right basal, medial and cortical nuclei volumes have been linked to social-emotional problems during childhood (Mueller et al. 2022). Meanwhile, increased right centromedial amygdala response to social-emotional events has been displayed in typically developing adolescents (Miller et al. 2021). However, our findings reveal no associations between whole and subnuclei amygdala volumes and social-emotional outcomes. Accordingly, no associations between reduced basolateral amygdala volumes and increased social anxiety in adults born very preterm have either been found (Schmitz-Koep et al. 2021b). In healthy developing young adults, in contrast, the experience of stress during the first half of pregnancy may have enduring effects on amygdala structure, and may consecutively predict depressive symptoms (Mareckova et al. 2022). Nonetheless, as mentioned above, rather than precise structures, networks may be what sustain social brain activity (Kennedy and Adolphs 2012).

Furthermore, with a small GA, both reduced and elevated FC are established between the left amygdala and other areas during the adult stage (Papini et al. 2016). Current findings show that low-risk preterm young adults have increased FC in the following three structures: left amygdala, right amygdala and MedFC. That is, FC was greater between left and right amygdala as well as between left and right amygdala and MedFC following low-risk prematurity when compared with adults born full-term. Nevertheless, as other studies have suggested, reduced strength between amygdalar and thalamic networks during childhood, as well as reductions in the intrinsic FC between the centromedial subdivision of the right amygdala and prefrontal cortex in young adults, may potentially underlie emotional deficits following very preterm delivery (Mueller et al. 2022; Papini et al. 2014).

Lastly, this study indicates that both the right amygdala – MedFC and left amygdala – MedFC's increased strengths were related to social-emotional outcomes in young adults born low-risk preterm. Higher FC between these areas is linked to optimal social-emotional adult functioning after low-risk prematurity. Likewise, better social-emotional abilities have been associated with improved engagement across different networks in children born very preterm (Siffredi et al. 2022). However, increased amygdala-ventral medial prefrontal brain FC has also been related to greater levels of sadness in typically developing infants (Thomas et al. 2019). Moreover, less mature social-emotional functioning during adolescence has been associated with positive frontoamygdala FC (Miller et al. 2021). That is, negative frontoamygdala FC has been deemed crucial in order to properly handle more demanding contexts concerning social-emotional processes (Callaghan and Tottenham 2016). As per Gee and colleagues (2013), accelerated amygdala-prefrontal development may be considered an ontogenetic adaptation in response to early adversity. Discrepancies found between studies could therefore be explained by different degrees of immaturity or by age-related improvements in emotion regulation caused by changes in activation and FC between prefrontal-amygdala circuits (Silvers et al. 2017).

This is the first study that we are aware of assessing social-emotional outcomes and amygdala structure and its FC in low-risk preterm and full-term individuals during young adulthood. In other words, unlike previous studies using heterogeneous preterm samples, this study employed neonatal and sociodemographic data to attain comparable groups, thus improving the results' generalizability. However, there was no longitudinal follow-up from early childhood to young adulthood so as to determine whether social-emotional outcomes or amygdala structure and its FC were developing commonly or not over time. Another drawback is sample size, which limits the interpretation of these results; albeit the first study to report the described findings in this population.

In conclusion, as discussed in this study, low-risk prematurity has no impact on social-emotional outcomes and amygdala volumes during young adulthood. This may suggest that preterm birth does not imply any atypical amygdalar development, since its damage impairs the recognition of social emotions (Adolphs et al. 2002). Nonetheless, the fact that social-emotional difficulties are displayed in the first years of life (Cheong et al. 2017; Johnson et al. 2015) suggests that the increase present in amygdalar FC with MedFC may be a compensatory brain mechanism developed to help overcome functioning deficiencies brought on by low-risk preterm delivery (Cheong and Doyle 2020). In particular, given that developmental dysfunction of the orbitofrontal-amygdala brain circuit found in autism is a critical factor in social-emotional cognition and behavioral self-regulation deficits (Bachevalier and Loveland 2006). However, additional research is needed to provide more data concerning brain FC development and its associations with social-emotional outcomes in larger low-risk preterm samples.

