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The interplay between prematurity,maternal stress and children's intelligence quotient at age 11

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The interplay between prematurity, maternal stress and children's intelligence quotient at age 11

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Prof. Vincent Barras

Foreword

I was hired as research assistant and then as a PhD student in the Research Unit of the Department of Child and Adolescent Psychiatry (SUPEA) at 50% between September 2013 and October 2018. My principal task was to collaborate to the second part of a longitudinal study started in 2009 and financed by Swiss National Science Foundation project NCCR Synapsy. This study focused on the long-term impact of preterm birth on child's development and his endocrine system at age of 9 years old. In this manner, I contacted families who participated to the first step of the study, I collected, coded and managed behavioural and cortisol data. My contract in the Research Unit finished before the end of data collection. In this manner, my thesis concerns another longitudinal study conducted in the Research Unit between 1998 and 2009 financed by the Swiss National Science Foundation, studying the impact of maternal psychological distress due to a preterm birth and the impact of the preterm birth on the mother-child relationship on the preterm born child's development. Along the way, I had the chance to collaborate with Prof. Micah Murray on a study concerning the impact of preterm birth on the child's cortical processing and discrimination of sounds of environmental objects. This was added to the study started in 2009, and I participated in EEG data collection, data management and analysis.

In the beginning of this work, my thesis directors were Dre Carole Müller-Nix and Prof. François Ansermet. However, both of them retired and Prof. Micah Murray kindly accepted to be my thesis director since May 2019.

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Finally, I am very grateful to Simon Tinguely who supported me in hard and better

moments, who improved his cooking competencies to prepare delicious dinner for me, bought beers, and says heartening words every day.

Summary

Every year, around 15 millions babies are born prematurely (<37 weeks of gestation) in the world (Blencowe et al., 2012). With improvement in medical technologies and care instructions, the number of survivors has increased during the last three decades. However, most of them have long-term developmental complications. Very preterm born children (born less than 33 weeks of gestational age) are more prone to present developmental difficulties, including academic difficulties. Studies show that although preterm born children have normal-range intelligence quotient (IQ) scores, they are nonetheless lower than their full-term born peers. These differences are usually attributed to lower gestational age, lower birth weight and lower socio-economic status than full-term children. However, these factors are insufficient to explain the heterogeneity in IQ scores.

Preterm birth is undeniably a stressful event for mothers and their babies. Mothers must cope with an unfamiliar neonatal intensive care unit and the distress related to the child's survival. Premature babies have to cope with an extrauterine world, despite the fact that their physiology is immature, and they have to endure painful care due to their perinatal problems. Studies show that stress associated with preterm birth affects the quality of mother-infant interactions and the infant's development. However, studies of the longer-term effects of stress on premature born children's IQ remain scarce.

This present thesis evaluated the impact of maternal post-traumatic stress disorder (PTSD) symptoms due to childbirth and the gravity of a child's perinatal problems on later IQ evaluated at age 11 years. Our results revealed that preterm born children have

lower IQ scores than full-term born children. Moreover, results showed that perinatal problems do not affect IQ score, whereas maternal PTSD symptoms affect IQ score in the preterm born group of children. The lower the mother's presentation of symptoms, the higher was the child's IQ at 11 years old.

This thesis highlights the importance of identifying and treating mothers at risk for presenting PTSD symptoms after a preterm birth to minimize transgenerational impact on the preterm child's cognitive development.

Résumé

Chaque année, environ 15 millions d'enfants naissent prématurés (<37 semaines de gestation) dans le monde (Blencowe et al., 2012). Avec les progrès dans les soins et les techniques médicales, le nombre de survivants a augmenté durant les trois dernières décennies. Cependant, la majorité d'entre eux ont des complications développementales sur le long terme. Les enfants nés grands prématurés (nés avant 33 semaines d'âge gestationnel) ont plus de risque de présenter des problèmes développementaux tels que des difficultés dans leur parcours scolaire. De nombreuses études ont montré que malgré un score se situant dans la moyenne, les enfants nés grand prématuré ont un quotient intellectuel (QI) plus bas que leurs pairs nés à terme. Cette différence est généralement attribuée à l'âge gestationnel plus bas, au poids de naissance plus bas, ainsi qu'au niveau socio-économique plus bas que les enfants nés à terme. Cependant, ces facteurs ne sont pas suffisants pour expliquer l'importante hétérogénéité dans le QI des enfants nés grands prématurés.

Une naissance prématurée est un événement très stressant à la fois pour la mère et le bébé. Les mères doivent faire face à l'unité de soins intensifs de néonatalogie qui leur est inconnue et gérer leur détresse concernant la survie de leur nouveau-né. Quant aux nouveau-nés prématurés, ils doivent s'adapter au monde extra-utérin alors que leur physiologie n'est pas encore mature et ils doivent subir des soins douloureux dus à leurs problèmes périnataux. Des études ont montré que le stress dû à la naissance prématurée péjore la qualité des relations mère-enfant ainsi que le développement du jeune enfant. Cependant, peu d'études portent sur l'effet à plus long terme de ce stress sur le QI de

l'enfant.

Le but de cette thèse est d'évaluer l'impact des symptômes du trouble de stress post-traumatique (PTSD) de la mère ainsi que des problèmes périnataux de l'enfant sur le QI à l'âge de 11 ans. Les résultats ont montré que les enfants nés grands prématurés ont un score de QI plus bas que les enfants nés à terme. De plus, les résultats ont révélé que la gravité des problèmes périnataux n'affecte pas le QI tandis que les symptômes PTSD de la mère affectent le QI des enfants nés grands prématurés. Plus la mère présente de symptômes, plus le QI de l'enfant né grand prématuré est bas.

De cette manière, cette thèse met en avant l'importance de considérer les symptômes PTSD de la mère suite à une naissance prématurée et souligne l'importance de proposer des interventions diminuant ces symptômes dans le but de permettre un meilleur développement cognitif des enfants nés grands prématurés.

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List of Abbreviations

ADHD	Attention-Deficit Hyperactivity Disorder
AUC	Area Under the Curve
CBCL	Child Behavior Checklist
EEG	Electroencephalography
FCC	Family-Centered Care
FT	Full-term
GA	Gestational Age
HPA	Hypothalamic-Pituitary-Adrenal
IQ	Intelligence Quotient
KC	Kangaroo Care
MANCOVA	Multivariate Analysis of Covariance
NICU	Neonatal Intensive Care Unit
PERI	Perinatal Risk Inventory
PPQ	Perinatal Post-traumatic Stress Questionnaire
PTSD	Post-Traumatic Stress Disorder
ROC	Receiver Operating Characteristic
SES	Socio-Economic Status
VIF	Variance Inflation Factor
VPT	Very Preterm
WISC-IV	Wechsler Intelligence Scale for Children (4th edition)

Chapter 1

Introduction

The aim of this thesis is to study the longitudinal impact of mother and child's stress due to preterm birth on preterm born child's intelligence quotient. More specifically, this thesis focuses on the effect of maternal post-traumatic stress disorder (PTSD) symptoms due to child's birth and the effect of the gravity of children's perinatal problems on intelligence quotient (IQ) of preterm born children at age 11 years. Preterm birth is associated with higher risk to present developmental difficulties, including cognitive development. It is well known that preterm born individuals have in general a lower intelligent quotient score than full-term born peers. However, this difference is variable between preterm-born individuals. The main factors typically considered to explain this heterogeneity are gestational age, birth weight and socio-economic status. Other factors, such as neurological development, are also taken into account to explain preterm born children's lower intelligence quotient. Considering the importance of societal costs and the impact on individual development, it appears important to better understand the mechanisms underlying cognitive difficulties after preterm birth in order to suggest better interventions to help preterm born children and their families.

In the Introduction, a general background concerning preterm birth, its consequences

on child's development, and the impact of the stress due to preterm birth on development will be presented. This introductory chapter is divided in three sections. In the first one, the preterm birth will be defined, and its epidemiology, etiology and risk factors will be presented. Then, in the second section, consequences of preterm birth on child's development (emotional, behavioral, cognitive difficulties and their comorbidity) will be presented. Finally, in the third part, the stressful event surrounding a preterm birth for the mother and the child will be explained and the consequences of this stress on the preterm born children's development will be exposed.

1.1 The preterm birth

1.1.1 Preterm birth: definition

Preterm birth is defined as birth of an alive baby before 37 completed weeks of gestation. Gestational age (GA) corresponds to the number of completed weeks after the first day of the last mother's menstrual period (Ananth, Joseph, Oyelese, Demissie, & Vintzileos, 2005; Behrman & Butler, 2007; Goldenberg, Culhane, Iams, & Romero, 2008). There are four categories of preterm birth's severity depending on GA (Chawanpaiboon et al., 2019; Purisch & Gyamfi-Bannerman, 2017; Torchin, Ancel, Jarreau, & Goffinet, 2015):

1. late preterm - birth between 34 and 36 weeks of gestation,
2. moderate prematurity - birth between 33 and 32 weeks of gestation,
3. severe prematurity - birth between 31 and 28 weeks of gestation,
4. extreme prematurity - birth before 28 weeks of gestation.

However, there are various classifications (e.g. three categories instead of four), depending on the domain of application such as research, international data comparison or prevention (Vogel et al., 2018). This lack of universal categories makes difficult to

compare all studies concerning premature birth. Furthermore, prematurity's severity can also be categorized depending on the birth weight.

Initially, birth weight was used to estimate the degree of prematurity and it is still used in some countries, such as the United Kingdom. Preterm birth's severity categorized according to birth weight commonly includes three sub-categories (S. Johnson, 2007; Tucker & McGuire, 2004):

1. low birthweight (<2500gr),
2. very low birthweight (<1500gr),
3. extremely low birthweight (<1000gr).

Generally, birth weight correlates with gestational age. However, this classification includes some babies born at term. Indeed, around one third of low birthweight babies are born at term and are considered "small for gestational age"; meaning that their birth weight is below the 10th percentile of the index of the population's distribution of birth weight by gestation.

Birth weight refers to "born too small" and gestational age to "born too early" (Behrman & Butler, 2007). Premature babies have immature organ systems and are unable to survive in extrauterine life by themselves. The degree of the baby's maturity is important for determination of mortality and morbidity of prematurity. The less the baby is mature, the more the baby has risk of mortality and morbidity. To date, there is no exact measure of a baby's maturity. However, over the past several decades, with increased use of prenatal ultrasound to measure fetal size, GA appears to be more accurate to estimate baby's maturity; GA is calculated using a combination algorithm of ultrasound and last menstrual period (Behrman & Butler, 2007; Vogel et al., 2018).

1.1.2 Epidemiology

Preterm birth concerns around 11.1% of births in the world, and this number varies between countries from 5 to 18% (Blencowe et al., 2012). In low-income countries, birth data are not systematically recorded and make difficult to have exact statistics (Simmons, Rubens, Darmstadt, & Gravett, 2010). In Switzerland, 7% of babies are born prematurely, and this number has remained stable during recent years (Table 1.1) (Federal Statistical Office of Switzerland, 2019).

Table 1.1 – Preterm birth statistics between 2015 and 2018 (Federal Statistical Office of Switzerland, 2019)

	2015	2016	2017	2018
Living births	86559	87883	87381	87851
Gestational weeks [%]				
22-27 weeks	0.3	0.3	0.4	0.4
28-31 weeks	0.7	0.6	0.6	0.6
32-36 weeks	6.1	6.1	6	6
At term (37-41 weeks)	92.3	92.4	92.5	92.4
After term (>42 weeks)	0.6	0.5	0.5	0.6
Mean birthweight [gr]	3289	3286	3295	3288
Low birthweight [%]				
<1000gr	0.5	0.5	0.5	0.5
<1500gr	1	1	1	1.1
<2500gr	6.5	6.6	6.4	6.5
Multiple births §				
twins	36.1	37.5	35.5	35.5
triples	0.9	1.3	0.8	1.1

§ Number of twins and triples for 1000 alive children

Most of the preterm births (60-70%) are late preterm. Moderate prematurity represents 20%, severe prematurity 15%, and extreme prematurity 5% of premature births (Frey & Klebanoff, 2016; Goldenberg et al., 2008). Preterm birth can be spontaneous, due to premature rupture of the membranes or medically indicated cause of maternal or fetal pathology (Goldenberg et al., 2008; Purisch & Gyamfi-Bannerman, 2017).

During the last three decades, the numbers of preterm born survivors has increased in high-income countries. This is due to the important improvements in medical techniques and care instructions in the neonatal intensive care unit (NICU). Moreover, the increasing number of multiple pregnancies due to improvement in assisted reproductive technology and the medically indicated preterm birth to reduce perinatal morbidity are other reasons contributing to increased numbers of prematurely born children (Goldenberg et al., 2008).

1.1.3 Etiology and risk factors

30-35% of preterm births are medically indicated due to pregnancy complication, 40-45% are spontaneous preterm births without rupture of membrane, and 25-30% of preterm births are due to spontaneous preterm birth with membrane rupture (Goldenberg et al., 2008).

Risk factors of preterm birth are multiple and can be due to maternal or fetal complication during pregnancy. Among these factors, there are maternal demographic factors, pregnancy history, adverse behaviors (e.g. smoking or alcohol drinking), genetic markers or intrauterine infection (Goldenberg et al., 2008; Purisch & Gyamfi-Bannerman, 2017; Harrison & Goldenberg, 2016). However, for two-thirds of preterm births there are no clear risk factors (Vogel et al., 2018).

Currently, it is well known that maternal demographic factors are an important component of preterm birth. Many researchers (Blumenshine, Egerter, Barclay, Cubbin, & Braveman, 2010; Peacock, Bland, & Anderson, 1995; L. K. Smith, Draper, Manktelow, Dorling, & Field, 2007; Thompson, Irgens, Rasmussen, & Daltveit, 2006) showed that low socio-economic status, low education and marital status (single mother) increase the risk of premature birth. However, it is difficult to explain their exact mechanisms on preterm birth.

Pregnancy characteristics and maternal health are also important considerations. Multiple-gestation pregnancies have higher risk of premature labor ; around 60% of twins are born preterm (Goldenberg et al., 2008) and in vitro fertilization increases the risk of premature birth too (McGovern, Llorens, Skurnick, Weiss, & Goldsmith, 2004). Stress, depression, body mass index and some diseases such as diabetes, asthma, hypertension or infections increase the risk of preterm birth too (Bussières et al., 2015; Goldenberg et al., 2008; Nadeau, Subramaniam, & Andrews, 2016; Simmons et al., 2010; Staneva, Bogossian, Pritchard, & Wittkowski, 2015).

Depending on the specific risk factors, there are risks for spontaneous preterm birth versus medically indicated preterm birth. Generally, preterm membrane ruptures are associated with intrauterine infection, multiple gestation or tobacco use (Simmons et al., 2010).

1.2 Consequences of preterm birth on child development

After pneumonia, medical complications due to preterm birth are the second leading cause of child death in the world (Liu et al., 2012). Decreasing gestational age is associated with increasing risk of mortality and developmental problems. In high-

income countries, around 90% of babies born after 28 weeks survive, whereas only 10% of them survive in low-income countries (Blencowe et al., 2012).

Due to the immaturity of their organs, preterm babies are prone to various neonatal complications. Most common neonatal complications associated to prematurity are at short term intraventricular cerebral, hemorrhage, hypothermia, hypoglycemia, sepsis, undernutrition; and the consequences at longer term are feeding difficulties, neurosensory difficulties and potentially cerebral palsy or cognitive deficits (Bastek et al., 2008; Purisch & Gyamfi-Bannerman, 2017; Simmons et al., 2010; Ward & Beachy, 2003). However, beside severe complications, "healthy" preterm children are nonetheless more prone to have developmental problems than full-term born children. These developmental difficulties concern all domains such as emotional and behavioral difficulties, motor skills, neurodevelopmental complication, endocrinal dysregulation or cognitive impairment (Foreman, Fielder, Minshell, Hurrion, & Sergienko, 1997; Habersaat et al., 2013; Magill-Evans, Harrison, der Zalm, & Holdgrafer, 2002; Treyvaud, Anderson, Lee, et al., 2009; Wolke & Meyer, 1999). In this section, only some of these developmental difficulties will be presented. Considering the important variation between studies of preterm gravity, age of assessment and methodology, this section will focus on outcomes of very preterm (namely moderate and severe prematurity) children and early childhood will be little discussed. Most studies concerning very preterm born children include in their participants children born less than 28 weeks of gestational age. In this manner, all studies concerning exclusively extremely preterm born children will not be take into account here.

1.2.1 Emotional and behavioral difficulties

Many meta-analysis (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Burnett et al., 2011; S. Johnson & Marlow, 2011; Somhovd, Hansen, Brok, Esbjorn, & Greisen, 2012)

reveal that preterm born children present more emotional and behavioral difficulties than their full-term peers; and this from early childhood (Arpi & Ferrari, 2013). Very preterm children have around three times higher risk presenting psychiatric disorders than full-term children (Bhutta et al., 2002; S. Johnson & Marlow, 2011; Treyvaud et al., 2013). More specifically, compared to their full-term peers, preterm born children have a higher prevalence of attention-deficit hyperactivity disorder (ADHD) (Bora, Pritchard, Moor, Austin, & Woodward, 2011; Delobel-Ayoub et al., 2009; Linnet et al., 2006) and present more internalizing problems[1] (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Bhutta et al., 2002; Burnett et al., 2011). Very preterm born adolescents aged between 11 and 20 years old have 2 times more risk than full-term adolescents to present anxiety symptoms in the clinical range (Somhovd et al., 2012).

Emotional and behavioral problems are usually associated with gestational age or birth weight; lower gestational age and birth weight increase the risk to present emotional and behavioral problems (Bora et al., 2011; Horwood, Mogridge, & Darlow, 1998; Lindström, Lindblad, & Hjern, 2009; Linnet et al., 2006; Loe, Lee, Luna, & Feldman, 2011; Pyhälä et al., 2017; Ritchie, Bora, & Woodward, 2018). Nevertheless, gestational age and birth weight do not explain heterogeneity in the degree of problems' severity. In this manner, other variables such as maternal sensitivity, severity of perinatal problems, brain anomaly or quality of mother-child interaction need to be explored in order to better understand mechanisms underlying this heterogeneity across preterm born children.