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Tables

Table 1

Neonatal, Sociodemographic and Cognitive Data

	Low-risk preterm n=33 mean±SD	Full-term n=29 mean±SD	Statistics (<i>p</i>)
<i>Neonatal data</i>			
GA. wks [range]	34.48±1.50 [30-36]	39.55±0.88 [38-42]	<i>U=957.00 (<0.001)</i>
BW. g	2158.10±345.14	3298.13±427.74	<i>t=-11.607 (<0.001)</i>
<i>Sociodemographic data</i>			
Gender. male/female	15/18	14/15	$X^2=0.05$ (0.82)
Age. yrs [range]	25.33±2.92 [20-30]	26.41±2.24 [21-32]	$t=-1.643$ (0.11)
Handedness right-handed/left-handed	30/3	26/3	$X^2=0.03$ (0.87)
Self-SES	38.36±14.68	49.93±12.49	<i>U=688.50 (0.003)</i>
Familial SES	42.06±14.92	37.07±13.80	<i>U=370.50</i> (0.13)
<i>Cognitive data</i>			
PPVT-III, receptive language	167.21±13.22	167.34±8.95	<i>U=420.50</i> (0.41)
RPM, analogical reasoning	24.15±5.73	24.48±4.28	$t=-0.26$ (0.80)

Note: SD: standard deviation; GA: gestational age; wks: weeks; BW: birth weight; g: grams; yrs: years; *U*: Mann-Whitney U test; *t*: Student-t test; X^2 : Chi-square test; SES: socioeconomic status; PPVT-III: Peabody Picture Vocabulary Test III; and RPM Raven's Advanced Progressive Matrices.

Table 2

Differences in Social-Emotional Outcomes between Low-Risk Preterm and Full-term Young Adults

	Low-risk preterm n=33 mean±SD	Full-term n=29 mean±SD	<i>F-Snedecor Statistic (p)</i>	η_p^2
<i>Social-emotional outcomes (adjusted for age and self-SES)</i>				
Happe's Strange Stories Test	6.59±1.37	6.71±1.27	0.90 (0.77)	.00
MJT	13.60±7.81	16.37±9.67	1.27 (0.27)	.02
Kirby DDT	0.66±0.26	0.71±0.24	0.43 (0.52)	.01
<i>Adult Self Report (ASR)</i>				
Anxious depressed	9.74±6.12	9.19±3.94	0.14 (0.71)	.00
Withdrawn	2.77±2.97	3.05±2.14	0.15 (0.70)	.00
Somatic complaints	3.18±3.19	2.39±2.80	0.86 (0.36)	.02
Thought problems	2.08±1.82	2.26±1.88	0.12 (0.73)	.00
Attention problems	6.36±4.60	7.93±3.90	1.79 (0.19)	.03
Aggressive behavior	4.32±3.39	5.18±4.33	0.63 (0.43)	.01
Rule-breaking behavior	2.07±2.10	2.23±2.84	0.05 (0.82)	.00
Intrusive behavior	1.95±1.64	1.91±1.89	0.01 (0.94)	.00
Internalizing problems	15.69±10.77	14.67±7.35	0.15 (0.70)	.00
Externalizing problems	8.36±5.67	9.49±7.07	0.41 (0.53)	.01
<i>Emotion Regulation Questionnaire (ERQ)</i>				
Cognitive Reappraisal	30.02±5.96	28.99±4.68	0.48 (0.49)	.01
Expressive Suppression	12.39±4.84	14.28±4.77	1.96 (0.17)	.03
<i>Composite score (adjusted for age and self-SES)</i>				
Social-emotional outcomes	0.04±0.53	-0.04±0.50	0.00 (0.95)	.00

Note: SD: standard deviation; SES: socioeconomic status; MJT: Moral Judgement Test; DDT: Delay-Discounting Task; and η_p^2 : partial eta squared.

Table 3

Differences in Whole and Subnuclei Amygdala Volumes between Low-Risk Preterm and Full-term Young Adults

	Low-risk preterm n=33 mean volume mm ³ ±SD	Full-term n=29 mean volume mm ³ ±SD	<i>F-Snedecor Statistic (p)</i>	η_p^2
<i>Whole amygdala volumes (adjusted for age, eTIV and self-SES)</i>				
Left amygdala	1714.71±204.67	1722.45±197.34	0.03 (0.86)	.00
Right amygdala	1818.53±217.36	1837.92±222.57	0.16 (0.69)	.00
<i>Left amygdala segmentation (adjusted for age, left amygdala volume and self-SES)</i>				
Lateral nucleus	621.61±72.34	630.50±77.01	1.68 (0.20)	.03
Basal nucleus	440.44±55.01	438.79±49.69	0.28 (0.60)	.01
Accessory basal nucleus	264.43±35.39	261.61±33.89	0.69 (0.41)	.01
Anterior amygdaloid area	53.81±7.91	55.27±7.83	1.21 (0.28)	.02
Central nucleus	45.05±7.30	43.28±7.84	1.61 (0.21)	.03
Medial nucleus	26.56±5.95	25.54±6.11	0.55 (0.46)	.01
Cortical nucleus	27.19±4.17	26.07±3.98	2.32 (0.13)	.04
Corticoamygdaloid transition	187.59±24.20	186.19±24.20	0.35 (0.56)	.01
Paralaminar nucleus	51.66±6.29	51.08±6.16	0.40 (0.53)	.01
<i>Right amygdala segmentation (adjusted for age, right amygdala volume and self-SES)</i>				
Lateral nucleus	668.92±82.36	669.13±85.81	0.00 (0.98)	.00
Basal nucleus	466.98±58.02	469.45±57.26	0.66 (0.42)	.01
Accessory basal nucleus	278.64±35.20	279.55±37.33	0.07 (0.79)	.00
Anterior amygdaloid area	58.90±8.96	59.81±8.81	0.40 (0.53)	.01
Central nucleus	48.74±8.35	46.84±6.75	1.50 (0.23)	.03
Medial nucleus	28.04±7.06	26.11±5.03	1.66 (0.20)	.03
Cortical nucleus	28.74±5.01	27.73±4.57	1.42 (0.24)	.02
Corticoamygdaloid transition	194.99±22.86	195.55±25.55	0.06 (0.81)	.00
Paralaminar nucleus	53.66±7.44	53.43±7.06	0.06 (0.81)	.00

Note: mm³: cubic millimeter; SD: standard deviation; eTIV: total intracranial volume; SES: socioeconomic status; and η_p^2 : partial eta squared.

Figures

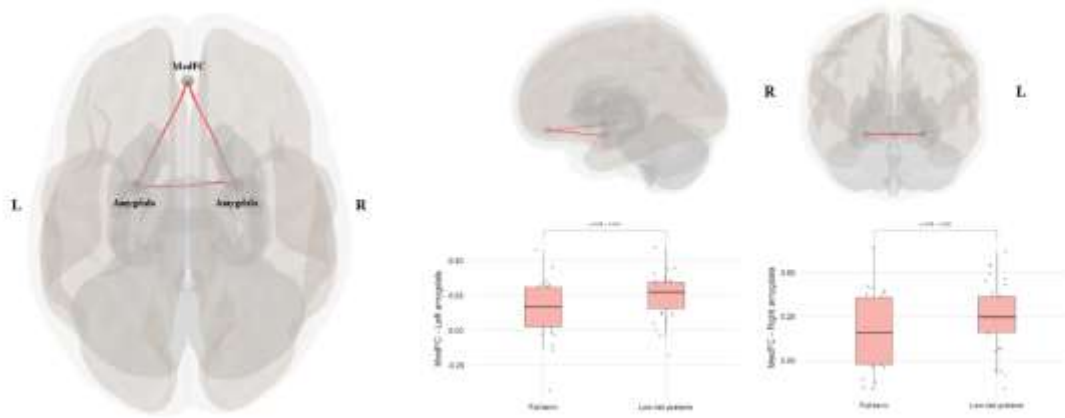


Figure 1. Left and Right Amygdala – MedFC FC Differences between Low-Risk Preterm and Full-Term Young Adults. Displayed results using CONN Toolbox 21.a and Jamovi 1.6.1.