ADHD is more frequent in very preterm children and it is one of the most frequent

[1]Usually, we distinguish externalizing and internalizing problems. Externalizing problems refer to disorders like aggression and rule-breaking behaviors. They are easily observable by others. Internalizing problems concern depression, anxiety, social withdrawal, somatic complaints, attention, and thought problems. Usually, they are more difficult to be observed by others than externalizing problems.

behavioral problems in preterm born children (Brydges, Reid, Fox, & Anderson, 2012; S. Johnson, 2007). Very preterm children have five times more risk to have ADHD diagnosis than full-term children (Bora, Pritchard, Chen, Inder, & Woodward, 2014; Botting, Powls, Cooke, & Marlow, 1997). This increased risk for preterm born children might be partly explained by cerebral tissue loss and possibly misdevelopment, without visible lesions, such as white matter injury (Bora et al., 2014).

Concerning internalizing problems, Faure et al. (2017) show that maternal sensitivity[2] during early childhood is protective to internalizing problems at age of 11. Their study shows that preterm born children present more internalizing problems than their full-term peers. However, preterm born children who have a sensitive mother have fewer internalizing problems than preterm born children who have less sensitive mother. Moreover, the severity of perinatal problems seems to influence the severity of internalizing problems. Dimitrova et al. (2018) showed that at 11 years old, very preterm born children with high perinatal risk present more internalizing problems than very preterm born children with low perinatal risk. Moreover, intelligent quotient (IQ) seems to mediate the association between very preterm birth and the presence of emotional difficulties and social skills in adolescence; lower IQ increasing emotional and social problems (Bayless, Pit-ten Cate, & Stevenson, 2008). Another study (Loe et al., 2011) shows the influence of IQ on general behavioral problems and on attentional problems; however, IQ does not contribute to anxiety or depression symptoms. Furthermore, Hack et al. (2005) show that IQ score, family expressiveness and score in internalizing problems at age of 8 years old are significant predictors of internalizing symptoms at 20 years old.

Very preterm born adolescents are described by their parents as having more

[2]Maternal sensitivity is the ability of the mother to perceive and respond adequately to her child's signals. The maternal sensitivity is considered as an important predictor of secure attachment (Shin, Park, Ryu, & Seomun, 2008).

emotional and behavioral problems and being less competent than full-term children (Dahl et al., 2006; Hall & Wolke, 2012). Nevertheless, when these difficulties are measured directly by asking adolescents, they perceive less problems than their full-term peers and feel similar competences than them (Dahl et al., 2006). As such, results concerning adolescent should be considered carefully.

This higher risk to present emotional difficulties persists into early adulthood (Burnett et al., 2011; Dahl et al., 2006; Lindström et al., 2009). Preterm born adults report more internalizing problems and more avoidant personality problems (Pyhälä et al., 2017). Very preterm born young adults have 1.68 times more risk to present a psychiatric disorder compared to full-term born adults and this risk ratio is linked with preterm categories (Lindström et al., 2009).

1.2.2 Academic achievement and cognition development

Despite the absence of neurodevelopmental impairment, preterm born children perform less well in school and they have more cognitive impairments than full-term born children (Aarnoudse-Moens et al., 2009; P. Anderson, 2014; Barre, Morgan, Doyle, & Anderson, 2011; Bhutta et al., 2002; S. Johnson, 2007; Kerr-Wilson, Mackay, Smith, & Pell, 2011; Pritchard et al., 2009; Saigal & Doyle, 2008; Twilhaar, de Kieviet, Aarnoudse-Moens, van Elburg, & Oosterlaan, 2018) and these impairments persist with age (Brydges et al., 2018). In this section, preterm difficulties concerning academic achievement, intelligence, executive functions and language competencies will be briefly presented.

Considering the heterogeneity of tests measuring learning difficulties, it is difficult to have a clear conclusion about very preterm born children's academic achievement. However, in general, very preterm born children have lower scores in mathematics, reading and spelling than their full-term peers (Aarnoudse-Moens, Oosterlaan, Duivenvoorden, van Goudoever, & Weisglas-Kuperus, 2011; Aarnoudse-Moens et al., 2009). Preterm

born children attended more special education (Aarnoudse-Moens et al., 2011; Ross, Lipper, & Auld, 1991), and 25% of preterm born children have to repeat a grade between 4 and 12 years old; in comparison, only 2.3% of full-term born children repeat a grade (Aarnoudse-Moens et al., 2011). Some of the learning difficulties are more inconspicuous and seem to be complex to detect. With transition to school and increasing age, slight delays become more apparent. Woodward, Clark, Bora, and Inder (2012) observed that between the ages of 4 and 6, the proportion of preterm born children with cognitive impairment increases. Preterm born children are 2-3 times more detected by their teacher as having lower school performances than average (Pritchard et al., 2009). Simple word reading difficulties seem to disappear with age, but lower level in complex word reading are maintained (Aarnoudse-Moens et al., 2011). Barre et al. (2011) conducted a meta-analysis concerning preterm born children aged from 2 to 12 years old and show that preterm born children present difficulties in expressive and receptive language. The disadvantage of learning difficulties seems to persist in early adulthood. At 27-29 years old, very preterm born young adults have lower educational level and lower incomes than full-term young adults (Mathiasen, Hansen, Nybo Anderson, & Greisen, 2009).

Executive functions concern all cognitive functions used for planned tasks such as shifting, working memory, processing speed or inhibition. Executive functions are associated with learning competences and intelligence (Brydges et al., 2012; St Clair-Thompson & Gathercole, 2006). Specifically, at 9-10 years old, processing speed and working memory are important factors explaining lower academic achievement in very preterm born children (Mulder, Pitchford, & Marlow, 2010; Rose, Feldman, & Jankowski, 2011). Very preterm born children from 4 to 17 years old are more prone to present executive function difficulties than full-term born children, and this impairment in executive function is linked with gestational age, birth weight and maternal education (Brydges et al., 2018; Luu, Ment, Allan, Schneider, & Vohr, 2011; Wolfe, Vannatta, Nelin, & Yeates, 2015). Moreover, in very preterm born children, executive function difficulties are associated with white matter abnormalities at term equivalent age (i.e.

39-41 weeks of gestation) (Woodward et al., 2012). Among full-term born adolescents, 1-3% present important impairments in executive functions, while in very preterm born adolescents this prevalence increases to 6-18% (Luu et al., 2011). Executive function impairments persist into young adulthood (Eryigit Madzwamuse, Baumann, Jaekel, Bartmann, & Wolke, 2015; Nosarti et al., 2007).

Many studies show that preterm born children have lower IQ scores than their full-term peers, although their IQ scores are in the normal range (Bhutta et al., 2002; S. Johnson, 2007; Kerr-Wilson et al., 2011). This difference persists into adulthood (Breeman, Jaekel, Baumann, Bartmann, & Wolke, 2017; Eryigit Madzwamuse et al., 2015). Considering the improvement of medical care in NICU and the extension of knowledge concerning the impact of preterm birth during past 25 years, the idea that contemporary preterm born children have less cognitive impairment than previous generations was suggested. However, P. Anderson (2014) shows that there is not impact of birth year on IQ score. Preterm born children's IQ is associated to gestational age; increasing gestational age is associated to higher IQ score (P. Anderson, 2014; Bhutta et al., 2002). On average, moderate preterm born (between 31 and 32 weeks of GA) have 8.4 points lower score, severe preterm born children (between 28 and 31 weeks of GA) have a 11.4 points lower and extreme preterm born children (less than 28 weeks of GA) have 13.9 points lower score compared to their full-term peers (P. Anderson, 2014). Furthermore, bigger inter-individual heterogeneity is observed in cognitive development of preterm born children than full-term children (Lundequist, Böhm, & Smedler, 2013). As emotional and behavioral difficulties, many studies explain cognitive impairment and heterogeneity by gestational age and birth weight. Also, parents' socio-economic status (SES) appears to be an important predictor to explain these difficulties (Wong & Edwards, 2013). Lower SES, lower maternal education and being born to a single mother increase the risk of neurocognitive delay (Weisglas-Kuperus et al., 2009; Woodward et al., 2014).

With technological improvement, studies concerning brain lesions, abnormal brain development and brain maturation of preterm babies have increased; and studies associating brain injuries or development and IQ were conducted. Preterm birth may be associated with risk of brain injury (Schneider, Vasung, Truttmann, & Huppi, 2014). White matter injury impacts child's cognitive, motor and emotional development (Schneider & Miller, 2019). Woodward et al. (2012) observed that at 4 and 6 years old, very preterm born children with white matter abnormality have more neurocognitive impairment than very preterm born children without white matter abnormalities. Furthermore, preterm birth may disturb brain development and maturation. Preterm birth is associated with delay in microstructural development of the cortical grey matter (Vinall et al., 2013). Magnetic resonance imaging (MRI) scans of 8 years old children reveal that preterm born children have smaller volume than their full-term peers in cortex, grey and white matter, ventricles (basal ganglia, amygdala, hippocampus and corpus callosum) and larger volume of ventricles (Peterson et al., 2000). The brain volume is associated with perinatal variables such as gestational age or Apgar score[3]. Furthermore, total, verbal and performance IQ scores are associated to brain volume, especially to sensorimotor and midtemporal brain regions (Peterson et al., 2000).

1.2.3 Comorbidity

Developmental impairments due to very preterm birth cannot be explained only by gestational age and birth weight. Despite important number of studies, mechanisms underlying the emergence of developmental difficulties in very preterm born children

[3]Apgar score is a method evaluating clinical state of newborn immediately after birth. Apgar score includes five components: skin's color, heart rate, reflexes, muscles tone and respiration. The score ranges from 0 to 10. Newborns without complications usually have a score of 7 and above (American Academy of Pediatrics, American College of Obstetricians and Gynecologists, Committee on Obstetric Practice, & others, 2006).

are not clearly understood. Most of behavioral and emotional difficulties are associated to other difficulties (Crump, Winkleby, Sundquist, & Sundquist, 2019; S. Johnson et al., 2016; Woodward et al., 2009), especially cognitive impairment (S. Johnson & Marlow, 2011). Forty-five percent of preterm born adults have comorbidities, while 37% of full-term born are concerned (Crump et al., 2019). Moreover, proportions of people with comorbidity increase with decreasing gestational age; 88% of extremely preterm born adults have comorbidities. Extremely preterm born children without neurosensory impairment, learning difficulties have in most of cases comorbidity with impairment in executive function, visuo-spatial and sensori-motor competencies (S. Johnson et al., 2016). In this manner, an integrative model taking into account biological and environmental factors is likely important (Montagna & Nosarti, 2016). For example, Loe et al. (2011) observed that preterm born child's IQ has a mediator effect on child's attentional problems. Another study (Chau et al., 2019) reveals that invasive procedures during NICU stay reduce brain volumes, and smaller brain volume links with poorer verbal comprehension.

One factor that impacts very preterm born children's difficulties has not been described: the influence of stress due to the preterm birth. Child's perinatal risk and mother distress can have a deleterious effect on the mother-child interaction, which in turn may impact the infant's outcomes such as behavioral symptoms and social development (Forcada-Guex, Pierrehumbert, Borghini, Moessinger, & Muller-Nix, 2006; Müller Nix et al., 2004; Pierrehumbert, Nicole, Muller-Nix, Forcada-Guex, & Ansermet, 2003). In this next section, the stress of mother and baby due to preterm birth will be exposed and the impact of this stress on child's development will be described.

1.3 Preterm birth: a stressful event for mother and newborn

In next section, the maternal stress and baby stress due to premature birth and NICU stay will be presented. Moreover, the impact of this stress on very preterm born children's development will be discussed.

1.3.1 Maternal stress

For every woman childbirth is a complex stressful event with physical and emotional impacts. The mother lives a personal transformation and may feel insecure about her parenting abilities (Nelson, 2003). The maternal transition begins early in the pregnancy and persists until many months after birth; typically until the mother feels that she controls the situation (Darvill, Skirton, & Farrand, 2010). In the case of preterm birth, this maternal stress is amplified. The premature birth disturbs the transition to parenthood and the building representation of self as parent (Spinelli et al., 2016). Because of medical care, presence of medical staff and the absence of physical contact, the mother cannot be an "active mother"; she cannot spontaneously interact with her preterm baby and take care of him. This can make the mother feel deprived of her parental role (Lupton & Fenwick, 2001). Mothers may feel disconnected from their baby and it can affect negatively the mother-child attachment (Feldman, Weller, Leckman, Kuint, & Eidelman, 1999; Müller Nix et al., 2004). The possible loss of the neonates tends mothers to have less bonding behaviors such as affiliative behaviors, lower attachment representation and less compulsive checking than mothers of full-term born babies (Feldman et al., 1999). Furthermore, the mother can feel guilty because she was not able to carry the baby to term (Spinelli et al., 2016).

After a preterm birth, parents must cope with the unfamiliar and high technological NICU environment, the distress related to the child's medical condition and survival, the separation from the baby and the inability to protect the baby from pain (Lau & Morse, 2003; Obeidat, Bond, & Callister, 2009; Tooten et al., 2013; Woodward et al., 2014). In this manner, the baby's NICU stay is challenging and stressful for parents, especially for mothers (Carter, Mulder, & Darlow, 2007; Ionio et al., 2016). Maternal stress due to baby's NICU stay is a risk factor to mother's negative feeling concerning her parental competencies (Pisoni et al., 2018). Mothers of preterm born babies present more psychological distress such as stress, worry, depression, anxiety and obsessive-compulsive behavior than mothers of full-term born babies (Garel, Dardennes, & Blondel, 2007; Ionio et al., 2016; Kersting et al., 2004; Miles, Holditch-Davis, Schwartz, & Scher, 2007; Padden & Glenn, 1997; Pisoni et al., 2019; Singer et al., 1999; Woodward et al., 2014). The risk of maternal psychopathology increases with infant's perinatal severity (Pisoni et al., 2018). During NICU stay, 85% of preterm born baby's mothers present depressive symptoms and this prevalence decreases after discharge (Pisoni et al., 2019). Mothers with depressive symptoms have less affiliative behavior and attachment representations (Feldman et al., 1999). At the child's age of 2 years, 26% of very preterm born children's parents report clinically significant mental health problems compared to full-term born children's parents of which 12% are concerned (Treyvaud, Anderson, Lee, et al., 2009).

The preterm birth and newborn's hospitalization can be traumatic for the mother. During a newborn's hospitalization and after discharge, mothers may present post-traumatic stress disorder (PTSD) symptoms such as avoidance, intrusive thoughts and increased arousal (see appendix A.1 for detailed criteria of PTSD) (Feeley et al., 2011; Ghorbani, Dolatian, Shams, Alavi-Majd, & Tavakolian, 2014). Seeing their infant in pain during the NICU stay is a stressful experience for mothers (Gale, Franck, Kools, & Lynch, 2004), and the more the neonate undergoes invasive procedure the more the mother may present PTSD's symptoms (Vinall, Noel, Disher, Caddell, & Campbell-Yeo,

2018). Around 50% of mothers have perinatal PTSD linked to their child's premature birth (Suttora, Spinelli, & Monzani, 2014). In their study, Holditch-Davis, Bartlett, Blickman, and Miles (2003) reported that at infant's 6 months (corrected age[4]) all mothers of preterm infants present at least one PTSD symptom and more than 50% of them have three symptoms. Symptoms do not decrease 14 months after preterm birth (Kersting et al., 2004). Moreover, mother's PTSD symptoms increase with child's prematurity gravity (Feeley et al., 2011; Pierrehumbert et al., 2003; Suttora et al., 2014).

1.3.2 Impact of maternal stress on very preterm born child's development

An adapted response to a child's signal is important to scaffold a child's development, such as self-regulation or social interaction (Feldman, 2007). Maternal PTSD symptoms and depression impact negatively the quality of mother-child interactions (Forcada-Guex et al., 2006; Müller Nix et al., 2004). Studies concerning the impact of maternal PTSD on a child's developmental outcomes are limited, and the heterogeneity of instruments measuring PTSD symptoms and children's outcomes makes difficult to formulate a general conclusion (Cook, Ayers, & Horsch, 2018).

Some studies (Bozkurt et al., 2017; Forcada-Guex et al., 2006; Singer et al., 1999) highlight the impact of maternal distress on the mother-child relationship and on child development. Ionio et al. (2017) showed that, at 3 months corrected age, mothers of preterm born babies are more distant and more intrusive during interaction with

[4]The corrected age is the age of the child from the expected date of birth. It is calculated by subtracting weeks of prematurity to the baby's chronological age. The corrected age is used for developmental assessment and it fits the preterm infant as a full-term born infant. The corrected age is used until child's 2-3 years.

their babies than the full-term babies' mothers. At infant's 6 months (corrected age), mothers of infants with high risk of perinatal problems and with PTSD symptoms are less sensitive and more controlling than mothers of full-term born infants. However, this difference seems to disappear at child's 12 months (Müller Nix et al., 2004). Maternal PTSD symptoms seem to affect children's cognitive outcomes. Parfitt, Pike, and Ayers (2014) showed that maternal PTSD is associated with developmental quotient at 17 months; however, this study concerned healthy and full-term born infants.

1.3.3 Newborn's stress

Premature birth and NICU stay are stressful for the newborn. The preterm newborn has to cope with the extrauterine world despite that his organs and physiologic systems are immature. At birth, the premature newborn is not ready to assume, for example, respiratory regulation or thermoregulation (Blackburn, 1998). Furthermore, the NICU environment itself – with machine noise, unpredictable sounds/alarms, light variability or temperature variations – is a stressful environment. Preterm newborns are not ready to manage the overwhelming sensory information of this extrauterine environment, and this milieu affects the neonates negatively by increasing heart and respiratory rates, and decreasing oxygen saturation (Blackburn, 1998; Bremmer, Byers, & Kiehl, 2003; A. N. Johnson, 2001; Nair, Gupta, & Jatana, 2003; Wachman & Lahav, 2011).

Considering that NICU is operated 24 hours per day, neonates are usually exposed to constant light despite lighting systems' adaptation. Without diurnal/nocturne rhythm, light in NICU may affect baby's development and can delay hospital discharge (Blackburn, 1998; Vásquez-Ruiz et al., 2014). Vásquez-Ruiz et al. (2014) provided a rhythmic cycle of light/dark to neonates. Their study showed that with a regular cycle of light, neonates have more stable heart rates, better concentration of oxygen, better circadian rhythm with a better cycle of melatonin concentration and faster weight gain.