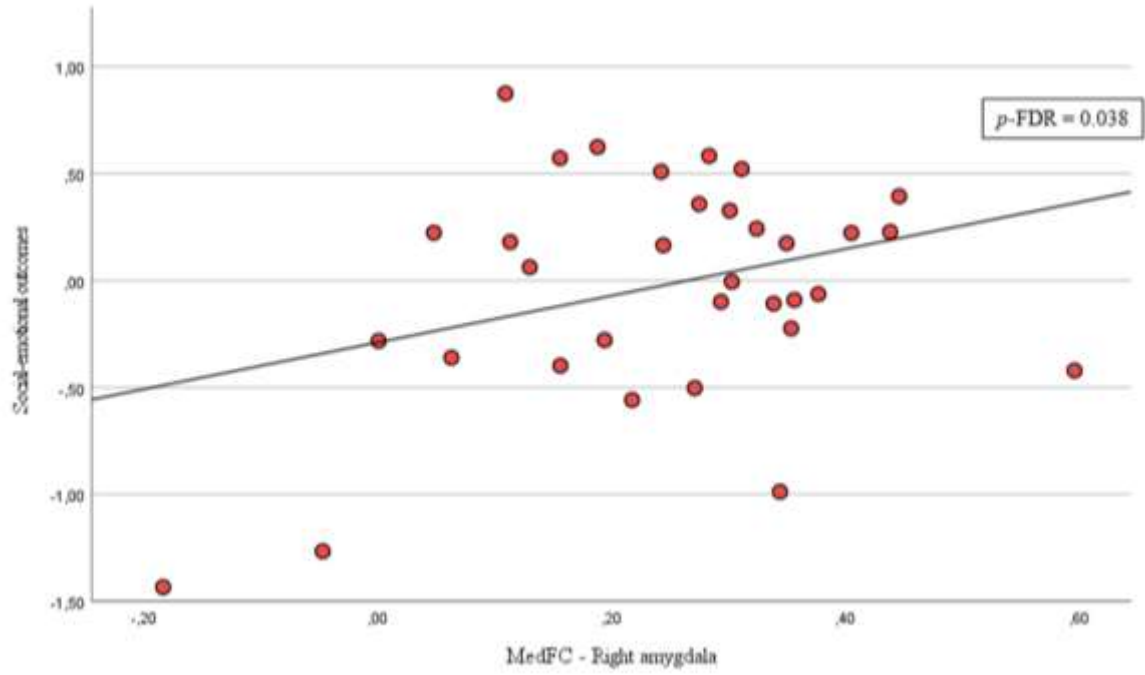


Figure 2. Right amygdala – MedFC FC Correlates with Social-Emotional Outcomes in Low-Risk Preterm Young Adults.

VI. Discussion

6. Discussion

There is a dearth of research focusing on neurodevelopmental outcomes in well-characterized samples in terms of clinical manifestations, and thus assessing the effect of high- and low-risk PB on cognition, mental health and brain development. Therefore, this thesis aimed to identify the neuropsychological profiles, early life environmental factors' impact on cognition and neuroimaging markers that could be descriptive of high- and low-risk PB.

This body of work provides additional scientific evidence suggesting that PB, both high- and low-risk, leads to general developmental differences in cognition, mental health and brain development. The data obtained and analyzed indicate that these adverse consequences are maintained over time. However, the clinical manifestations at birth (i.e., GA and neonatal brain injury) as well as environmental factors in the first years of life will determine its severity. Specifically, maternal care seems to be crucial during childhood for cognitive development, while SES appears to impact cognition throughout adolescence and young adulthood in analyzed sample.

Cognition during childhood was within the normal range in *studies I* and *II*; however, children born preterm with or without prenatal brain injury continued to lag behind their full-term peers in a number of domains related to intellectual functioning (Luu et al., 2009), as well as in scholastic achievement (Brydges et al., 2018; Flores et al., 2021). Nevertheless, in this thesis project the presence of neonatal brain injury fosters more severe long-term neurodevelopmental impairments (i.e., cognitive and behavioral problems), as other authors have proposed (Mathur & Inder, 2009; Miller et al., 2005; Rees et al., 2022). Regarding MLPT birth, minor or more specific adverse cognitive outcomes have been found in the context of reduced medical and environmental risk, as already seen during infancy (Hodel et al., 2017); however, lower cognitive scores are

commonly exhibited when compared to those born at term (Arhan et al., 2017). In *studies I and II*, in the absence of neonatal brain injury, any degree of PB influences cognitive functioning leading to altered neurodevelopment, even over time (Allotey et al., 2018). Nonetheless, different neuropsychological profiles were observed in *study II*, as moderate preterm-born children displayed worse general cognitive functioning compared to their full-term peers. That is to say, the severity of adverse developmental consequences seems to be influenced by GA.