Neonates in the NICU are also exposed to noise (e.g. telephones, alarms, incubator doors or staff conversation) (Bremmer et al., 2003). Noise in the NICU exceeds the recommended volume of 45 dB (S. W. Smith, Ortmann, & Clark, 2018). In the same way as light, noise affects negatively the physiologic stability and neurodevelopment of preterm born babies (Wachman & Lahav, 2011). Despite the deleterious impact of noise on neonates' development, the number of studies concerning this problematic remains poor and it is difficult to have clear recommendations to reduce NICU's noise (Almadhoob & Ohlsson, 2015). During the last decades, however, there is an important awareness concerning neonates' exposure to environmental stress during their stay in the NICU. Currently, interventions to reduce neonates' stress are increasing (Aita, Johnston, Goulet, Oberlander, & Snider, 2012; Bremmer et al., 2003; Holsti, MacLean, Oberlander, Synnes, & Brant, 2019; Kennedy et al., 2001; Khalesi, Khosravi, Ranjbar, Godarzi, & Karimi, 2017; Vásquez-Ruiz et al., 2014; Wachman & Lahav, 2011), but not all of them seem to be effective. The wearing of goggles and earmuffs for 4 hours per day to reduce light and noise - and presumably at the same time the stress - does not improve the physiological stability and does not reduce pain responses during procedures (Aita, Goulet, Oberlander, Snider, & Johnston, 2015; Aita et al., 2012). Another study (Kennedy et al., 2001) similarly showed the ineffectiveness of goggles. Goggles were worn from birth to 31 weeks' postmenstrual age to reduce light. The neonates with goggles had neither greater weight gain nor shorter hospital stays than neonates without goggles. In this manner, light reduction with goggles does not (yet) seem to be an effective way to improve the comfort of the NICU stay. According to Aita et al. (2012), the ineffectiveness of this practice may be explained by the fact that reducing visual and auditory information input may enhance responsivity of other sensory systems, such as the tactile system, and therefore does not make handling less stressful for neonates.

Kangaroo care[5] (KC) is an effective practice to improve neonates' physiological

[5]KC consists to a skin-to-skin contact between the baby and parent. This practice was developed

stability and reduces the risk of mortality (Conde-Agudelo & Diaz-Rossello, 2016). With KC, preterm born babies' stress and risk of infection are reduced and KC has positive effects on heart and respiratory rates, and oxygen saturation and improves sleep organization, weight gain (Boundy et al., 2016; Dodd, 2005; Johnston et al., 2003; Conde-Agudelo & Diaz-Rossello, 2016). Moreover, benefits of KC are observed in early childhood biopsychosocial outcomes (Akbari et al., 2018). Despite the important benefits of KC, parent's time to practice KC is limited. In this manner, machines imitating breathing motion and heartbeats' sounds or human skin were created. While they are not as efficient as real skin-to-skin contact to reduce neonates' heart's rate (Kommers et al., 2018), they do seem effective in reducing pain reaction (Holsti et al., 2019).

Family-centered care (FCC) improves neonates development too. The main purpose of FCC is that parents should have an active role in neonates' care (Gooding et al., 2011; Ortenstrand et al., 2010). In FCC, there is an important collaboration between parents and medical staff and parents can stay 24 hours/day in NICU (Gooding et al., 2011). Visiting hours are flexible as possible to all family members and activities supporting family to cope with the stress due to baby's stay in NICU are offered (for more details, see Gooding et al. (2011)). Studies (Gooding et al., 2011; Ortenstrand et al., 2010; Yu et al., 2017) showed that FCC decrease length of hospital stay and neonate's neurobehavioral performances.

Another stress factor is the invasive medical procedures such as artificial ventilation, artificial feeding, heel lances, and nurses' manipulations (Barker & Rutter, 1995; Grunau, Holsti, & Peters, 2006). However, assessment of pain is difficult in neonates. Maitre, Stark, et al. (2017) showed that cortical responses to painful procedures are not systematically associated to cries and grimaces. Behavioral and physiological information such as cries, facial expressions and heart rates are not sufficient to evaluate painful experi-

in Colombia in 1978 (Charpak et al., 2005).

ences of neonates (Relland, Gehred, & Maitre, 2019). The stress due to repeated painful neonatal procedures (pain-related stress) alters physiologic mechanisms and impacts negatively the child's developmental outcomes. More precisely, the neonatal pain-related stress alters brain responses and microstructures, the Hypothalamic-Pituitary-Adrenal (HPA) axis and behavioral neurodevelopment of the very preterm born children (Grunau et al., 2005; Maitre, Key, et al., 2017; Vinall & Grunau, 2014).

Stress and HPA axis alteration

The HPA axis is the hormonal system regulating stress by releasing cortisol (Graham, Heim, Goodman, Miller, & Nemeroff, 1999). Studies on animals and humans (Anand, Coskun, Thrivikraman, Nemeroff, & Plotsky, 1999; Grunau et al., 2005; Grunau, Weinberg, & Whitfield, 2004) show that a chronic exposure to stress alters the neuroendocrinal system and the ability to cope with stressful situations. Due to their immature physiologic system, premature babies are particularly vulnerable to pain and stress, and their HPA axis system is altered (Anand, 1998). In early childhood, the HPA axis is altered in very preterm born children. At six months corrected age, Habersaat et al. (2013) showed that very preterm born infants have lower diurnal cortisol levels than full-term infants. This difference seems to decrease in later childhood (7-14 years old); preterm born children's diurnal cortisol curve is more similar to their full-term peers (Brummelte et al., 2015; Buske-Kirschbaum et al., 2007; Ruys et al., 2017). However, preterm born children have a slightly higher level of cortisol in the morning (Buske-Kirschbaum et al., 2007) or bedtime depending of studies (Brummelte et al., 2015). The consequence of the number of invasive procedures on alteration of HPA axis was also studied, but the results do not appear consistent and vary with age. Indeed, Grunau et al. (2005) show that invasive procedures are associated with lower cortisol responses in extremely preterm born neonates, but not for very preterm neonates. In contrast, Brummelte et al. (2015) revealed that the number of painful

medical procedures in the NICU impacts cortisol level at 7 years old; preterm born children who had more medical procedures have lower cortisol levels in the morning at 7 years old, and this concerns especially boys.

Impact of HPA axis alteration on child's development

The dysregulation of the neuroendocrine system (HPA axis and corticotropin-releasing factor[6]) impacts the emergence of psychiatric disorders such as depression or anxiety (Arborelius, Owens, Plotsky, & Nemeroff, 1999); disorders that preterm born children are more prone to have during their life. At 8 and 18 months of corrected age, a higher number of skin-breaking procedures and higher number of days on mechanical ventilation are associated with lower cognitive and psychomotor outcomes (Grunau et al., 2009). At 18 months corrected age, alteration of cortisol level links with anxiety and depressive symptoms in very preterm born children (Brummelte et al., 2011). Also, preterm children aged between 18 and 60 months who have an increased cortisol reactivity to stress have more internalizing and attention problems (Bagner, Sheinkopf, Vohr, & Lester, 2010). Moreover, the impact of neuroendocrinal alteration on child's development persists in later childhood. In preterm born children aged 7 years old, cortisol reactivity to stress is positively correlated to child's thought problems and negatively correlated to child's attention problems. More interestingly, these correlations are not present in full-term born children (Brummelte et al., 2015). Ranger, Synnes, Vinall, and Grunau (2014) showed that medical pain and morphine exposure during NICU stay and parenting stress at child's 7 years contribute to the emergence of internalizing problems in very preterm born children.

[6]The corticotropin-releasing factor is a hormone secreted by the hypothalamus involved in the stress response.

Impact of pain-related stress on brain development

Pain-related stress alters the preterm born child's brain at many levels too. Skin breaking procedures during NICU stay reduce preterm born neonate's white matter and subcortical grey matter maturation (Brummelte et al., 2012). At term equivalent age, preterm babies have a smaller brain volume in frontal and parietal regions, and the degree of alteration is linked to increased exposure to pain-related stress (G. C. Smith et al., 2011). Painful procedures, glucose exposure to manage baby's pain during NICU, and newborns' gender impact early brain development too. Schneider et al. (2018) observed that exposure to painful procedures and glucose is linked to slower growth of the thalamus, basal ganglia and total brain volume, and girls are more impacted than boys. Furthermore, this exposure appears to be linked with poorer neurodevelopmental outcomes at 18 months (corrected age). Later in childhood, alteration in brain structure is still present in preterm born children. At 7 years old, the cortex thickness decreases with the increase of medical procedures during NICU stay. Specifically, frontal, parietal and temporal regions are impacted (Ranger et al., 2013). Chau et al. (2019) show that higher exposure to pain-related stress in NICU is associated to smaller volume in the limbic system (region of hippocampus, amygdala and thalamus). In turn, the smaller limbic system is linked to poorer cognitive performance and increased externalizing behavior problems in preterm born children aged of 8 years old.

1.4 Summary and research question

Preterm birth is a stressful event for both parents and the preterm born child, and can have long-term consequences. Several months later, mothers may present PTSD symptoms and/or depression while preterm born children present a large spectrum of developmental difficulties. The severity of preterm born children's difficulties has an

important heterogeneity. This is in part explained by gestational age and birth weight; the more the child is born premature, the more is his risk to have developmental problems. However, these two factors are not sufficient to explain developmental difficulties, and other factors need to be considered to better understand mechanisms underlying these difficulties. In the Introduction, we focused on emotional, behavioral, academic and cognitive difficulties. Most of studies considered only gestational age and/or birth weight. The impact of maternal and child's pain-related stress were briefly described. Most of the studies considering the impact of maternal emotional distress concern early childhood. Studies concerning later impact, such as early adolescent, remain few (Breeman et al., 2017; Ranger et al., 2013; Treyvaud et al., 2016). Adolescence is an important period in the life with rapid brain development and important physiological and psychosocial changes (Viner et al., 2015). In this manner, adolescence may be a vulnerable period exacerbating developmental difficulties.

The current thesis examined other factors than gestational age and birth weight to explain the lower IQ of very preterm born children. More specifically, the aim of this thesis is to consider the impact of child's perinatal risk factors and the mother's PTSD symptoms due to the premature birth of the child on child's IQ at age of eleven.

Chapter 2

Methods

2.1 Context of the study

This research was financed by the Swiss National Science Foundation[1] and the National Centre of Competence in Research (NCCR) Synapsy. The NCCR Synapsy brings together scientists from the University of Geneva, Lausanne and Basel, EPFL, the Friedrich Miescher Institute for Biomedical Research and psychiatry departments of University Hospital of Lausanne and Geneva. The purpose of NCCR Synapsy is to better understand the biological basis of psychiatric disorders and their origin, and to improve the quality of life of patients.

The NCCR Synapsy is composed of two axis of research – the genetic factors and the environmental factors – and five work packages: the 22q11 Deletion Syndrome, Biomarkers of Early Psychosis, Autism Spectrum Disorder, Developmental Stress, and

[1]SNF Grants # 32-49712.96 "Parental representations and outcomes of prematurity: a socio-emotional and neuro-developmental approach" and # 325100-120334 "Behavioural and emotional problems in 10-year-old children born premature".

Mood Disorders.

The current study is part of the Developmental Stress Work Package that studies how the severe stress due to significant adverse life events impacts individual development from birth to adulthood.

In the University Service of Child and Adolescent Psychiatry of the University Hospital of Lausanne, two cohorts of preterm born children were followed. The first one (Cohort I) between 1998 and 2009, and the second one (Cohort II) between 2005 and 2019. The main purpose of these studies was to better understand the neurodevelopmental and socio-emotional development of very preterm born children. More specifically, the aim of the Cohort I study was to better understand the effect of maternal psychological distress due to a preterm birth, the impact of the preterm birth on the mother-child relationship and consequences on the child's development. In the Cohort II study, the main aim was to study the impact of preterm birth on endocrinal system and the impact of an intervention program on the mother-infant relationship.

The present work is part of the Cohort I study and focused on the impact of PTSD symptoms and perinatal risk gravity on child's cognitive development.

2.2 Type of study

This study is a clinical cohort study. The study is composed of two groups. The first one is the "very preterm group" (VPT group). It is composed of dyads of mothers and their preterm born child. The second group is the "full-term group" (FT group). It is composed of dyads of mothers and their full-term born child.

Follow-up assessments were conducted during the neonatal period, at child's 6 months of age (corrected age for preterm born infants), at child's 18 months of age

(corrected age for preterm born infants), and when the child was 11 years old. The participants partook in the study between 1998 and 2009.

2.3 Hypothesis of the study

Preterm birth is a stressful event for parents and preterm born child, and it may have long-term consequences on child's development. Most of the studies explain cognitive difficulties of preterm born children by gestational age and birth weight. However, other factors such as pain-related stress, brain development delay or mother mental well-being may be associated with child's cognitive difficulties. The aim of this study was to see if maternal PTSD symptoms due to birth and child's perinatal problems' gravity affect IQ score of preterm born children, as well as full-term born children, at age of 11. More specifically, we expected that the gravity of the child's perinatal risk and the number/intensity of the mother's PTSD symptoms due to very preterm birth affect negatively the child's intelligence abilities at early adolescence.

2.4 Participants

2.4.1 Very Preterm group

All infants born at 33 weeks or less GA between December 1997 and January 1999, hospitalized in the NICU of the University Hospital Center of Lausanne were considered for inclusion in the VPT group. Infants with malformation or chromosomal abnormalities and parents with psychiatric illness, drug abuse or lack of fluency in French were excluded. One hundred and five families were eligible to participate. Among them, 20 refused to participate, 12 infants died, and 4 infants were excluded for developmental problems and visual impairment (i.e. strabismus) at 6 months of age (corrected age). At 18 months

of age (corrected age), the remaining 69 children were met. Between 18 months of age and the 11-year follow-up, 32 participants dropped out (e.g. refused to participate or were unreachable). At the 11-year follow-up, three participants were excluded due to missing data, and one child was excluded for neuromotor disability. Finally, 33 children without any severe health problems composed the VPT group (Figure 2.1).

2.4.2 Full-term group (control group)

Healthy full-term infants and their mothers (GA > 37 weeks) were recruited between December 1997 and January 1999 from the maternity ward of the same university hospital centre as the VPT group . Exclusion criteria were: difficulties during pregnancy or delivery, infant with chromosomal abnormalities or malformation, and a parent with psychiatric illness, drug abuse or lack of fluency in French. Around 100 families were contacted. Among them, 32 families accepted to participate. Between the assessment at 18 months of age and the 11-year follow-up, 10 participants dropped out. One participant was excluded for missing data. At the 11-year follow-up, 21 children comprised the FT group (Figure 2.1).

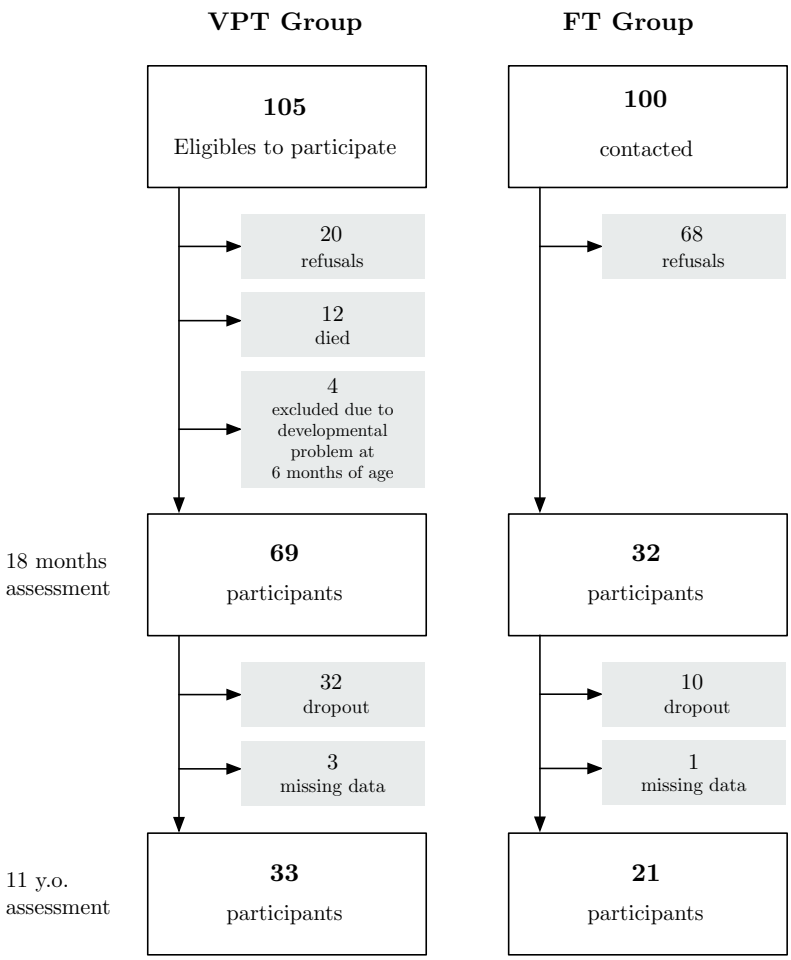

Figure 2.1 – Enrolment of participants

2.4.3 Group's characteristics

Demographic and neonatal characteristics of the two groups and dropout are presented in Table 2.1. Concerning demographic data, no difference is observed between VPT and FT group in child's gender, nationality, mother's marital status and mother's age at childbirth. However, a difference is observed for the socio-economic status (SES); mothers of VPT group have lower SES score than mothers of FT group. Concerning neonatal data, expected differences are observed: VPT children have lower gestational age, lower birth weight, lower head circumference, and the mothers present more often

multiple births than the FT group.

Concerning participant and dropout between assessments at 18 months-old and 11 years-old, no difference is observed for FT group. However, in the VPT group, results show difference in SES. In the dropout group the SES score is lower than the participants group. Furthermore, we observe differences in the mother age at child's birth (lower for dropout group) and in the child's birth weight (lower weight in dropout group).

2.5 Procedure

Families were recruited during the NICU stay for the VPT group and during the stay in the maternity ward for the FT group. The mother was informed about the study and asked to sign a consent form for participation in the study. Sociodemographic data and data regarding the infant's perinatal problems were collected during the hospitalization period. During the study, every family had a referent person from the research team. To fix every appointment, a letter was sent to the family containing information about the next assessment. Then, the referent person called the family to fix the date of the assessment. The referent person was present during each evaluation. At the child's age of 6 months, infant's development, mother's representation of her child, mother's psychological state, and mother-child interaction were assessed. At around 18 months (FT: $M = 18.35$ months, $SD = 0.40$; VPT: $M = 18.37$ months (corrected age), $SD = 0.52$), the assessment was similar, and evaluation of mother PTSD's symptoms were evaluated. At the 11-year assessment (FT: $M = 11.25$ y.o., $SD = 0.17$; VPT: $M = 11.47$ y.o., $SD = 0.27$), the child participated in the assessment of their intellectual abilities, socio-emotional development and a semi-structural interview. Mothers filled questionnaires and participated in a semi-structural interview. For the 11-year follow-up,

Table 2.1 – Demographic and perinatal data

	Included			Dropout			
	1. Full-term $n = 21$	2. Very Preterm $n = 33$	Comparison	3. Full-term $n = 10$	4. Very Preterm $n = 33$	Dropout analysis	
Socio-demographic	n (%)	n (%)	χ_{1-2}	n (%)	n (%)	χ_{1-3}	χ_{2-4}
Gender (girls)	13 (61.9)	18 (54.5)	0.28	4 (40.0)	12 (36.4)	1.56	2.20
Nationality (Swiss)	17 (81.0)	22 (66.70)	1.83	6 (60.0)	16 (48.5)	4.07	7.13
Parental Status (married)	14 (66.7)	26 (78.9)	.98	8 (80.0)	29 (87.9)	1.06	3.16
	M (SD)	M (SD)	t_{1-2}	M (SD)	M (SD)	t_{1-3}	t_{2-4}
SES	2.91 (0.58)	2.55 (0.53)	2.32*	2.80 (0.97)	2.19 (0.60)	-.48	-2.59*
Mother's age at child's birth (yrs)	32.05 (4.31)	32.18 (4.61)	-0.11	32.10 (4.75)	30.12 (4.57)	.06	-1.83†
Neonatal							
Gestational Age (wks)	40.00 (1.29)	30.53 (2.11)	20.48**	40.00 (0.71)	30.32 (2.00)	.031	-.41
Birth weight (gr)	3305.24 (529.18)	1452.88 (382.85)	13.89**	3272.00 (343.86)	1273.33 (384.89)	-.25	-1.90†
Head circumference at birth (cm)	34.56 (0.99)	28.07 (2.39)	13.49**	34.27 (1.97)	27.22 (2.53)	-.51	-1.35
Multiple birth (singletons, n (%))	21 (100.0)	23 (69.7)	7.81*	10 (100.0)	25 (75.8)	-	1.17

SES: Socio-Economic Status. † $p < 0.1$; * $p < 0.05$; ** $p < 0.01$

a new consent form was signed by the mother for her child and for her own participation in the study.

All the procedures were performed in accordance with the relevant guidelines and regulations, and were evaluated and approved by the Vaudois Ethics Committee for research in humans.

2.6 Measures

The present work concerns only a small part of the Cohort I study. In this manner, only measures used as part of this thesis work will be presented. Data collected at the child's age of 6 months were not used in this work.

2.6.1 Measures during the neonatal period

During the neonatal period, socio-demographic data such as the child's gender, nationality, and the mother's age were obtained from participants. An adapted version of the Hollingshead Four Factor Index of Socioeconomic Status (Pierrehumbert, Ramstein, Karmaniola, & Halfon, 1996) was used to assess parent's socioeconomic status. For each parent the parents' education level score and work position score is obtained. Scores are rated on a 4-point scale; higher score means higher SES (see appendix A.2 for detailed coding categories). For each parent, a total score combining level of education and professional level is calculated. Finally, a SES score is calculated by averaging parents' scores.

The gravity of the infant's perinatal problems was evaluated with the Perinatal Risk Inventory (PERI) (Schemer & Sexton, 1991). The PERI is an 18-item inventory assessing perinatal factors such as Apgar scores, gestational age, infant's head circumference,

electroencephalogram, the duration of ventilation, presence or absence of sepsis and/or meningitis, and presence or absence of congenital infection (for details see appendix A.3). Each item's range is from 0 to 3 on an ordinal scale. The total score is obtained by summing all items. Higher scores means higher perinatal risk. In this study, a single nurse from the NICU completed the PERI calculation at the child's discharge from the hospital.

2.6.2 Measures at child's 18 months of age

The French version of the Perinatal Posttraumatic stress Questionnaire (PPQ) (Pierrehumbert et al., 2004; Quinnell & Hynan, 1999) was used to assess the mother's PTSD symptoms associated with the child's birth. The PPQ assesses maternal PTSD symptoms that appeared since the child's birth and persisted at least one month, during the 6 months after birth. It is a 14-item questionnaire and it is dichotomously scored. The questionnaire is based on DSM-IV (American Psychiatric Association, 1994) criteria of PTSD. The clinical threshold is fixed at 5 points – score under 6 means no PTSD (Pierrehumbert et al., 2004). The instruction to the respondent is to remember if they experienced the described symptoms – i.e., Did you have several bad dreams of giving birth or of your baby's hospital stay?, Were you more irritable or angry with other than usual? (for details see appendix A.4).

2.6.3 Measures at child's age of 11 years old

The child's intelligence abilities were measured at 11 years using the fourth edition of Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2005). This test was choose because it is largely used in the world for cognitive assessment. The administration takes 65 to 80 minutes. The test provides five standardized scores ($M = 100$; $SD = 15$): IQ score – measuring general intellectual ability – and contains

four composites:

1. Verbal Comprehension Index,
2. Perceptual Reasoning Index,
3. Working Memory Index and
4. Processing Speed Index.

The Verbal Comprehension Index evaluates the child's ability to understand and use spoken language. The Verbal Comprehension subscale contains three subtests: Vocabulary, Similarities and Comprehension. Vocabulary assesses the child's word knowledge and the child's verbal fluency. The child has to explain presented words (e.g. What is the alphabet?, What is a cow?). Similarity assesses abstract verbal reasoning. In this subtest, the adult says two words and the child has to find the similarity between them (e.g. How red and blue are alike? – Both are colours). Comprehension assesses general social knowledge. During this subtest, the child has to respond to social questions (e.g. Why is it important to brush your teeth?).

The Perceptual Reasoning Index measures non-verbal fluid reasoning skills, spatial processing and visual-motor integration. The Perceptual Reasoning Index is composed of Block Design, Matrix Reasoning and Picture Concepts subtests. During Block Design, the child must reproduce a figure by using coloured block. This subtest evaluates the visual-spatial reasoning and the ability to analyse, synthesize and reproduce a form. Matrix Reasoning assesses non-verbal reasoning and concept formation. During this subtest, a matrix of abstract figures is presented to the child and he/she must find the missing figure. Picture Concepts measures the categorical and fluid reasoning. Two or three rows of images are presented to the child. He/she has to choose a picture on each row that are similar.

The Working Memory Index measures the ability to memorise new information, retrieve the information and attention span. The Working Memory Index is composed

of two subtests: Digit Span and Letter-Number Sequencing. Both subtests evaluate working memory and attention. During the Digit Span, the adult says a sequence of numbers, and the child has to repeat it in the same order and in a second part, the child has to repeat it in reversed order. For Letter-Number Sequencing, the adult says a sequence of letters and numbers, and the child has to repeat the sequence with the letters in alphabetical order and numbers in numerical order.

The Processing Speed Index measures the speed, accuracy, ability to identify, discriminate information and complete a task. The Processing Speed Index is composed of two subtests: Coding and Symbol Research. In Coding, each number 1 to 9 are paired with a different symbol. The task consists to write the correct symbol under each presented number. Coding assess the working memory and visual-motor dexterity too. Symbol Research subtest consist to observe if the target symbol is present in the group of symbols. This subtest is affected by concentration.

2.7 Data analyses

Statistical analyses were conducted with SPSS for Windows (version 23.0 Armonk, NY: IBM Corp.). By convention, significance was set at $p < 0.05$.

To compare WISC-IV scores between groups, Student's t-tests were computed. Considering significant differences between groups in SES scores and child's age during 11-year assessment, Multivariate Analysis of Covariance (MANCOVA) were also performed to compare IQ and WISC-IV's subscales scores between groups.

Then, to observe association between SES, PERI, PPQ and WISC-IV scores, Bravais-Pearson bivariate correlations were quantified. Moreover, partial Bravais-Pearson bivariate correlations controlling SES and child's age at 11-years assessment were performed. Considering the multiple comparison, false discovery rate corrections were

performed on all correlations.

In order to assess the effect of PERI and PPQ on IQ at 11 years old, hierarchical regressions were computed. Due to significant differences between groups in SES scores and child's age during 11-year assessment, both of them were included as controlling variables in the model's first step. In the second step, group (FT = 0; VPT = 1), PERI and PPQ scores were included. In the last step, either interaction between group and PPQ, or interaction between PPQ and PERI were introduced, separately. In this analysis, variance inflation factor (VIF), tolerance and residual distribution were controlled.

Finally, receiver-operating characteristic (ROC) curves and area under the curve (AUC) analyses were used to determine if PERI, PPQ, IQ and Comprehension Verbal scores can differentiate VPT and FT children.

Chapter 3

Results

3.1 Child's perinatal risk and mother's PTSD symptoms

Student's t-tests were conducted to compare PERI and PPQ scores in VPT and FT groups. The expected differences were observed for both scores. Children of the VPT group had higher scores in PERI than the FT group (VPT: $M = 4.82$, $SD = 3.04$; FT: $M = 0.19$, $SD = 0.51$; $t(52) = -8.568$, $p < 0.01$), and the VPT group mothers had higher scores in PPQ than the FT group (VPT: $M = 4.33$, $SD = 3.17$; FT: $M = 1.29$, $SD = 1.62$; $t(52) = -4.062$, $p < 0.01$).

3.2 Differences in intelligence abilities between FT and VPT group

Results revealed group differences with small effect sizes for IQ and Verbal Comprehension scores at the assessment at age 11 years old (Table 3.1). The FT group was younger and had higher IQ and Verbal Comprehensive scores than the VPT group. MANCOVA, with SES and child's age during 11-year assessment as covariates, revealed a trend for a difference between groups ($F_{(1,53)} = 2.258$, $p < 0.10$, $\eta_p^2 = 0.125$) for IQ score and a reliable group difference for Verbal Comprehension ($F_{(1,53)} = 5.164$, $p < 0.05$, $\eta_p^2 = 0.149$).

Table 3.1 – Age and WISC-IV score at 11-years-old assessment

	Full-term	Very Preterm		
	M (SD)	*M (SD)*	*t*	*Effect size* (η^2)
Age (yrs)	11.25 (0.17)	11.47 (0.27)	-3.44**	0.19
WISC-IV scores				
Total IQ	114.62 (13.10)	106.00 (14.74)	2.185*	0.08
Verbal Comprehension	119.81 (12.33)	110.03 (13.37)	2.700**	0.12
Perceptual Reasoning	108.10 (16.03)	104.12 (14.95)	0.926	0.02
Working Memory	102.14 (9.16)	96.85 (15.25)	1.594	0.05
Processing Speed	109.67 (13.47)	104.45 (16.54)	1.210	0.03

* $p < 0.05$; ** $p < 0.01$

3.3 Correlations

Bravais-Pearson bivariate correlations between child's age at 11-year assessment, SES, PERI, PPQ and IQ and Verbal Comprehension scores were computed (Table 3.2). After false discovery corrections, results revealed that SES had a marginally significant positive correlation with IQ score. Higher SES scores were associated with higher IQ scores but a small effect size is observed (Cohen, 1988, 1992). Moreover, PERI and PPQ scores correlated significantly and negatively with IQ scores. Higher PERI and PPQ scores were associated with lower IQ scores.

For Verbal Comprehension scores, a negative correlation was observed with PERI score; higher PERI scores were associated with lower Verbal Comprehension scores. All statistically significant correlations had a small effect size. Partial correlations, controlling for age at 11-year assessment and SES score, revealed similar results to Bravais-Pearson bivariate correlations but with smaller effect size. Furthermore, Bravais-Pearson bivariate correlations were conducted by splitting FT and VPT groups. After false discovery rate correction, results revealed no significant correlation in either group.

Table 3.2 – Bravais-Pearson bivariate correlations and partial correlations

	Age	SES	PERI	PPQ	IQ	Verbal Comprehension
Age		-0.12	0.19	0.17	-0.12	-0.08
SES	-		-.37**	-.39**	.28*	.24†
PERI	-	-		.55**	-.36**	-0.42
PPQ	-	-	.46**		-.32*	-0.23
IQ	-	-	-.28*	-0.23		.69**
Verbal Comprehension	-	-	-.37**	-0.14	.67**	

Notes. SES: Socio-Economic Status, PERI: Perinatal Risk Inventory score, PPQ: Perinatal Posttraumatic stress Questionnaire score.

Above the diagonal, Bravais-Pearson coefficient correlation; under the diagonal, partial correlation controlling age and SES score.

† $p < 0.1$; * $p < 0.05$; ** $p < 0.01$

3.4 Effect of PERI and PPQ on child's IQ score

To study the effect of PERI and PTSD symptoms on IQ at 11 years old, hierarchical regressions were computed. IQ score was significantly explained by the step 3b ($F_{(6,46)} = 2.333$, $p < 0.05$, $R^2 = 0.262$, $R^2_{\text{change}} = 0.24$, $p < 0.05$) of the regression model and in particular by the interaction between PPQ and group (Table 3.3) but the effect size ($f^2 = 0.092$) was small (Selya, Rose, Dierker, Hedeker, & Mermelstein, 2012). In the VPT group, higher PPQ for the mother was linked with a lower IQ score for the child ($\beta = -.365$, $p < 0.05$), whereas in the FT group this link was not significant ($\beta = .315$, $p > 0.05$) (Figure 3.1).

Likewise, the model of Verbal Comprehension score was significant ($F_{(7,46)} = 2.399$, $p < 0.05$, $R^2 = 0.267$, $R^2_{\text{change}} = 0.27$, $p < 0.05$). PPQ of the mother could reliably predict the child's Verbal Comprehension score. The interaction between PPQ and

group was also significant (Table 3.3) but the effect size ($f^2 = 0.096$) was small (Selya et al., 2012). However, post-hoc linear regressions revealed no significant effects for either group alone (Figure 3.2).

3.5 Receiver operating characteristic analysis

To determine if VPT and FT children can be reliably classified based on the PERI, PPQ, IQ and Verbal Comprehension scores, ROC analyses were performed and evaluated using the area under the curve (AUC) versus a null hypothesis of chance classification. Unsurprisingly, PERI provided nearly perfect classification of VPT from FT children, with an AUC approaching 1 (Table 3.4) with large effect size (Rice & Harris, 2005). Notably, child's IQ score at age 11 as well as the mother's PTSD symptoms as recalled at 18 months after the child's birth (i.e. PPQ) also led to reliable classification of the child as VPT versus FT (Table 3.4 and Figure 3.3) with a medium effect size (Rice & Harris, 2005).

Table 3.3 – Hierarchical regression model predicting total IQ score and Verbal Comprehension score at 11 years of age

IQ TOTAL

Steps	*Predictors*	R^2	*B*	*SE B*	β	*t*	*p*
step 1	SES	.09	6.91	3.45	.27	2.00	.05
	Child's age		-4.65	7.68	-.08	-.61	.55
step 2	SES	.17	3.54	3.74	.14	.95	.35
	Child's age		-1.44	8.42	-.03	-.17	.87
	Group		-.63	6.1	-.02	-.10	.92
	PERI		-.97	.88	-.22	-1.11	.27
	PPQ		-.63	.79	-.13	-.80	.43
step 3a	SES	.17	3.57	3.80	.14	.94	.35
	Child's age		-1.45	8.51	-.03	-.17	.87
	Group		-0.74	6.41	-.03	-0.12	.91
	PERI		-.96	.90	-.22	-1.07	.29
	PPQ		-0.60	0.91	-.13	-0.66	.51
	PPQxPERI		-0.01	0.18	-.01	-0.06	.95
step 3b	SES	.24*	3.97	3.62	0.16	1.1	.28
	Child's age		-.60	8.15	-.01	-.07	.94
	Group		-7.32	6.69	-.25	-1.10	.28
	PERI		-.84	.85	-.19	-1.00	.33
	PPQ		3.00	1.90	.63	1.58	.12
	PPQxGroup		**-4.23**	**2.03**	**-.73**	**-2.08**	**.04**

VERBAL COMPREHENSION

Steps	*Predictors*	R^2	*B*	*SE B*	β	*t*	*p*
step 1	SES	.06	5.66	3.28	.24	1.73	.09
	Child's age		-2.70	7.30	-.05	-.37	.71
step 2	SES	.20	2.51	3.45	.10	.73	.47
	child's age		2.45	7.77	.05	.31	.75
	Group		-3.93	5.60	-.14	-.70	.49
	PERI		-1.345	.811	-.323	-1.659	.104
	PPQ		.24	.73	.05	.33	.75

step 3a	SES	.21	2.80	3.48	.12	.80	.43
	Child's age		2.31	7.80	.04	.30	.77
	Group		-5.28	5.88	-.19	-0.90	.37
	PERI		-1.24	.82	-.30	-1.51	.14
	PPQ		0.56	0.84	.12	0.67	.51
	PPQxPERI		-0.13	0.16	-.12	-0.79	.44
step 3b	SES	.27*	2.91	3.33	.12	.87	.39
	Child's age		3.24	7.51	.06	.43	.67
	Group		-10.21	6.16	-.36	-1.66	.10
	PERI		-1.22	.79	-.29	-1.56	.13
	PPQ		**3.64**	**1.75**	**.81**	**2.08**	**.04**
	PPQxGroup		**-3.97**	**1.87**	**-.73**	**-2.12**	**.04**

Notes. SES: Socio-Economic Status, PERI: Perinatal Risk Inventory score, PPQ: Perinatal Posttraumatic stress Questionnaire score, * $p < 0.05$ for R^2 change