In relation to memory more specifically, the findings of *study I* established the negative impact of being born preterm with GM-IVH on its performance, which has already been shown in heterogeneous preterm samples (Dorner et al., 2018). High-risk preterm children with GM-IVH also had lower scores in the first immediate recall condition, involving less engagement of the hippocampus compared to the succeeding trials due to cumulative memory load. Hence, children born preterm with atypical brain development have difficulty retaining key data over short periods of time, which may extend beyond reduced hippocampal volumes as some authors have proposed in preterm toddlers with subependymal or mild intraventricular hemorrhages and developmental amnesia (Isaacs et al., 2003; Ross et al., 1996). However, low-risk PB (i.e., without GM-IVH) did not lead to a poorer memory performance; PB *per se* may have no effect on memory among those regarded to be at a lower risk of neurological abnormalities from childhood onwards (Brunnemann et al., 2013; Heinonen et al., 2018).

Concerning adolescent and adult stages, in *study IV* lower scores in more cognitive domains were found in individuals born high-risk preterm when compared to low-risk PB, suggesting negative developmental outcomes increase progressively as GA decreases (Allen et al., 2010). However, both preterm groups had poorer general cognitive function regardless of being high- or low-risk preterm adolescent and young adult. According to

MLPT, being born at 33-34 weeks was proven to have a greater influence on intellectual performance during adulthood than being born at 35-36 weeks (Ekeus et al., 2010); a potential difference between newborns born moderate and late preterm as already seen in *study II* across childhood. Yet, MLPT birth had a minor impact on intellectual performance during adulthood, based on *study III* meta-analysis research, suggesting a possible catch up as in other studies (Romeo et al., 2012; Tideman, 2000). Similarly, according to *study V*, adolescents and young adults born low-risk preterm displayed a poorer performance in only certain cognitive domains than those controls born full-term. As aforementioned, in childhood, PB without neonatal brain injury leads to poorer cognitive function during adolescence and the young adult stage.

As per *study III*, the consequences of MLPT on psychiatric disorders are often minimal, if present, when compared to those born EPT or VPT. MLPT birth did not have a significant impact on the prevalence of psychiatric disorders in adulthood (Dalziel et al., 2007; Lahti et al., 2015; Sammallahti et al., 2017; Upadhyaya et al., 2020). Nevertheless, the risk of suffering from a psychiatric disorder and being hospitalized for it rise with a lower GA (Lindström et al., 2009; Moster et al., 2008; Nosarti et al., 2012). That is to say, there is a higher likelihood of suffering from any mental, substance use, mood, or psychotic disorders than full-term born adults. Furthermore, deliveries between 32 and 36 weeks GA have been related to a higher risk of delayed social competence in the first two years of life (Cheong et al. 2017; Johnson et al. 2015). However, in accordance with *studies II, IV, V and VI*, no evidence of social-emotional impairment was found to be brought on by low-risk PB. More specifically, overall, no differences were detected in emotional-behavioral problems during childhood, adolescence and young adulthood. Additionally, adolescents and young adults born low-risk preterm and their full-term counterparts displayed comparable life satisfaction, resilience and personality

outcomes. Similar to our findings, preterm social phenotypes have not been identified from childhood onwards (Dean et al., 2021).

In addition, as exhibited in *study III*, MLPT birth along with other clinical and/or sociodemographic characteristics may raise the potential risk of long-term unfavorable consequences in this population. Likewise, PB *per se* may also increase susceptibility to environmental influences as stated by the findings of *studies II* and *IV*. According to several authors, the dual burden of PB and other neonatal variables connected to immaturity at birth, such as postnatal growth (i.e., SGA), may impair cognitive functioning and psychiatric wellness in individuals born preterm during adulthood (Heinonen et al., 2016, 2018; Lahti et al., 2015; Nomura et al., 2009; Suikkanen et al., 2020). However, aspects other than care-related risk factors may affect long-term cognition in the preterm-born population (Wolke, 2019). For example, better academic outcomes in children born preterm have been associated with higher parental education, parental childcare, stability of family composition and geographic residence (Gross et al., 2001). Parent-child bonding has also been linked to brain growth in commonly developing children (Hidalgo et al., 2019) and those born preterm (Treyvaud et al., 2021). *Study II's* data indicates that differences in maternal care may compromise neurodevelopment following PB and impact cognition during childhood, particularly in children born moderately preterm. Yet, maternal responsiveness has been linked to verbal performance and IQ in both preterm and full-term children (Erickson et al., 2018). Positive parenting has been found to have long-term benefits for infants born prematurely (Cheong et al., 2020); as per our results, high maternal care scores reduced the influence of immaturity at birth on general cognitive functioning during childhood.