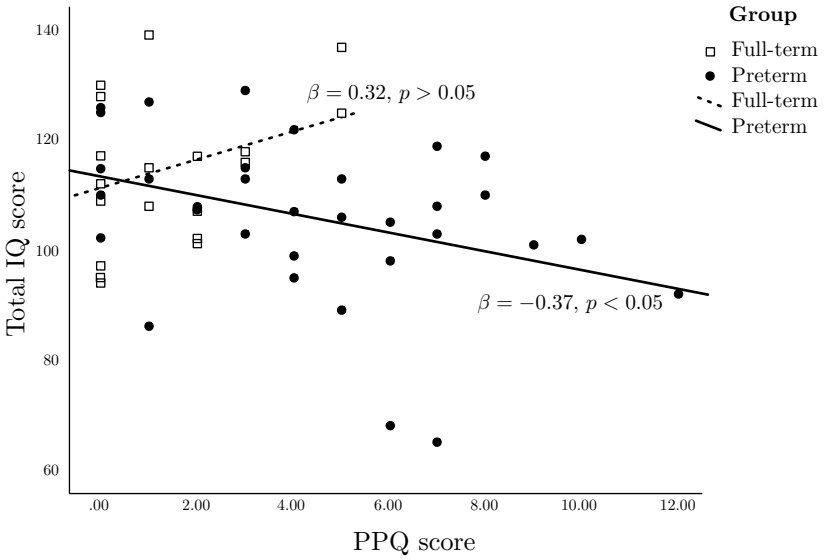

Figure 3.1 – Effect of interaction between groups and PPQ on IQ score

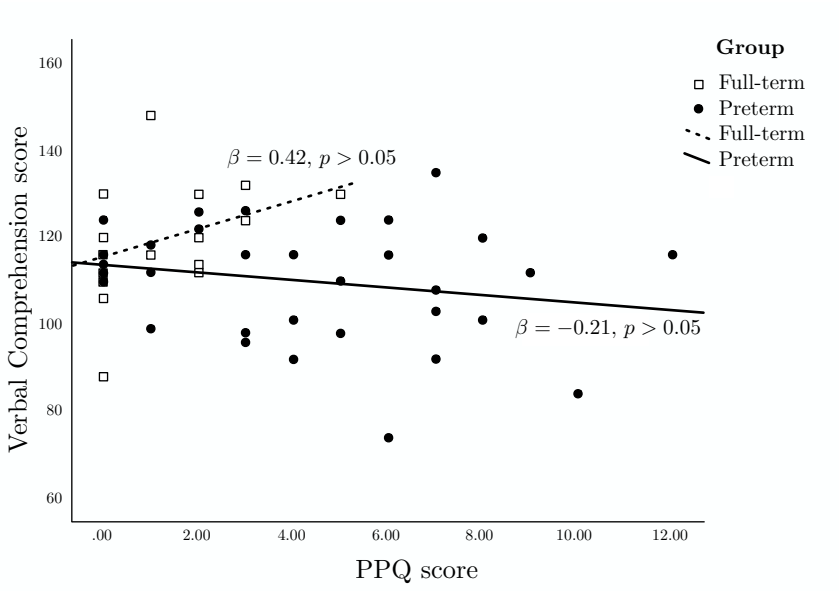

Figure 3.2 – Effect of interaction between groups and PPQ on Verbal Comprehension score

Table 3.4 – The area under the curve (AUC) values and their statistical significance for each of the tested variables for the classification of FT vs. VPT children.

Variable	AUC (±s.e.m.)	*p*-value (vs. H0 of AUC = 0.50)	95% Confidence Interval	
			Lower bound	Upper bound
PERI	0.99(0.01)	<0.001	0.97	1.00
PPQ	0.79(0.06)	<0.001	0.67	0.91
Verbal Comprehension*	0.70(0.07)	0.02	0.55	0.84
IQ total*	0.65(0.08)	0.06	0.50	0.81

The asterisk indicates that the classification was based on smaller values being predictors of positive state (i.e. classification as VPT).

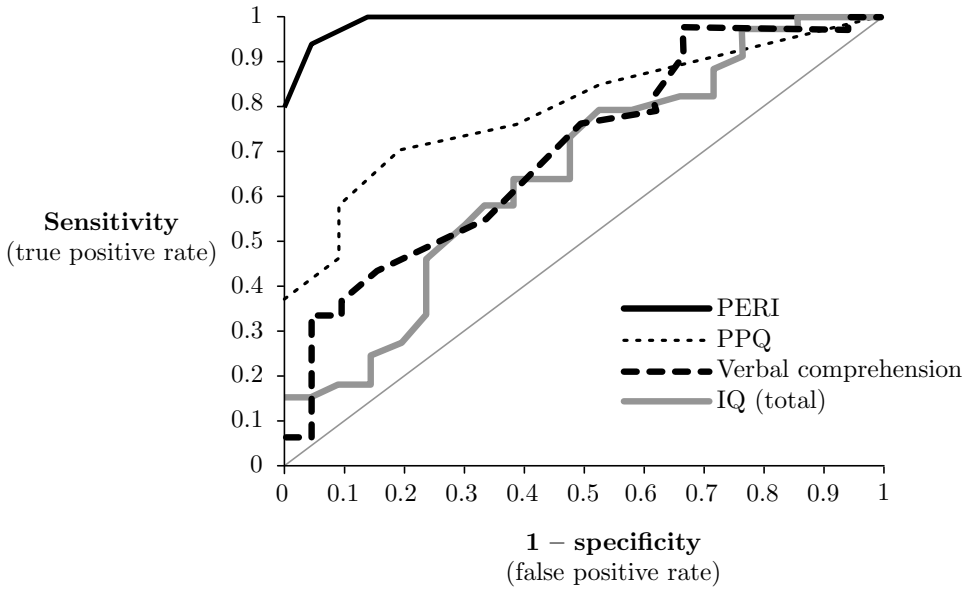

Figure 3.3 – Area under the ROC curve for the classification of FT vs. VPT children. The grey line indicates chance levels. Specific values are detailed in Table 3.4.

Chapter 4

Discussion

4.1 Summary of results

Many studies show that preterm born children have lower IQ scores than their full-term peers. To explain this difference, studies usually focus on gestational age, birth weight and parental education (or other metrics of socio-economic status). Moreover, most prior studies focused on the effects during early childhood. Preterm birth is a stressful event for both mother and baby. Considering the negative impact that stress may have on mother-child interaction and child's developmental outcomes, the purpose of this thesis was to consider consequences of child's perinatal risk and the mother's PTSD symptoms due to birth on the child's intelligence abilities evaluated at 11 years old. It was hypothesized that both the child's perinatal risk gravity and the mother's PTSD symptoms affect negatively the child's intelligence abilities.

This thesis reveals that although perinatal factors explain in part preterm born children's difficulties, maternal emotional distress appears to be an important predictor for the child's intelligence abilities during early adolescence. The results reveal that

child's perinatal risk does not present long-term consequences on the child's intelligence abilities, at least as measured here. More specifically, when SES and age are controlled, the hierarchical regression analysis revealed in the VPT group that maternal PTSD symptoms affect later child's intelligence abilities, while child's perinatal risk does not. The more the mother has PTSD symptoms when the child was 18 months old, the lower is the preterm born child's IQ scores at 11 years old. In addition, our results show that maternal PTSD symptoms affect negatively child's verbal competencies, independently of whether or not the child was in the FT or VPT group.

In this manner, the results emphasize the importance of considering not only the preterm born child's medical situation, but also the mother's mental well-being in the child's favorable development. These results are in agreement with previous studies revealing poor impact of child's perinatal complications on intelligence abilities, but stronger influences of familial factors, such as stability in the family, parenting stress and the quality of the mother-infant relationship (Breeman et al., 2017; Gross, Mettelman, Dye, & Slagle, 2001; Grunau et al., 2009; Wolke, Jaekel, Hall, & Baumann, 2013).

4.2 Limitations

This study presents several limitations. First, the results may not be totally representative of preterm born children's full cognitive development. Indeed, due to the exclusion criteria (e.g. exclusion at 6 months of age of children with developmental problems), the study's sample was composed of healthy children with relatively few problems. However, having only healthy preterm born children in VPT group was an advantage to have a more relevant comparison between FT and VPT groups. Furthermore, the dropout analysis (Table 2.1) revealed that in VPT group, families who participated at the 11-year assessment had higher SES scores, the mothers were older, and the children presented lower PERI scores than the dropout group. This may have resulted in some

selection bias.

Another limitation is the timing of the mother's PTSD symptoms assessment. In this study, maternal PTSD symptoms were assessed with the PPQ at when the child was 18 months old. Usually, the PPQ is used to evaluate the PTSD's symptoms during the 6 months after birth. In this manner, the results may not correctly reflect the mother's PTSD symptoms at and around the child's birth and may therefore be less reliable than if the questionnaire was completed earlier. However, using another questionnaire, Kersting et al. (2004) study revealed that 14 months after birth, mothers of preterm born children do not present a significant decrease of their PTSD symptoms. The implication is that measures at 18 months are likely highly correlated with what one would have measured earlier.

Finally, children's WISC-IV score in this study presents some limitations. The WISC-IV's mean score is usually at 100. However, in our sample, the mean is higher for both FT and VPT groups; especially in the FT group with almost one standard deviation higher score (i.e. 15 points). We can suppose that our experimenters were more lenient in their scoring than those usually performing the testing. Such notwithstanding, the magnitude in differences in scores between FT and VPT groups fit with previous researches (Bhutta et al., 2002).

4.3 General discussion and future perspectives

Many studies (Faure et al., 2017; Forcada-Guex et al., 2006; Jaekel, Pluess, Belsky, & Wolke, 2015; K. E. Smith, Landry, & Swank, 2006; Treyvaud, Anderson, Howard, et al., 2009) showed the essential function of mother-child interaction quality – more exactly,

the maternal sensitivity and responsiveness[1] – to enhance preterm born children's outcomes. Premature birth and the maternal emotional distress due to premature birth have a deleterious impact on mother-child interactions (Forcada-Guex, Borghini, Pierrehumbert, Ansermet, & Müller-Nix, 2011). Indeed, when compared with mothers of full-term infants, mothers of preterm infants are less sensitive and more controlling in mother-infant interactions, and a controlling pattern is more frequent in mothers with higher PTSD's symptoms (Müller Nix et al., 2004). Furthermore, compared to infants with sensitive mothers, infants with controlling mothers present less favorable outcomes at 18 months. Infants with controlling mothers present more eating problems, lower self-help and social abilities, and lower receptive and expressive language abilities (Forcada-Guex et al., 2006). Maternal anxiety during the child's NICU stay predicts poorer cognitive development and increase of internalizing problems in 24 months old very low birth weight infant (Zelkowitz, Na, Wang, Bardin, & Papageorgiou, 2011). Synchronicity in mother-infant interaction influences positively cognitive and emotional competences in early childhood (Treyvaud, Anderson, Howard, et al., 2009), and longer-term positive effects of sensitive parenting were demonstrated too. Wolke et al. (2013) revealed that for prematurely born children, sensitive parenting during middle childhood is particularly significant on school success at 13 years old. Longer-term effects of maternal stress related to infant's NICU stay on child's development have also been observed. Breeman et al. (2017) observed that 37.6% of the variance in the cognitive abilities of young adults born very preterm is explained by morbidity, neonatal treatment and social environmental factors measured during the first 5 months of life. Preterm born adults with parents who visit them less frequently during NICU stay, who have less pleasure with the infant and who are less confident in infant's care, have around 10 points lower IQ scores than adults who had good early infant-parent

[1]Responsiveness differs from sensitivity. Responsiveness refers to the ability to give a warm and sensitive support and provide an appropriate level of stimulation to support child's learning (K. E. Smith et al., 2006).

relationship (Breeman et al., 2017).

The studies mentioned above show the importance of sensitive and responsive maternal (parental) behavior for favorable development, and the results of the present work show the negative impact of maternal PTSD's symptoms on child's development. Maternal mental well-being is especially beneficial for preterm born children than full-term born children (Landry, Smith, & Swank, 2006; Shah, Robbins, Coelho, & Poehlmann, 2013; K. E. Smith et al., 2006). This particular influence of environmental factors may be explained by the diathesis-stress model (Gueron-Sela, Atzaba-Poria, Meiri, & Marks, 2015; Jaekel et al., 2015). The diathesis-stress model highlights the fact that a poor environment impacts more negatively individuals with vulnerability factors than individuals without vulnerability factors. In this manner, the diathesis-stress model suggests that considering preterm born babies' physiological immaturity and lower self-regulation, preterm born babies are more dependent to their environment – in particular the mother's emotional distress – to regulate their behavior (Gueron-Sela et al., 2015). Some studies (Jaekel et al., 2015; Shah et al., 2013; K. E. Smith et al., 2006) observed the negative impact of maternal distress on preterm born children's cognitive abilities. Shah et al. (2013) observed no differences between different preterm groups (i.e. very preterm, moderate preterm and late preterm) in infant's IQ score at 36 months of age. Nevertheless, they observed that parenting quality affects IQ scores, and the impact of parenting quality varied depending of prematurity severity: infants who experienced more negative parenting have lower IQ scores and this link is more important in very preterm born infants than late preterm born infants. Longer-term effects were observed too. Premature children's academic achievement at 8 years-old are more affected by low parental sensitivity than those of full-term children (Jaekel et al., 2015). Moreover, a consistent sensitive parenting during childhood is more beneficial on cognitive competencies at 10 years-old for preterm born children with neonatal risk than preterm born children with low neonatal risk (K. E. Smith et al., 2006). By revealing the negative influence of maternal PTSD symptoms on premature young adolescents'

intelligence abilities, our results are in line with the diathesis-stress model.

Considering the impact of maternal responsiveness and/or sensitivity on a preterm born child's development, it appears important to offer an intervention improving maternal responsiveness and sensitivity. Interventions focused on the mother-child relationship are more effective than interventions focused on the child or parent only (Spittle, Orton, Anderson, Boyd, & Doyle, 2015). Early intervention (between one week before discharge and 12 weeks after discharge) enhancing parents' understanding of their child and promoting sensitive and positive interaction with their child is positive for child's outcomes (Landry et al., 2006; Landsem, Handegård, Ulvund, Kaaresen, & Rønning, 2015; Nordhov et al., 2010). In families who benefitted from early intervention, preterm born children aged of 9 years old report more physical well-being and parents perceived their preterm born children with higher emotional and school-related life well-being than families without intervention (Landsem et al., 2015). Similar intervention seems to be effective for general cognitive competencies at 5 years old (Nordhov et al., 2010), but this effect disappears at 7 and 9 years old (Hauglann et al., 2015; Spittle et al., 2016). However, other studies reveal that an early intervention enhances slightly mathematics skill at age of eight and decreases maternal anxiety and depression symptoms (Spittle et al., 2016). The beneficial effect of early interventions remains unclear, but it seems to have a positive effect on cognitive development during infancy and disappear in school age (Orton, Spittle, Doyle, Anderson, & Boyd, 2009). There are many explanations of the absence of longer-term effects of early interventions. First, early interventions may not be very effective because the infant's brain is not mature enough to assimilate information for a lasting effect. In which case, middle childhood would arguably be more appropriate for longer positive effects on the child's development (Wolke et al., 2013). Alternatively, and by the same logic, early interventions may not be either sufficiently long or intense. Secondly, a consistency in maternal sensitivity during childhood seems necessary for cognitive improvement (Landry, Smith, Swank, Assel, & Vellet, 2001). Finally, intervention programs vary in frequency, duration and

when in the lifetime the intervention is conducted. This complicates the comparison of efficacy of intervention programs on preterm born children's outcomes.

Intervention programs enhancing quality of mother-interaction seem to have a positive impact on child's development. However, intervention concerning specifically maternal PTSD symptoms are also important to consider. As mentioned below, PTSD symptoms affect quality of mother-child interaction; mothers with PSTD's symptoms are more controlling and less sensitive than mothers with less PTSD's symptoms (Müller Nix et al., 2004). In this manner, interventions focusing on reduction of maternal PTSD's symptoms may be a good way to enhance the quality of mother-child relationships and to reduce preterm born children's negative outcomes. Studies testing efficacy of interventions focused on PTSD's symptoms are limited (McKenzie-McHarg et al., 2015) and only short-term effects on reduction of maternal traumatic symptoms have been studied. Shaw et al. (2013) suggest a trauma-focused cognitive behavior therapy with a 6-session intervention targeting, among other things, psychoeducation, relaxation, and change in child's negative perception. This study's results showed in the intervention group, a reduction of traumatic symptoms at child's 6 months of age. Jotzo and Poets (2005) intervention program suggests an early crisis intervention during baby's NICU stay. Their intervention consists of providing relaxation techniques, explanations concerning stress and trauma reactions, and coping strategies. At NICU discharge, mothers of the intervention group present less traumatic symptoms than mothers from the control group. Horsch et al. (2016) suggest another type of intervention: expressive writing paradigm. During this intervention, mothers are invited to write 15 minutes during 3 consecutive days about their feelings and thoughts about the most traumatic experience related to the childbirth. Horsch et al. (2016) showed a reduction of PTSD and depressive symptoms and improvement in health status at child's 6 months of age (corrected age). However, there is no study evaluating the impact of intervention focused on maternal PTSD symptoms on the quality of the mother-child relationship. In this manner, further research is needed to evaluate that.

Favorable environmental and social factors are important to improve preterm born children's developmental outcomes, and effects of these factors on neurological development and repercussion on preterm born child's behaviors and cognition are important to consider too. Considering the immaturity of preterm born babies in NICU, it is important to study the impact of this particular sensory environment on preterm born children's development. The ability to select the pertinent information in the environment is essential to learn social behavior and cognitive development. Multisensory processes are important in healthy cognitive development (Denervaud, Gentaz, Matusz, & Murray, 2020). Evidence suggests that early sensory deficits correlate with later cognitive difficulties (Hövel et al., 2015) and it is suggested that they might lay at the core of developmental challenges (Ayres & Robbins, 2005; Maitre, Key, et al., 2017).

In this manner, with our Cohort II of preterm born children, the study of the impact of child's sound processing on child's outcomes is ongoing. The aim of that study is to better understand the auditory processing of preterm born children and full-term children aged of 10 years old by using electroencephalography (EEG). The paradigm consists of presenting two semantic categories of sounds of environmental objects to children and to test if very preterm born children's auditory sensory and semantic processing is similar to full-term born children. The first category is "living object" sounds – such as bird, dog, scream. The second category is "man-made object" sounds – such as piano, bicycle's bell, telephone sounds (for details see Murray, Camen, Andino, Bovet, and Clarke (2006)). Participants performed an auditory 'oddball' detection task with living vs. man-made sounds and event-related potentials were measured. Our first results reveal that very preterm born children and full-term born children have similar performance (reaction time and accuracy) in the task. However, differences are observed in brain auditory object processing: preterm born children present higher amplitude response to man-made sounds while full-term born children present higher amplitude response to living sounds. Furthermore, our previous results reveal that in very preterm

born children, the Child Behavior Checklist[2] (CBCL) internalizing score correlates with topographic patterns of the sound of living and man-man objects. More specifically, the more child presents internalizing problems, the less topographic differences between categories of sounds are observed (for more details, see appendix A.5).

To face sensory experience alteration, music interventions are suggested in some hospitals and this kind of intervention seems to have positive effects on preterm born infant. For example, a music intervention consisting of exposing babies to music with headphones 5 times per week during their NICU stay increases preterm born babies' brain networks (Lordier et al., 2019). At 12 months old, compared to preterm born infants who did not benefit from intervention, preterm born infants who benefited from music intervention have more similar fear reactivity to full-term born infants (Lejeune et al., 2019). However, there is no evidence that this intervention improves cognitive competencies at 12 and 24 months of age (Lejeune et al., 2019). Music intervention seems to have a positive effect on cardio-pulmonary system too (D. E. Anderson & Patel, 2018). Studying the impact of the sensory environment on later preterm born child's development is an ongoing line of active research and will surely bear important results with clear clinical applications.

[2]The CBCL is a questionnaire filled by parents, teachers or children. It assesses child's emotional and behavioral problems. It is composed of eight syndrome scales: anxious/depressed, withdrawn, attention problems, somatic complaints, agressive behavior, rule-breaking behavior, thought problems and social problems. Withdrawn, somatic complaints and anxious/depressed correspond to internalizing problems. Agressive behavior and rule-breaking behavior correspond to externalizing problems (Achenbach & Ruffle, 2000).

Chapter 5

Conclusion

During the last three decades, the number of preterm born survivors has increased, especially in high-income countries. Many studies (P. Anderson, 2014; Bhutta et al., 2002; Ritchie et al., 2018; Treyvaud et al., 2013) show that preterm born children present more often developmental difficulties such as cognition development, behavioral problems, academic achievement difficulties than their full-term peers. Birth weight and gestational age are important factors to explain the degree of preterm born children's developmental difficulties. Nevertheless, these two factors and socio-economic status are not sufficient to explain the heterogeneity between preterm born children in IQ scores. Preterm birth is a stressful event for both mother and baby. Many lines of research (Grunau et al., 2009; Ranger et al., 2013, 2014; G. C. Smith et al., 2011) reveal the negative impact of stress on mother-child relation quality and child's development. Most previous studies concern early childhood, and longer-term effects of stress and preterm birth on adolescents' development were largely unknown.

The aim of this thesis was to observe if stress, more specifically child's perinatal problem severity and mother PTSD's symptoms due to childbirth, may contribute in the heterogeneity in preterm born children's IQ score at 11 years old. Results showed

that child's perinatal problems do not explain lower IQ score in preterm born children. However, mother PTSD's symptoms impact negatively cognitive outcomes of preterm born children.

This thesis highlights the importance to consider maternal psychiatric well-being, more specifically the impact of maternal PTSD's symptoms, in healthy preterm born child's cognitive development. Consequences of preterm birth on child's cognitive development are multi-factorial; neonatal factors are important to consider but other factors such as child's social and sensory environments are important to consider too. In order to suggest better help and prevention to reduce developmental difficulties, all these aspects need to be considered. Studies show the essential role of maternal responsiveness in optimal child's development, and interventions to improve maternal responsiveness are studied. However, studies and intervention programs concerning specifically maternal PTSD's symptoms due to preterm birth remain poor (McKenzie-McHarg et al., 2015) and may be an interesting way to reduce preterm born children's difficulties. Finally, this thesis focused on maternal PTSD's symptoms but all family members – especially fathers – should be considered too to improve preterm born child's development.

Chapter 6

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Appendix A

A.1 Posttraumatic Stress Disorder - Diagnostic Criteria of DSM-V[1]

A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:

1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others.
3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse).

   Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:

1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

   Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).

   Note: In children, there may be frightening dreams without recognizable content.
3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of

[1]excerpted from DSM-V (American Psychiatric Association, 2013)

awareness of present surroundings.)

Note: In children, trauma-specific reenactment may occur in play.

4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:

1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest or participation in significant activities.
6. Feelings of detachment or estrangement from others.
7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
2. Reckless or self-destructive behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.

G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functionning.

H. The disturbance is not attribuable to physiological effect of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).

2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

   Note: To use this subtype, the dissociative symptoms must not be

attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

A.2 Hollingshead Four Factor Index of Socioeconomic status: SES Coding[2]

Formation professionnelle

1 point : École primaire sans formation professionnelle. Apprentissage de niveau primaire non terminé

2 points : École primaire avec formation professionnelle terminée ou école secondaire sans formation professionnelle ; études secondaires en cours

3 points : École secondaire et/ou apprentissage technique et/ou école professionnelle non universitaire terminée ; domaine de la santé, de l'éducation, social, technique, sans formation universitaire

4 points : École secondaire et universitaire terminées ; école technique ou commerciale supérieure.

Situation professionnelle

1 point : Employé, ouvrier non qualifié, manœuvre, vendeur, employé de secrétariat, jeune fille au pair, assistante maternelle non agrée

2 points : Employé, ouvrier qualifié, contremaitre, chef de rayon, secrétaire, éducateur, infirmier, gendarme, assistante maternelle agrée. Secrétaire de direction ou secrétaire médicale : 2.5, Étudiant en école professionnelle : 2.5

3 points : Artisan, petit patron, professeur en primaire et en secondaire, commerçant à son compte, psychologue, technicien, ingénieur ETS, médecin-assistant, étudiant université

4 points : Profession libérale, indépendant, médecin cabinet, avocat cabinet, cadre supérieur, patron d'entreprise, haute administration, professeur à l'université

[2] Pierrehumbert et al., 1996

A.3 Perinatal Risk Inventory Questionnaire[3]

1. Apgar score: less than 3 at 1 min, 5 or less at 5 min, or less than 3 at 1 min in a neonate requiring intubation before 5 min
   - 0 No neurobehavioral abnormalities
   - 1 Hyperalert
   - 2 Mild hypotonia
   - 3 Severe hypotonia
2. Electroencephalogram (EEG)
   - 0 Normal EEG or not performed
   - 1 Abnormal EEG, but normal at discharge
   - 2 Abnormalities on EEG (not flat or periodic) with continued abnormalities at discharge
   - 3 Periodic or flat EEG with continued abnormalities at discharge
3. Seizure (nonmetabolic)
   - 0 No problem
   - 1 Suspected seizure; not treated with anticonvulsants
   - 2 One or more seizures with response to a single anticonvulsant
   - 3 One or more seizures with resistance to therapy requiring 2 or more anticonvulsants
4. Intracranial haemorrhage
   - 0 Negative computed tomography or ultrasound, or not performed
   - 1 Subarachnoid haemorrhage with seizures or grade I and grade II intraventricular haemorrhage
   - 2 Grade III intraventricular haemorrhage
   - 3 Grade IV intraventricular haemorrhage
5. Hydrocephalus (evidence of increased pressure)
   - 0 No evidence of hydrocephalus on ultrasound or computed tomography
   - 1 Suspected on clinical basis; resolved without treatment
   - 2 Hydrocephalus confirmed on ultrasound or computed tomography; without shunt; treated medically or repeated intraventricular taps

[3] Schemer & Sexton, 1991

3 Hydrocephalus confirmed on computed tomography or ultrasound; shunt required

6. Computed tomography or ultrasounds without evidence of hydrocephalus, or intracranial haemorrhage, but other CNS findings
   - 0 Negative computed tomography or ultrasound or not done
   - 1 Abnormal findings with return to normal prior to discharge
   - 2 Identified abnormalities not specified elsewhere without return to normal prior discharge
   - 3 Loss of parenchyma, decreased mental or other abnormalities which may result in parenchymal injury not specified elsewhere
7. Premature with weight >3rd percentile (appropriate for gestational age); if score <10th percentile, item 8
   - 0 >32 wks
   - 1 32-30 wks
   - 2 29-27 wks
   - 3 26-24 wks
8. Weight fit gestational age (Dubowitz or estimated date of confinement)
   - 0 Appropriate for gestational age
   - 1 <10th percentile for weight, but >3rd percentile
   - 2 <3rd percentile for weight
   - 3 <3rd percentile for weight, with a 2 or 3 in other categories of perinatal index
9. Dysmorphic features
   - 0 None or 1 dysmorphic feature
   - 1 Two minor dysmorphic features
   - 2 Three or more minor dysmorphic features, or 1 major feature, with normal chromosome
   - 3 Chromosomal abnormalities or a syndrome known to be associated with developmental disabilities such as Down syndrome or foetal alcohol syndrome
10. Ventilation
    - 0 No ventilated
    - 1 Seven days or less
    - 2 Eight to 21 days

3 >21 days or clinical diagnosis of bronchopulmonary dysplasia with tachypnoea

11. Head growth (premature infant hospitalized 6 wks or more)
    0 Head size >10% and 90%< for gestational age with 3,5 cm or greater growth in first 6 wks
    1 Initial head circumference in the 5th-10th percentile with 3.5 cm or greater growth in first 6 wks
    2 Initial head circumference in >3rd percentile with less than 3.5 cm growth in the first 6 wks
    3 Initial head circumference <3rd percentile for gestational age with <3.5 cm for the first 6 wks
12. Head growth (term infants hospitalized >3 wks)
    0 Initial head circumference >10th percentile with average head growth $\geq$ 0.3 cm/wk
    1 Initial head circumference >10th percentile with average head growth $<$ 0.29 cm/wk
    2 Initial head circumference below the 10th percentile with average head growth $>$ 0.3 cm/wk
    3 Initial head circumference below the 10th percentile with average head growth $<$ 0.29 cm/wk
13. Polycythemia (venous haematocrit)
    0 Hematocrit <65%
    1 Hematocrit >65% and <70% without exchange transfusion
    2 Hematocrit >65% without symptoms with exchange transfusion
    3 Hematocrit >65% requiring exchange transfusion because of hypoglycemia, lethargy, apnea, or seizures
14. Meningitis
    0 None
    1 Suspected diagnosis on clinical or laboratory basis without bacterial or viral confirmation
    2 Confirmed diagnosis with or without seizures with adequate tone and state control within 72h
    3 Confirmed diagnosis with persistent hypotonia or obtunded state or seizures

which persist for more than 72h

15. Hypoglycemia (regardless of gestational age. <1.7 mmol/L [30mg/dL] on heelstick)
    - 0 No hypoglycaemia
    - 1 Hypoglycemia without symptoms; requiring oral feeding only
    - 2 Hypoglycemia with lethargy or hypotonia; requiring treatment with intravenous glucose
    - 3 Hypoglycemia with seizures; requiring treatment with intravenous glucose, glucagon, or corticotropin
16. Congenital infection
    - 0 No suspicion of congenital infection
    - 1 Suspected, but without viral or serologic confirmation
    - 2 Suspected, may include small for gestational age || only, with viral or serologic confirmation
    - 3 Clearly identified diagnosis by culture or serology associated with signs and symptoms, i.e., jaundice, chorioretinitis, or hepatosplenomegaly
17. Hyperbilirubinemia
    - 0 Not requiring therapy
    - 1 Mild; requiring phototherapy or single exchange
    - 2 Hyperbilirubinemia requiring 2 or more exchange transfusion
    - 3 Hyperbilirubinemia requiring 2 or more exchange transfusion and associated with neurologic changes such as lethargy or increased irritability
18. Associated medical problems such as hydrops, ROP, cyanotic heart disease, BPD, necrotizing enterocolitis (no-CNS)
    - 0 No associated medical problems complicating the neonatal course
    - 1 Associated medical problem suspected, but not substantiated
    - 2 Established neonatal problems, but resolved prior to discharge
    - 3 Persistent medical problem at time of discharge such as grade III ROP, ileostomy, supplemental oxygen requirement, nasogastric tube

A.4 Perinatal Posttraumatic stress Questionnaire[4]

Very Preterm group version

Encerclez le « OUI » si vous avez traversé l'une de ces expériences depuis la naissance de votre bébé. N'encerclez le « OUI » que si l'expérience en question a duré plus d'un mois ?

1. **OUI - NON** Avez-vous eu plusieurs fois de mauvais rêves au sujet de l'accouchement ou du séjour de votre bébé à l'hôpital ?
2. **OUI - NON** Avez-vous eu à plusieurs reprises des mauvais souvenirs concernant l'accouchement ou le séjour de votre bébé à l'hôpital ?
3. **OUI - NON** Avez-vous eu parfois soudainement l'impression de revivre la naissance de votre bébé ?
4. **OUI - NON** Avez-vous essayé d'éviter de penser à l'accouchement ou au séjour de votre bébé à l'hôpital ?
5. **OUI - NON** Avez-vous évité de faire certaines choses qui pourraient faire resurgir des émotions concernant l'accouchement ou le séjour de votre bébé à l'hôpital (comme, par exemple, ne pas regarder un programme de télévision sur les bébés) ?
6. **OUI - NON** Étiez-vous incapable de vous souvenir de certains moments concernant le séjour de votre bébé à l'hôpital ?
7. **OUI - NON** Avez-vous perdu de l'intérêt pour vos occupations habituelles (par exemple pour votre travail, votre famille) ?
8. **OUI - NON** Vous êtes-vous senti(e) seul(e) ou à l'écart des autres (par exemple, pensiez-vous que personne ne vous comprenait) ?
9. **OUI - NON** Est-ce qu'il est devenu plus difficile pour vous de ressentir de la tendresse ou de l'amour avec les autres ?
10. **OUI - NON** Avez-vous eu une difficulté inhabituelle à vous endormir ou à rester endormi(e) ?
11. **OUI - NON** Étiez-vous plus irritable et colérique avec les autres que d'ordinaire ?

[4]Pierrehumbert et al., 2004; Quinnell & Hynan, 1999

12. **OUI - NON** Avez-vous eu plus de difficultés à vous concentrer, qu'avant l'accouchement ?
13. **OUI - NON** Êtes-vous devenu(e) plus à fleur de peau (par exemple, vous êtes-vous senti(e) plus sensible aux bruits ou sursautiez-vous plus facilement) ?
14. **OUI - NON** Vous est-il arrivé de ressentir de la culpabilité à propos de la naissance de votre enfant sans pouvoir vous raisonner ?

Full-term group version

Encerclez le « OUI » si vous avez traversé l'une de ces expériences depuis la naissance de votre bébé. N'encerclez le « OUI » que si l'expérience en question a duré plus d'un mois ?

1. **OUI - NON** Avez-vous eu plusieurs fois de mauvais rêves au sujet de l'accouchement ou du séjour de votre bébé à la maternité ?
2. **OUI - NON** Avez-vous eu à plusieurs reprises des mauvais souvenirs concernant l'accouchement ou le séjour de votre bébé à la maternité ?
3. **OUI - NON** Avez-vous eu parfois soudainement l'impression de revivre la naissance de votre bébé ?
4. **OUI - NON** Avez-vous essayé d'éviter de penser à l'accouchement ou au séjour de votre bébé à la maternité ?
5. **OUI - NON** Avez-vous évité de faire certaines choses qui pourraient faire resurgir des émotions concernant l'accouchement ou le séjour de votre bébé à la maternité (comme, par exemple, ne pas regarder un programme de télévision sur les bébés) ?
6. **OUI - NON** Étiez-vous incapable de vous souvenir de certains moments concernant le séjour de votre bébé à la maternité ?
7. **OUI - NON** Avez-vous perdu de l'intérêt pour vos occupations habituelles (par exemple pour votre travail, votre famille) ?
8. **OUI - NON** Vous êtes-vous senti(e) seule ou à l'écart des autres (par exemple, pensiez-vous que personne ne vous comprenait) ?
9. **OUI - NON** Est-ce qu'il est devenu plus difficile pour vous de ressentir de la tendresse ou de l'amour avec les autres ?

10. **OUI - NON** Avez-vous eu une difficulté inhabituelle à vous endormir ou à rester endormi(e) ?
11. **OUI - NON** Étiez-vous plus irritable et colérique avec les autres que d'ordinaire ?
12. **OUI - NON** Avez-vous eu plus de difficultés à vous concentrer, qu'avant l'accouchement ?
13. **OUI - NON** Êtes-vous devenu(e) plus à fleur de peau (par exemple, vous êtes-vous senti(e) plus sensible aux bruits ou sursautiez-vous plus facilement) ?
14. **OUI - NON** Vous est-il arrivé de ressentir de la culpabilité à propos de la naissance de votre enfant sans pouvoir vous raisonner ?

A.5 Poster presented in International Multisensory Research forum, May 2017[5]

[5]For this study, I participated to recruitment of participants, collection and management of all data, analysis and poster's creation.

Links between sensory processing and internalizing problems in prematurely-born 10-year-old children

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Introduction

Premature birth affects 10% of worldwide births. Improvement in neonatal care increases the number of preterm birth survivors. Many studies showed that preterm-born children are more prone to develope behavioral problems (e.g. ADHD) or internalizing problems (depression, anxiety). A better understanding of psychosocial and biological vulnerability aspects in preterm-born children is important in order to prevent these and similar issues [1]. Studies showed that different variables as neonatal pain, cortisol level or mother sensitivity predict, in part, preterm born children's internalizing problems [2,3,4]. It is important to also evaluate the impact of time spent in neonatal intensive care unit (NICU) and its particular sensory environment in the development of premature-born children [11].

The aim of this study was to characterize putative links between sensory processing and measures of behavior problems in 10 years old premature born children.

Impaired auditory perceptual functions have been increasingly documented in premature infants using electroencephalography (EEG) and more specifically auditory evoked potentials (AEPs). For instance, healthy preterm born infants (6-12 months of age) showed impaired perceptual narrowing (i.e. preferential processing of sounds of their native language) that in turn predicted language impairments at age 2yrs [5]. Also, premature infants have impaired AEP correlates of maternal voice recognition [6]. These data were acquired in premature and full-term infants at the same postmenstrual age, suggesting that sensory experiences in premature infants are altered and contribute to disorganized object representations.

To date, scant neuroscientific data have been published describing perceptual disorganization in prematurely born adolescents or providing links between brain activity and clinical assessments.