Furthermore, our findings showed that disparities in SES during childhood could interfere with brain remodeling following central nervous system illnesses (i.e., neonatal

brain injury) that impact cognition during adolescence and young adulthood. In *study IV*, child differences in SES backgrounds moderated the impact of PB on adolescent-young adult cognition, particularly following high-risk PB. Based on the above, the effect of environmental factors on future cognitive functioning appears to be persistent (Pérez-Pereira et al., 2020). Children who were both born prematurely and came from low-income families had lower cognitive performance (Beauregard et al., 2018), and this lasted until middle age (Ekeus et al., 2010). Moreover, the consequences of brain damage on cognition are minor in children with highly educated mothers (Benavente-Fernández et al., 2019; Joseph et al., 2018). Similarly, our results exposed that the greatest familial SES levels protected the influence of PB on cognitive development in adolescent and adult years.

At brain level, in children born preterm (high- and low-risk PB), memory performance was related to the right CA-field volumetric values in *study I*. Interestingly, in this thesis project decreased hippocampal volumes have only been identified in preterm children, which have been suggested to be probably due to adverse pre-perinatal factors (Salvan et al., 2014; Schiller et al., 2018). For instance, brain injury induced by VPT birth may disrupt the development of several memory circuits (Nosarti & FroudishWalsh, 2016). Current structure-function connection has been previously exhibited between reduced hippocampal growth and memory in ELBW preterm adults with perinatal morbidity (Aanes et al., 2015). Nevertheless, differences in hippocampal volume may not fully explain memory performance as it is not the only brain structure that may be involved (Curtis et al., 2006; Irzan et al., 2019).

Later in life, no differences in bilateral global CTh values (i.e., left and right global CTh) were detected in *study V*. Consistent with our findings, a decline in CTh between the ages of 15 and 20 correspond to a comparable developmental trajectory in individuals

born preterm and full-term (Rimol et al., 2016). Conversely, in a current low-risk preterm sample, regional CTh increases were identified in the right inferior temporal gyrus; as reported in temporal regions' surface area and assumed to reflect a delayed maturational path throughout childhood following VPT birth (Vandewouw et al., 2020). Moreover, brain volumes were not found to be reduced or increased in low-risk preterm young adults. Yet, the low-risk preterm sample had a non-significant increased WM volume, which is hypothesized to be due to cortical dysgenesis induced by a combination of normal brain development processes and perinatal brain injuries (Allin et al., 2004). These lesions, commonly detected at term-equivalent age after MLPT birth (Kelly et al., 2016), were not considered for current data. Lastly, in this thesis, low-risk preterm-born young adults had reduced subcortical volumetric values exclusively in the thalamus. Curiously, at term-equivalent age and in the absence of significant WM abnormalities, the thalamocortical system's development is disrupted (Ball et al., 2012). However, our findings from *study V* do not resemble reduced volumetric values in the putamen, caudate, and hippocampus found in preterm samples, although heterogeneous (Meng et al., 2016).

As per *study V*, a regionally altered WM microstructure was also identified particularly in the corpus callosum (i.e., forceps minor) in young adults born low-risk preterm. The early extrauterine exposure has been linked to WM microstructure alterations, which are detected not only at term-equivalent age but also in young adulthood (Irzan et al., 2021). Indeed, in this thesis project, low-risk preterm young adults exhibit increased regional AD and MD in a wide range of brain areas, a conclusion that has previously been described in infants born low-risk preterm (Kelly et al., 2016). The cellular substrates underlying these findings could assume altered axonal packing density and water content (Dibble et al., 2021). However, the trajectory of WM microstructure

following PB has also been found to be comparable to that of typically developing neonates during childhood (Adrian et al., 2023).

Lastly, although *study VI* showed that low-risk preterm birth had no impact on whole and subnuclei amygdala volumes throughout young adulthood, it did show an increase in the FC strength between the left and right amygdala and MedFC. The social brain, including its malfunction and recovery, is best understood through large-scale networks as opposed to isolated structures (Kennedy & Adolphs, 2012). Particularly given that social-emotional cognition and behavioral self-regulation deficits in autism are significantly influenced by an altered orbitofrontal-amygdala brain circuit (Bachevalier & Loveland 2006). In other words, following the early onset of social-emotional difficulties after MLPT birth (Cheong et al. 2017; Cheong & Doyle 2020; Johnson et al. 2015), increased amygdalar FC with MedFC might be a compensatory brain mechanism designed to address the function deficits caused by low-risk PB.

The current thesis has some limitations, including the total sample size as well as the sample size of each group; and therefore, results must be interpreted with caution. For example, the sample size in some of the studies was insufficient to investigate if there would be differences in cognitive performance based on which neonatal brain injury they had (i.e., PVL and GM-IVH). Furthermore, despite the fact that our analyses were age-controlled, the studies included in this thesis project cover an extensive age range. Unlike previous research, which used heterogeneous preterm populations, this thesis has well-characterized samples because it distinguishes between individuals born preterm with and without brain injury that is absolutely required when analyzing the potential influence of PB based on clinical manifestations in cognition and brain development. However, despite the term *low-risk PB* being based on the literature and clinical classifications (i.e., GA and BW), it's not commonly used by clinicians in clinical settings. As a result, unlike

groupings based only on GA or BW, we must be cautious with our findings since it might be more difficult to classify and examine low-risk PB especially in the long term. In addition, it employs stringent standards to verify the replication of the findings (i.e., neonatal and sociodemographic data). Unfortunately, there was no longitudinal follow-up from early infancy to adulthood to determine if neurodevelopmental outcomes remained stable, declined, or upgraded over the years.

Addressing specific limitations from *study III*, the differing sample selection methods and assessment tools by the different studies make comparison difficult. Some studies utilized evaluation instruments that had only been validated in the country of study, or gave insufficient details concerning their validity, making a comparison difficult again. Another drawback of *study III* is that the studies included focused on Scandinavian populations who had undergone treatment in prenatal and neonatal care units many years ago. This may be inaccurate for everyday functioning data for neonates treated with current medical approaches, and the generalizability of present findings to other ethnicities may also be limited. Finally, the inability to conduct meta-analysis studies with all cognitive and psychiatric domains due to the small number of studies available limits the quality of our results.

To conclude, all of the studies mentioned here try to contribute to the identification of potential descriptive markers using trustworthy approaches in order to enhance PB follow-up. The findings might provide more scientific evidence to justify the inclusion of cognitive and neuroimaging indicators in the prognosis of PB, in both high- and low-risk preterm samples. As a result, while much work remains to be done regarding the inclusion of cognitive and brain alterations in PB care, the current thesis suggests that the use of standardized long-term follow-ups may be potentially useful without ignoring the impact of different environmental factors during the first years of life.

Despite the limitations, we believe that this body of work makes a unique contribution to the knowledge of PB from a neuroscientific point of view (i.e., psychological, neuropsychological, and social perspectives). Taking into account that in Spain around 20,000 premature babies are born annually, there are few resources to support affected individuals and their families. That is why, as a result of this compendium of works as well as the interdisciplinary professional collaborations generated (e.g., EXPRESS Study), an association will be founded from the Basque-Navarre Society of Neuropsychology to respond to this situation. We also believe that these contributions are only the beginning of a journey that will go much further. And that, in any case, they will serve to better understand and address the specific characteristics and needs of this population.

VII. Conclusions

7. Conclusions

The main conclusions derived from the current thesis project through the studies presented can be summarized as follows:

- Children, adolescents, and young adults born prematurely, with or without neonatal brain injury, continued to lag behind their full-term peers in a variety of cognitive domains.
- Neonatal brain damage promotes more severe long-term neurodevelopmental deficits as well as the GA-related gradient appears to have negative developmental effects. However, MLPT may also increase the potential risk of long-term adverse outcomes.
- When compared to adults born EPT or VPT, the effects of MLPT on psychiatric illnesses are frequently small. However, low-risk preterm-born adults are more likely to suffer from any mental, substance use, mood, or psychotic problems than those born at term.
- Based on the analyzed sample, no indication of social-emotional deficits after low-risk PB have been identified during childhood, adolescence and young adulthood.
- Different early life environmental factors may influence brain remodeling following PB and impact cognition depending on the developmental stage, particularly in those with smaller GA. Maternal care appears to be key to cognitive development throughout childhood, but child differences in SES appears to influence cognition during adolescence and young adulthood.
- At brain level, both global and regional hippocampal volumetric reductions were observed in children born high-risk preterm with GM-IVH. In children born

preterm (i.e., high- and low-risk PB) memory performance was related to the right hippocampal CA-field volume.