Methods

Participants

- 17 children born very preterm (< 33 weeks GA)
- Age mean = 10. 38 y.o. (SD= 0.64)
- 10 ♀, 7 ♂

EEG Stimuli

- Sounds of environmental objects (500ms in duration)
  - 60 sounds representing living objects (3 exemplars of 20 different objects) – e.g. bird, scream, dog.
  - 60 sounds representing man-made objects (3 exemplars of 20 different objects) – e.g. bicycle bell, piano, telephone.
- Target (10% probability) detection across 4 blocks of trials, counterbalancing semantic category

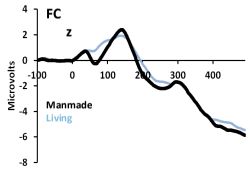
Behavior Problems

- Child Behavior Checklist for age 6-18 (CBCL, Achenbach, 1991)
  Filled by parents / 113 items / 8 syndrome scales / 2 broad grouping : Internalizing (consists of anxious/depressed, withdrawn/depressed and somatic complaints) & Externalizing (consists of rule-breaking and aggressive behavior)
- Mean internalizing problem = 58.24 (SD= 8.11) / Mean externalizing problem = 46.76 (SD = 8.18)

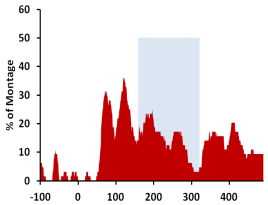
EEG acquisition & analyses

- 64-channel continuous EEG @1024Hz digitization (Biosemi ActiveTwo System)
- Peri-stimulus epochs: -100 to 500ms; pre-stimulus baseline correction
- Analyses of ERP waveforms and global dissimilarity, using Cartool (http://brainmapping.unige.ch/cartool-php), RAGU (Koenig et al., 2011) and STEN (http://www.unil.ch/fenl/page97748.html) software

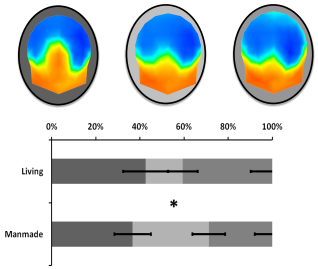
Results



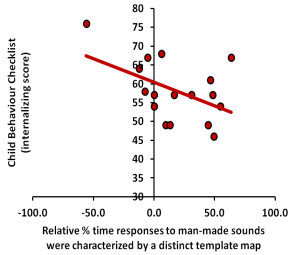
- **AEPs to sounds of objects included typical age-appropriate components [8,9].**
- **These components appear less distinct in responses to sounds of living objects in prematurely born children at age 10 years.**



- **AEPs to sounds of living and man-made objects differed over large portions of the electrode montage from ~70ms post-stimulus onset and thereafter (paired randomization test; p<0.05 for a minimum of 10ms continuously).**



- **Hierarchical topographic clustering identified three template maps over the 158-320ms post-stimulus period.**
- **Single-subject fitting based on spatial correlation indicated that there is a differential contribution of the three maps for the two types of sounds ($F(2,15)=3.65$; $p=0.05$; $\eta_p^2=0.33$). Post-hic contrasts revealed that the light grey map differentially characterized responses to sounds of living and man-made objects (p=0.032)**
- **Different topographies are indicative of distinct configurations of active brain networks.**



- **Clinical assessments were taken (CBCL – internalizing score)**
- **There was a significant negative correlation between the internalizing score of the CBCL and the extent to which responses to semantic categories of sounds were characterized by distinct AEP topographies ($r(15)=0.48$; $p=0.05$).**
- **Less distinct AEP responses were associated with higher scores of internalizing problems.**

Conclusions & Outlook

- Prematurely born children exhibit differences between auditory evoked potentials to sounds of environmental objects that are generally comparable to those from healthy adults. Differential responses to semantic categories were observed from ~70ms post-stimulus onwards as has been reported in Murray et al. 2006 [12].
- Distinct topographic distributions characterized responses to living and man-made semantic categories over the 158-320ms post-stimulus period.
- There was a correlation between the CBCL internalizing score and the differences between the topographic patterns of the sounds of living and man-made objects. The more the child had internalizing symptoms, the less distinct the topographic difference between semantic categories. This provides a link between clinical measures and the integrity of semantic representations established from sensory processing.

These results may indicate long-term effects of prematurity in conjunction with an atypical sensory environment during early life on auditory semantic representations and their link to psychopathology symptoms.

Acknowledgements

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A.6 Article published in Scientific Reports

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SCIENTIFIC REPORTS

OPEN

The interplay between prematurity, maternal stress and children's intelligence quotient at age 11: A longitudinal study

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Very premature children (<33 weeks of gestational age (GA)) experience greater academic difficulties and have lower, though normal-range, intelligence quotients (IQs) versus their full-term peers. These differences are often attributed to GA or familial socio-economic status (SES). However, additional factors are increasingly recognized as likely contributors. Parental stress after a child's premature birth can present as post-traumatic stress disorder (PTSD) symptoms and can in turn reinforce difficulties in parent-child interaction pattern. Following a longitudinal design, we studied the interplay between a premature child's perinatal history and maternal PTSD symptoms on intelligence abilities assessed at 11 years of age. Thirty-three very preterm and 21 full-term mother-children dyads partook in the study. Children's perinatal risk was evaluated at hospital discharge, maternal PTSD symptoms were assessed when the children were 18 months old, and children's IQ was measured at 11 years old. IQ was significantly lower for preterm than full-term children, without reliable influences from perinatal risk scores. However, lower maternal PTSD symptoms predicted higher IQ in preterm children. This preliminary study highlights the importance detecting maternal PTSD symptoms after a preterm birth and suggests interventions should target reducing maternal PTSD symptoms during early childhood to enhance very preterm children's intelligence development.

Approximately 10% of babies are born prematurely (<37 weeks of gestation), and the number of survivors has increased due to medical, nursing and technological improvements in the neonatal intensive care unit (NICU)[1]. Preterm-born children, even those without severe neurological disabilities, present more difficulties than their full-term peers in academic achievement, persisting into early adolescence[2–6]. These difficulties can manifest as lower intelligence quotient (IQ) scores for preterm-born children than their full-term peers. The magnitude of this difference is reported to be approximately one standard deviation (i.e. roughly 10 points) lower than the average IQ score of full-term children. However, it is noteworthy that preterm children's IQ scores nonetheless remain in the normal range[7]. Moreover, this difference persists into adulthood and exhibits an influence from the familial socio-economic status (SES)[8,9].

Such notwithstanding, it is undeniable that the premature birth of a child is particularly difficult emotionally both for the child and the parents and can be a traumatic event[10]. Premature newborns' development is immature, and they are physiologically unready for the extra-uterine environment[11]. Moreover, during the NICU stay, the sensory environment is highly atypical; there is separation from the mother, and painful and stressful medical care is often necessary[12–15]. These experiences have a widespread impact on later developmental outcomes,

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including in the endocrine system, brain microstructure, cognition and behavior[11,13,16–21]. Concerning the separation from the mother and the alteration of the sensory environment, a study on rat pups[22] showed that the lack of tactile stimulation inhibits the secretion of growth hormones and activity of ornithine decarboxalase. In turn, these alterations affect tissue differentiation processes (e.g. brain development). The same study showed that human preterm born infants who benefited from tactile stimulation have better performance in cognitive and motor assessments than infants without tactile stimulation. Moreover, previous studies[23–25] showed the beneficial effect of skin-to-skin care on preterm-born child's development. Painful medical care also seems to impact the child's IQ development. Grunau, *et al.*[15] showed that the more often a preterm baby had skin-breaking procedures during the stay in NICU, the lower was the IQ score at 18 months of age. Studies in rats and humans[20,26] showed that neonatal pain increases cell death in cortical areas and reduces white matter, and Peterson *et al.*[21] showed that smaller cortical volume is associated to lower IQ scores. Moreover, Vinall *et al.*[27] showed that the greater is the number of invasive procedures during the NICU stay, the lower is the fractional anisotropy value of the superior white matter, which was in turn associated with lower IQ scores at 7 years old.

During the child's hospitalization and after discharge, mothers can present post-traumatic stress disorders (PTSD) symptoms such as avoidance, intrusive thoughts and increased arousal. Rates of PTSD symptoms vary across studies, but are ~15–18% in mothers with perinatal complications (reviewed in Cook *et al.*[28]). The symptoms do not appear to diminish during the first 14 months after the child's birth[29], and the frequency is higher still among mothers with premature children that also have many perinatal issues[30]. Previous work likewise would indicate that mothers with emotional distress are less sensitive (i.e., less able to perceive and respond correctly to the child's signals and needs) to her infant's signals and is consequently less available to scaffold her child's development by providing appropriate and reinforcing responses, in turn impacting negatively on the child's outcomes such as affective and behavioural symptoms, social development and neurodevelopmental outcomes[31–34].

Links between maternal PTSD symptoms and children's outcomes beyond infancy remain unresolved and were the focus of the present study. Few studies have considered the severity of perinatal problems, varying for every premature baby, and maternal PTSD symptoms on a preterm-born child's outcomes[17,28]. Moreover, those that did consider the child's and mother's NICU experience investigated early childhood outcomes only[15]. Considering the lack of longitudinal studies and the importance of the transition period to early adolescence (physical and social changes, brain structural reorganization and academic challenges), the purpose of this study was to examine impact of the infant's perinatal risk factors and the mother's PTSD symptoms due to premature birth on the child's intellectual abilities at 11 years old. We expected that high perinatal risk and high numbers of PTSD symptoms would affect negatively a child's intelligence abilities at early adolescence.

Results

Drop- out analyses. Table 1 shows socio-demographic and neonatal data as well as Perinatal Posttraumatic stress Questionnaire (PPQ) scores at 18 months of age for included and dropped out participants. In the full-term (FT) group, results revealed no differences. In the very preterm (VPT) group, results showed a difference in SES scores, the mother's age at childbirth, birth weight and PErinatal Risk Inventory (PERI) scores. Included participants had higher SES scores, older mothers, higher birth weight, and lower PERI scores than dropped out participants.

Socio-demographic, neonatal, and descriptive data. At the child's birth, VPT participants had lower SES than FT participants. Expected differences between groups were observed for GA, birth weight, head circumference, PERI and PPQ scores. Furthermore, 100% of FT mothers had PPQ scores below clinical threshold (Table 1). At the 11-year-old assessment, results revealed group differences with small effect sizes for age of assessment, IQ and Verbal Comprehension scores (Table 2). The FT group was younger and had higher IQ and Verbal Comprehensive scores than the VPT group. MANCOVA, with SES and child's age during 11-year assessment as covariates, revealed a trend for a difference between groups ($F_{(1,53)} = 2.258$, $p < 0.10$, $\eta_p^2 = 0.125$) for IQ score and a reliable group difference for Verbal Comprehension ($F_{(1,53)} = 5.164$, $p < 0.05$, $\eta_p^2 = 0.149$).

Correlations. Bravais-Pearson bivariate correlations (colloquially referred to in the literature as Pearson correlations) between child's age at 11-year assessment, SES, PERI, PPQ and IQ and Verbal Comprehension scores were computed (Table 3). After false discovery corrections, results revealed that SES had a marginally significant positive correlation with IQ score. Higher SES scores were associated with higher IQ scores. Moreover, PERI and PPQ scores correlated significantly and negatively with IQ scores. Higher PERI and PPQ scores were associated with lower IQ scores. For Verbal Comprehension scores, a negative correlation was observed with PERI score; higher PERI scores were associated with lower Verbal Comprehension scores. All statistically significant correlations had small effect sizes. Partial correlations, controlling for age at 11-year assessment and SES score, revealed similar results to Bravais-Pearson bivariate correlations, but with smaller effect sizes. Furthermore, Bravais-Pearson bivariate correlations were conducted separately for the FT and VPT groups. After false discovery rate correction, results revealed no significant correlations in either group.

Hierarchical regression analysis. To study the effect of PERI and PTSD symptoms on IQ at 11 years old, hierarchical regressions were computed. IQ score was significantly explained by the step 3b ($F_{(6,46)} = 2.333$, $p < 0.05$, $R^2 = 0.262$, $R^2_{change} = 0.24$, $p < 0.05$) of the regression model and in particular by the interaction between PPQ and group (Table 4). In the VPT group, higher PPQ for the mother was linked with a lower IQ score for the child ($\beta = -0.365$, $p < 0.05$), whereas in the FT group this link was not significant ($\beta = 0.315$, $p > 0.05$) (Fig. 1). Likewise, the model of Verbal Comprehension score was significant ($F_{(7,46)} = 2.399$, $p < 0.05$, $R^2 = 0.267$,

	Included			Dropout			
	1. Full-term	2. Very Preterm		3. Full-term	4. Very Preterm		
	n = 21	n = 33	Comparison	n = 10	n = 33	Dropout analysis	
Socio-demographic	n (%)	n (%)	χ^{1-2}	n (%)	n (%)	χ^{1-3}	χ^{2-4}
Gender (girls)	13 (61.90)	18 (54.50)	0.28	4 (40.00)	12 (36.40)	1.56	2.2
Nationality (Swiss)	17 (81.00)	22 (66.70)	1.83	6 (60.00)	16 (48.50)	4.07	7.13
Parental Status (married)	14 (66.70)	26 (78.90)	0.98	8 (80.00)	29 (87.90)	1.06	3.16
	M (*SD*)	*M* (*SD*)	t^{1-2}	*M* (*SD*)	*M* (*SD*)	t^{1-3}	t^{2-4}
SES	2.91 (0.58)	2.55 (0.53)	2.32*	2.80 (0.97)	2.19 (0.60)	−0.48	−2.59*
Mother's age at child's birth (yrs)	32.05 (4.31)	32.18 (4.61)	−0.11	32.10 (4.75)	30.12 (4.57)	0.06	−1.83†
Neonatal			U^{1-2}			U^{1-3}	U^{2-4}
Gestional Age (wks)	40.00 (1.29)	30.53 (2.11)	0.00**	40.00 (0.71)	30.32 (2.00)	97.50	496.5
Birth weight (gr)	3305.24 (529.18)	1452.88 (382.85)	0.00**	3272.00 (343.86)	1273.33 (384.89)	101.50	390.50*
Head circumference at birth (cm)	34.56 (0.99)	28.07 (2.39)	0.00**	34.27 (1.97)	27.22 (2.53)	91.50	364.50
PERI	0.19 (0.51)	4.82 (3.04)	6.50**	0.40 (0.84)	6.55 (4.24)	104.50	403.00†
			χ^{1-2}				
Multiple birth (singletons, n (%))	21 (100.00)	23 (69.70)	7.81*	10 (100.00)	25 (75.80)	—	1.17
Maternal stress at child's 18 month of age							
	M (*SD*)	*M* (*SD*)	U^{1-2}	*M* (*SD*)	*M* (*SD*)	U^{1-3}	U^{2-4}
PPQ	1.29 (1.62)	4.33 (3.17)	141.00**	1.00 (2.29)	4.12 (3.31)	68.00	505.50

Table 1. Demographic and perinatal data. Note. SES: Socio-Economic Status, PERI: Perinatal Risk Inventory score, PPQ: Perinatal Posttraumatic stress Questionare score, χ: Pearson Chi-square, *t*: t of Student, *U*: U of Mann-Whitney. $^{\dagger}p < 0.1$; $^{*}p < 0.05$; $^{**}p < 0.01$.

	Full term	Very Preterm		
	M (SD)	*M (SD)*	*t*	*Effect size* (η^2)
Age	11.25 (0.17)	11.47 (0.27)	−3.44**	0.19
WISC-IV scores				
Total IQ	114.62 (13.10)	106.00 (14.74)	2.185*	0.08
Verbal Comprehension	119.81 (12.33)	110.03 (13.37)	2.700**	0.12
Perceptual Reasoning	108.10 (16.03)	104.12 (14.95)	0.926	0.02
Working Memory	102.14 (9.16)	96.85 (15.25)	1.594	0.05
Processing Speed	109.67 (13.47)	104.45 (16.54)	1.210	0.03

Table 2. WISC-IV scores at 11-years assessment. Note. WISC-IV: Wechsler Intelligence Scale for Children – Fourth Edition, IQ: Intelligence Quotient. $^{*}p < 0.05$; $^{**}p < 0.01$.

	Age	SES	PERI	PPQ	IQ	Verbal Comprehension
Age	—	−0.12	0.19	0.17	−0.12	−0.08
SES	—	—	−0.37**	−0.39**	0.28*	0.24†
PERI	—	—	—	0.55**	−0.36**	−0.42
PPQ	—	—	0.46**	—	−0.32*	−0.23
IQ	—	—	−0.28*	−0.23	—	0.69**
Verbal Comprehension	—	—	−0.37**	−0.14	0.67**	—

Table 3. Bravais-Pearson bivariate correlations and partial correlations. Notes. SES: Socio-Economic Status, PERI: Perinatal Risk Inventory score, PPQ: Perinatal Posttraumatic stress Questionnaire score. Above the diagonal, Bravais-Pearson coefficient correlation; under the diagonal, partial correlation controlling age and SES score. $^{\dagger}p < 0.1$; $^{*}p < 0.05$; $^{**}p < 0.01$.

$R^2_{change} = 0.27$, $p < 0.05$). PPQ of the mother could reliably predict the child's Verbal Comprehension score. The interaction between PPQ and group was also significant (Table 4). However, post-hoc linear regressions releveled no significant effects for either group alone (Fig. 2).