- In the absence of neonatal brain injury, regional CTh increases were identified in the right inferior temporal gyrus after PB. Moreover, global brain volumes were not found to differ between low-risk preterm and term young adults. However, reduced subcortical volumetric values were found in the thalamus in low-risk preterm born young adults.
- A regionally altered WM microstructure was identified, particularly in the corpus callosum, in young adults born low-risk preterm compared to their full-term peers.
- Although low-risk PB had no impact on whole and subnuclei amygdala volumes, increments in the FC strength between the left and right amygdala and MedFC were identified across young adulthood. Moreover, both the right amygdala – MedFC and left amygdala – MedFC's increased strengths at cluster level were related to social-emotional outcomes only in those low-risk preterm born young adults.

Conclusiones

Las principales conclusiones derivadas de los estudios descritos en el presente proyecto de tesis pueden resumirse de la siguiente manera:

- Los niños, adolescentes y adultos jóvenes nacidos prematuramente, con o sin daño cerebral neonatal, siguen puntuando por detrás de sus homólogos nacidos a término en diversos dominios cognitivos.
- El daño cerebral neonatal promueve déficits de neurodesarrollo más graves a largo plazo, así como el gradiente relacionado con la edad gestacional parece tener efectos negativos sobre el desarrollo. Sin embargo, el nacimiento prematuro moderado y tardío también puede aumentar el riesgo potencial de resultados adversos a largo plazo.
- En comparación con los individuos nacidos muy o extremadamente prematuros, el impacto del nacimiento prematuro moderado y tardío sobre las enfermedades psiquiátricas suele ser leve. Sin embargo, los adultos prematuros de bajo riesgo tienen más probabilidades de sufrir algún problema mental, de consumo de sustancias, del estado de ánimo o psicótico que los nacidos a término.
- De acuerdo a la muestra analizada, no se han identificado indicios de déficits socioemocionales tras un parto prematuro de bajo riesgo durante la niñez, adolescencia y adultez temprana.
- Diferentes factores ambientales en las primeras etapas de la vida pueden influir en la remodelación cerebral tras el nacimiento prematuro e impactar en la cognición dependiendo de la etapa de desarrollo, particularmente en aquellos con menor edad gestacional. El cuidado materno parece ser clave para el desarrollo cognitivo a lo largo de la infancia, mientras que las diferencias tempranas en el

estatus socioeconómico parecen influir en la cognición durante la adolescencia y la adultez temprana.

- A nivel cerebral, se observaron reducciones volumétricas tanto globales como regionales del hipocampo en niños nacidos prematuros de alto riesgo con hemorragia intraventricular de la matriz germinal. En niños nacidos prematuros, tanto de alto como de bajo riesgo, el rendimiento mnemotécnico se relacionó con los volúmenes del hipocampo CA derecho.
- En ausencia de lesión cerebral neonatal, se identificaron aumentos regionales del grosor cortical en el giro temporal inferior derecho tras el nacimiento prematuro. Además, no se observaron diferencias en los volúmenes cerebrales globales entre los adultos prematuros de bajo riesgo y aquellos nacidos a término. Sin embargo, se encontraron valores volumétricos subcorticales reducidos en el tálamo en los prematuros de bajo riesgo durante la adultez temprana.
- Se identificó una microestructura regionalmente alterada de la sustancia blanca, particularmente en el cuerpo calloso, en adultos prematuros de bajo riesgo en comparación con sus pares nacidos a término.
- Aunque el nacimiento prematuro de bajo riesgo no tuvo impacto en los volúmenes de la amígdala total y regional, se identificaron incrementos en la fuerza de la conectividad funcional entre la amígdala izquierda y derecha y la corteza frontal media a lo largo de la edad adulta. El aumento de la fuerza de la amígdala derecha - corteza frontal media como de la amígdala izquierda - corteza frontal media se relacionaron con los resultados socioemocionales en adultos jóvenes prematuros de bajo riesgo.

VIII. References

8. References

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