Receiver operating characteristic (ROC) analysis. To determine if VPT and FT children could be reliably classified based on the PERI, PPQ, IQ and Verbal Comprehension scores, ROC analyses were performed and

Steps	Predictors	R^2	B	SE B	β	t	p
IQ total							
step 1	SES	0.09	6.91	3.45	0.27	2.00	0.05
	Child's age		−4.65	7.68	−0.08	−0.61	0.55
step 2	SES	0.17	3.54	3.74	0.14	0.95	0.35
	Child's age		−1.44	8.42	−0.03	−0.17	0.87
	Group		−0.63	6.1	−0.02	−0.10	0.92
	PERI		−0.97	0.88	−0.22	−1.11	0.27
	PPQ		−0.63	0.79	−0.13	−0.80	0.43
step 3a	SES	0.17	3.57	3.80	0.14	0.94	0.35
	Child's age		−1.45	8.51	−0.03	−0.17	0.87
	Group		−0.74	6.41	−0.03	−0.12	0.91
	PERI		−0.96	0.90	−0.22	−1.07	0.29
	PPQ		−0.60	0.91	−0.13	−0.66	0.51
	PPQxPERI		−0.01	0.18	−0.01	−0.06	0.95
step 3b	SES	0.24*	3.97	3.62	0.16	1.1	0.28
	Child's age		−0.60	8.15	−0.01	−0.07	0.94
	Group		−7.32	6.69	−0.25	−1.10	0.28
	PERI		−0.84	0.85	−0.19	−1.00	0.33
	PPQ		3.00	1.90	0.63	1.58	0.12
	PPQxGroup		**−4.23**	**2.03**	**−0.73**	**−2.08**	**0.04**
Verbal comprehension							
step 1	SES	0.06	5.66	3.28	0.24	1.73	0.09
	Child's age		−2.70	7.30	−0.05	−0.37	0.71
step 2	SES	0.20	2.51	3.45	0.10	0.73	0.47
	child's age		2.45	7.77	0.05	0.31	0.75
	Group		−3.93	5.60	−0.14	−0.70	0.49
	PERI		−1.345	0.811	−0.323	−1.659	0.104
	PPQ		0.24	0.73	0.05	0.33	0.75
step 3a	SES	0.21	2.80	3.48	0.12	0.80	0.43
	Child's age		2.31	7.80	0.04	0.30	0.77
	Group		−5.28	5.88	−0.19	−0.90	0.37
	PERI		−1.24	0.82	−0.30	−1.51	0.14
	PPQ		0.56	0.84	0.12	0.67	0.51
	PPQxPERI		−0.13	0.16	−0.12	−0.79	0.44
step 3b	SES	0.27*	2.91	3.33	0.12	0.87	0.39
	Child's age		3.24	7.51	0.06	0.43	0.67
	Group		−10.21	6.16	−0.36	−1.66	0.10
	PERI		−1.22	0.79	−0.29	−1.56	0.13
	PPQ		**3.64**	**1.75**	**0.81**	**2.08**	**0.04**
	PPQxGroup		**−3.97**	**1.87**	**−0.73**	**−2.12**	**0.04**

Table 4. Hierarchical regression model predicting total IQ score and Verbal Comprehension score at 11 years of age. Note. SES: Socio-Economic Status, PERI: Perinatal Risk Inventory score, PPQ: Perinatal Postraumatic Questionnaire score, $*p < 0.05$ for R^2 change.

evaluated using the area under the curve (AUC) versus a null hypothesis of chance classification. Unsurprisingly, PERI provided nearly perfect classification of VPT from FT children, with an AUC approaching 1 (Table 5). Notably, the child's IQ score at age 11 as well as the mother's PTSD symptoms as recalled at 18 months after the child's birth (i.e. PPQ) also led to reliable classification of the child as VPT versus FT (Table 5 and Fig. 3).

Discussion

It is well known that preterm born children have lower IQ scores than their full-term peers[2]. To explain this impairment most researchers focus on GA, birth weight and parental education. Moreover, most prior studies focused on early childhood. The purpose of this study was to consider consequences of child's perinatal risk and the mother's PTSD symptoms due to birth on the child's intelligence abilities at 11 years old. It was hypothesized that both the child's perinatal risk and the mother's PTSD symptoms around the time of the birth itself affect negatively the child's intelligence abilities, extending even into early adolescence. Our principal discovery is that although perinatal factors explain in part preterm born children's difficulties at birth, maternal emotional distress appears to be a better predictor for intelligence abilities during early adolescence. The child's perinatal risk itself did not seem to have direct, long-term consequences on the child's intelligence abilities at 11 years old. However,

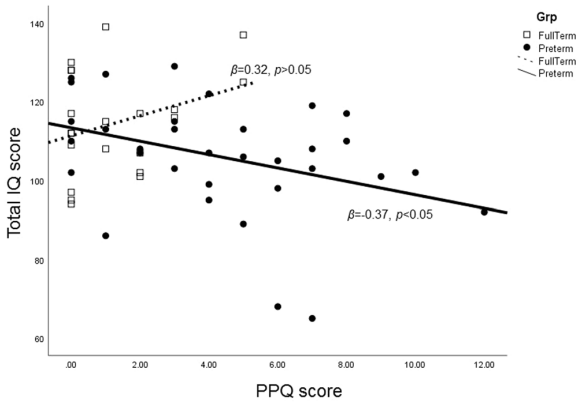

Figure 1. Effect of interaction between groups and PPQ on IQ score.

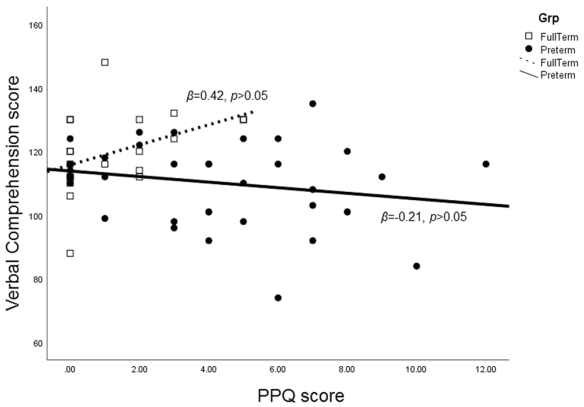

Figure 2. Effect of interaction between groups and PPQ on Verbal Comprehension score.

Variable	*AUC (±s.e.m.)*	*p-value (vs. H_0 of AUC = 0.50)*	*95% Confidence Interval*	
			Lower bound	*Upper bound*
PERI	0.99(0.01)	<0.001	0.97	1.00
PPQ	0.79(0.06)	<0.001	0.67	0.91
Verbal Comprehension*	0.70(0.07)	0.02	0.55	0.84
IQ total*	0.65(0.08)	0.06	0.50	0.81

Table 5. The area under the curve (AUC) values and their statistical significance for each of the tested variables for the classification of FT vs. VPT children. The asterisk indicates that the classification was based on smaller values being predictors of positive state (i.e. classification as VPT).

this may be partially explained by the overlap between the predictors "group" and "PERI". Differentiating their respective contributions to long-term outcome will surely benefit from continued research. Collectively, the results emphasize the importance of considering not only the preterm born child's medical situation, but also the mother's mental well-being in the child's favorable development.

When SES and age were controlled, the hierarchical regression analysis revealed in the VPT group that maternal PTSD symptoms affected later child's intelligence abilities, while the child's perinatal risk does not. More specifically, the more the mother reported PTSD symptoms when the child was 18 months old, the lower was the preterm born child's IQ scores at 11 years old. In addition, our results show that maternal PTSD symptoms affect negatively child's verbal competencies independently of whether or not the child was in the FT or VPT group.

These results are in agreement with previous studies revealing poor impact of child's perinatal complications on intelligence abilities, but still show strong influences of familial factors, such as stability in the family, parenting stress and the quality of the mother-infant relationship[9,15,35,36]. Many studies[33,37,38] showed the importance of maternal sensitivity and responsiveness in the interactions with their infants to enhance preterm born children's

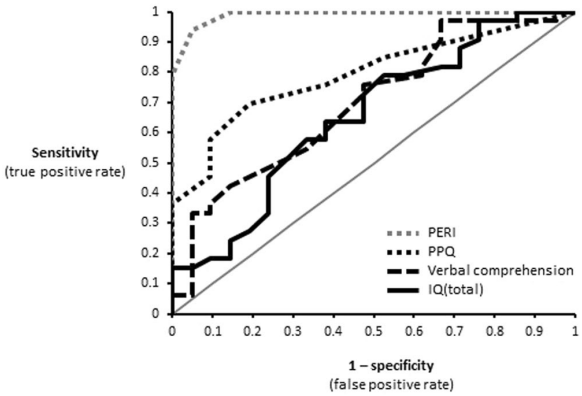

Figure 3. Area under the ROC curve for the classification of FT vs. VPT children. The gray line indicates chance levels. Specific values are detailed in Table 5.

outcomes. For example, Woodward *et al*. showed that at 4 years old children whose mothers experienced more stress in the NICU have more delays in language development than children whose mothers experienced lower stress[39]. Maternal emotional distress due to premature birth has a deleterious impact on mother-child interactions[40]. More precisely, when compared with mothers of full-term infants, mothers of preterm infants are less sensitive and more controlling in mother-infant interactions, and the controlling pattern is more frequent in mothers with higher PTSD symptoms. Furthermore, compared to children with sensitive mothers, children with controlling mothers present more behavior and affective problems, and lower developmental outcomes[33,37]. The long-term positive effect of sensitive parenting was also demonstrated by Wolke *et al*., revealing that for premature born children, the positive impact of sensitive parenting during middle childhood is particularly evident in school success at 13 years old[36]. This preterm children's responsiveness to environmental factors is explained by the diathesis-stress model[34,38]. Diathesis stress suggests that considering preterm babies' physiological immaturity and lower self-regulation; they are more dependent on their environment, in particular the mother's emotional distress, to regulate their behavior[34]. By revealing the plausible negative influence of maternal PTSD symptoms on premature young adolescents' intelligence abilities, our results strengthens support of the diathesis-stress model and the importance to consider maternal emotional distress and its effect on mother-infant interaction, in preterm born children development.

Our study had several limitations that we briefly discuss here. First, the PPQ was completed when the child was aged 18 months. This may not exclusively reflect the mother's PTSD symptoms at the child's birth and may be less reliable than if the questionnaire had been completed earlier. However, we supposed that reporting mother's PTSD symptoms at child's 18 months assess better persistent impressions of the child's early life environment, rather than solely events linked exclusively to the birth itself. Moreover to provide an index of the stability of this measure, we observed that the PPQ completed when the child was aged 18 months is comparable to the scores when the PPQ was again completed when the child was 11 years old ($r = 0.72$. $p < 0.001$), suggestive of high test-retest reliability. Such notwithstanding, it is important to recognize that the PPQ is completed by the participant and is therefore subjective; though it is based on DSM-IV criteria. Future research incorporating biological markers such as cortisol may be necessary to further substantiate the validity of this measure, though stress hormone levels are not a direct index of PTSD severity nor specificity to motherhood-related stress. Relatedly, our study did not assess directly the impact of child-mother interaction quality on intelligence development. Rather, we defined indirect, but quantifiable metrics. Still, it will be useful for future work to assess which metrics and which specific interactions (both in terms of their quantity and quality) are particularly reflective of maternal PTSD and/or contributing to the child's IQ. Another limitation is that participants' IQ scores were higher than usually reported. However, the score difference between VPT and FT we observed is consistent with the published literature[2]. Finally, our results may not be totally representative of preterm born children intelligence development. Indeed, our sample was composed of healthy preterm-born children with few developmental problems. The dropout analysis revealed that in the VPT group, the families who participated at the 11-year-old follow-up had higher SES scores, had older mothers, and had children who presented lower PERI scores than in the dropout group. While not invalidating our discoveries here, this pattern nonetheless suggests that longitudinal studies less mobilize families with lower SES probably for multiple reason that need a careful attention from researchers[41,42].

Considering the long-term deleterious impact of maternal PTSD symptoms on preterm-born children's intelligence abilities, detecting early maternal PTSD symptoms is a prime concern. An intervention to reduce PTSD symptoms in preterm-born children's mothers appears essential to enhance preterm born child's cognitive development. Borghini *et al*. revealed that early intervention reduces maternal PTSD symptoms at child's 12 months and enhances mother-child interaction quality[43]. However, early intervention presents benefits in early childhood, but appear to have poor long-term effects[44]. Considering the potential impact of maternal PTSD symptoms, we can suggest a longer intervention with focus on maternal emotional distress more than mother-child interaction.

In conclusion, this study revealed that in healthy preterm children, the child's perinatal risk does not predict intelligence abilities in early adolescence. However, maternal PTSD symptoms due to premature birth appear to be a factor that can affect negatively later child's intelligence abilities. The present study is consistent with previous studies concerning childhood and underlines the influence of other variables than the child's GA or birth weight. However, further studies are needed to confirm these preliminary results. The current study highlights the importance of early detection of maternal PTSD symptoms and by extension interventions that help long-term emotional regulation in mothers and that target mother-child interactions improvement during development.

Methods

Procedure. The present study is a part of a longitudinal clinical cohort study. After the child's birth, the mother was informed about the study and asked to sign a consent form for participation in the research. Socio-demographic and infant's perinatal risk data were collected during the hospitalization period. At the child's age of both 18 months and also 11 years, a detailed information letter concerning the study was sent to families. Then, mothers were contacted by phone to fix an assessment in the hospital. At approximately 18 months (FT: $M = 18.35$ months, $SD = 0.40$; VPT: $M = 18.37$ months (corrected age), $SD = 0.52$), the mother filled in questionnaires, and at the 11-year follow-up (FT: $M = 11.25$ y.o., $SD = 0.17$; VPT: $M = 11.47$ y.o., $SD = 0.27$) children participated in an assessment including intellectual abilities. Informed consents were signed by mother (for her child and her participation to the study) at child's birth and at the 11-year follow-up. All the procedures were performed in accordance with relevant guidelines and regulations and were evaluated and approved by the Vaudois Cantonal Ethics Committee for research in humans.

Participants. All infants born at 33 weeks or less GA during 1998 and hospitalized in the NICU of the university hospital center were considered for inclusion in the VPT group. Infants with malformation or chromosomal abnormalities and parents with psychiatric illness, drug abuse or without fluency in French were excluded. 105 families were eligible to participate. Among them, 20 refused to participate, 12 infants died, and 4 infants were excluded for developmental problems and visual impairment (i.e. strabismus) at 6 months of age (corrected age). At 18 months of age (corrected age), the remaining 69 children were met. Between 18 months of age and the 11-year follow-up, 32 participants dropped out (e.g. refused to participate or were unreachable). At the 11-year follow-up, three participants were excluded due to missing data, and one child was excluded for neuromotor disability. Finally, 33 children without any severe health problems due to prematurity composed the VPT group.

Healthy full-term infants (GA > 37 weeks) were recruited from the maternity ward of the same university hospital center. Exclusion criteria were difficulties during pregnancy or delivery, a parent with psychiatric illness, drug abuse or lack of fluency in French. Among 36 children, 4 participants dropped out (e.g. refused to participate or were unreachable) between birth and the session at 18 months of age. Then, 10 participants dropped out between the session at 18 months of age and the 11-year follow-up. One participant was excluded for missing data. At the 11-year follow-up, 21 children comprised the FT group.

Measures. *Socio-Economic Status (SES).* SES was assessed using an adapted version of the Hollingshead Four Factor Index of Socioeconomic Status[45]. The total score combined parents' education level and work position. SES score is rated on a 4-point scale; higher score means higher SES.

Child's perinatal problem's gravity. The gravity of the infant's perinatal problems was evaluated with the Perinatal Risk Inventory (PERI[46]). The PERI is an 18-item inventory assessing perinatal factors such as Apgar scores, gestational age, infant's head circumference, electroencephalogram, the duration of ventilation, presence or absence of sepsis and/or meningitis, and presence or absence of congenital infection. Each item range is from 0 to 3 on an ordinal scale. The total score is obtained by summing all items. Higher score means higher perinatal risk. A single nurse from the NICU was trained and then completed the PERI calculation at the infant's discharge from the NICU based on the infant's medical file. No data were missing in the PERI form.

Maternal PTSD symptoms. The French version of the Perinatal Posttraumatic stress Questionnaire (PPQ[47,48]) was used to assess the mother's PTSD symptoms due to the child's birth. The PPQ assesses maternal PTSD symptoms that appeared since the child's birth and persisted at least one month, during the 6 months after birth. It is a 14-item questionnaire and it is dichotomously scored. The questionnaire is based on DSM-IV[49] criteria of PTSD. The clinical threshold is fixed at 5 points – score under 6 means no PTSD[48]. The instruction to respondent is to remember if they experimented the described symptoms (i.e., Did you have several bad dreams of giving birth or of your baby's hospital stay?, Were you more irritable or angry with other than usual?). Mothers filled in the PPQ at the time when the child was 18 months of age.

Child's intelligence abilities. The child's intelligence abilities were measured at 11 years using the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV[50]). The test provides five standardized scores ($M = 100$; $SD = 15$): IQ score - measuring general intellectual ability - and four subscales scores containing verbal comprehension, perceptual reasoning, working memory and processing speed.

Statistical analyses. First, Shapiro-Wilks' tests was used to verify if data are normally distributed. To compare socio-demographic data between VPT, FT groups and dropout participants, we used Student's t-tests for normally-distributed and numeric data, and χ^2 tests for nominal data. Considering that neonatal data and PPQ scores were not normally distributed, Mann-Whitney's tests were conducted. Student's t-tests were also used to compare WISC-IV scores between groups. Considering significant differences between groups in SES scores and child's age during 11-year assessment, Multivariate Analysis of Covariance (MANCOVA) were performed to

compare IQ and WISC-IV's subscales scores between groups. To observe association between SES, PERI, PPQ and WISC-IV scores, Bravais-Pearson bivariate correlations were quantified. Moreover, partial Bravais-Pearson bivariate correlations controlling SES and child's age at 11-years assessment were performed. Considering the multiple comparison, false discovery rate corrections were performed on all correlations. To study the effect of PERI and PTSD symptoms on IQ at 11 years old, hierarchical regressions were computed. Due to significant differences between groups in SES scores and child's age during 11-year assessment, both of them were included as controlling variables in the model's first step. In the second step, group (FT = 0; VPT = 1), PERI and PPQ scores were included and in the last step, either interaction between group and PPQ, or interaction between PPQ and PERI were introduced separately. Considering the plausible overlapping between group and PERI in this analysis, VIF, tolerance and residual distribution were checked and revealed no issues related to collinearity. Moreover, the achieved power (1-β) was computed with the G*Power software[51]. For a large effect size (i.e., those with clinical relevance, $f^2 = 0.35$), 54 participants and 6 predictors achieved a power of 0.88 to detect significant results, which is considered to be sufficient[52]. Finally, receiver-operating characteristic (ROC) curves and area under the curve (AUC) analyses were used to determine if PERI, PPQ, IQ and Comprehension Verbal scores can differentiate VPT and FT children, and if IQ score can differentiate mothers with or without PTSD. It was unnecessary here to apply a procedure to control for missing data because participants with missing data were removed from analyses. Any Statistical analyses were conducted with SPSS for Windows (version 23.0 Armonk, NY: IBM Corp).

Data Avaibility

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

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Author Contributions

F.A., A.B. and C.M.N. are responsible for the study concept and design. The analysis and interpretation of data was carried out by H.T., S.U. and M.M.M. The manuscript was drafted by H.T., S.U. and M.M.M. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

Additional Information

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