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Child development following fetal adversities. From neural to interactive processes of socio-emotional vulnerability in Intrauterine Growth Restricted infants

Coordinator: Ch.mo Prof. Giuseppe Sartori

Supervisor: Ch.ma Prof.ssa Alessandra Simonelli

Co-Supervisor: Ch.mo Prof. Fabio Aiolli

Ph.D. Student:
Chiara Sacchi (1144266)

"Il venerdì, prima ancora che si alzasse qualcuno, tornò a sorvegliare l'aspetto della natura, finché non ebbe il minimo dubbio che continuava ad essere lunedì."

[Márquez, G. G. (1968).
Cent'anni di solitudine]

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Summary

Recent years have witnessed a proliferation of contributions on antenatal growth vulnerabilities and the long-term consequences on neurodevelopment and health outcomes. Knowing the pre- and perinatal factors exposing neurodevelopment and behavioral growth would benefit early clinical decision making and timely interventions. The present doctoral thesis organizes a series of studies within the field of clinical developmental psychology investigating a model of the fetal origin of neurodevelopment. Specifically, the study of Intrauterine Growth Restriction (IUGR) is the doorway and the keystone for exploring the role of antenatal adversity in founding developmental cascades of effects drifting biobehavioral trajectories towards at-risk outcomes.

The IUGR describes a set of nutritional anomalies affecting fetal maturation and exposing to high risk the post-natal growth. Most of the approaches investigating such adversity address urgent medical questions on etiopathology, fetal management and long-term prediction of health and mental health outcomes. The downside of this displacement is that the focus on the postnatal experience of the social and relational world in infants and children with IUGR is largely left behind. This issue clouds the comprehension of the relationship between antenatal and postnatal influences and further, of the complexity necessary to properly describe IUGR developmental trajectories. In the attempt to bring this lens to the observation of neuro and behavioral development following IUGR and to connect antenatal growth with the postnatal experiences, we designed a series of studies aimed at expanding the comprehension of the putative neuro-behavioral mechanisms linking growth restriction to

later outcomes. Besides, achieving this goal would lay the ground for further exploring the potential routes of reversing mechanisms, thus aspiring in being clinically informative.

The studies presented in this thesis are embedded in an integrated theoretical framework and a multimethod approach where child development results from multiple and transactional processes involving the interdependency of biological and environmental influences. Specifically, Chapter 1 describes a meta-analytic study ascertaining the effect of growth restriction on cognitive outcome and intellectual risk across childhood. Our findings robustly reveal that across infancy, childhood and middle-childhood individuals with Intrauterine Growth Restriction have systematically lower cognitive scores, increased borderline intellectual functioning and intellectual risk, compared to appropriate for gestational age (AGA) peers. Consistent results are reported for IUGR samples with either antenatal diagnosis or at-birth identification, as well as for comparisons within the study of preterm and term-born groups.

Chapter 2 presents a cohort study investigating grey matter volumes around the time of birth in very preterm (VTP) IUGR and AGA newborns. Findings prove extensive alterations in brain volumes characterizing IUGR perinatal brain development. Additionally, the study identifies IUGR VPT cognitive and motor performances in toddlerhood as significantly lower than the ones of AGA VPT peers. Interestingly, perinatal volumetric alterations did not exert a predictive role on such outcomes, opening at the presence of further processes involved in these developmental trajectories.

In line with this hypothesis, Chapter 3 presents the rationale and methods of a longitudinal case-control study investigating social and emotion processing in IUGR term-born infants, as putative neural and behavioral mechanisms translating antenatal vulnerability into atypical developmental outcomes. Extracted from this study, Chapter 4 reports on behavioral differences in between IUGR and AGA term-born infants during mother-infant

interactions and on later cognitive outcomes. Preliminary findings suggest IUGR peculiar patterns of mother and infant interactive behaviors, with significantly lower levels of maternal structuring at 4 months and reduced infant's responsiveness at 9 months. Also, they confirm later IUGR cognitive and motor risk as evaluated at 12 months of age.

Finally, considering such mother-infant interactive vulnerability, Chapter 5 proposes the application of a pediatric video-feedback intervention to support parents of a Small for Gestational Age (SGA; birth weight below the 10^{th} centile) newborn. Findings for this family allow to observe that the intervention holds parental worries about infant's physical growth and sustains their mentalization abilities to recognizing his communicative skills and progressively identifying the self- and emotional regulatory abilities.

Overall, our findings point out that fetal adversity, as described by IUGR, is a significant risk factor interesting child neurodevelopment, early exposing the brain and behavioral growth and parent-infant relational experiences. The studies proposed show the significance of observing multilevel processes and mechanisms that compose the crucial steps of a developmental cascade of cognitive and behavioral risk in order to understand the complexity of IUGR development. Consequently, in order to ameliorate the developmental outcomes of these children, constant and synergic research efforts should be directed to integrate different perspectives of study, explore the neighboring biobehavioral processes and to develop empirically-driven interventions targeting the processes of highest plasticity in IUGR development.

General introduction

FETAL GROWTH AND CHILD DEVELOPMENT

General introduction

Fetal development lays the foundation for postnatal growth. From a theoretical standpoint, approaches to the study of infant mental health, developmental psychopathology and neurobiology of human development are shifting backward the sensitive epochs emphasizing the role of antenatal life and of fetal and perinatal adverse experiences (Batalle, Edwards, & O'Muircheartaigh, 2018; Nelson & Bosquet, 2000; Wiggins & Monk, 2013). Empirically, fetal growth has been associated with perinatal morbidity and mortality (Baschat & Galan, 2018), stress reactivity and behavioral problems (Johnson & Marlow, 2014), cognitive functioning, later mental health and adverse health risks and outcomes (Godfrey & Barker, 2001; O'Donnell & Meaney, 2016). The present dissertation describes a model of infant neurodevelopment following Intrauterine Growth Restriction (IUGR), exploring a biobehavioral cascade of effects interesting the first two years of life and potentially underpinning later childhood outcomes.

In this introductory chapter we first describe the Intrauterine Growth Restriction (IUGR) as antenatal adversity interesting fetal development. We provide an overview of the theoretical formulations and the concepts within the field of fetal development sustaining its complex and fundamental role in neurodevelopment and child behavior. Secondly, we focus on the current models within a clinical-developmental framework describing the intricate biobehavioral processes characterizing child development. Last, we present the research perspective we developed at the crossroad of these formulations, explored on the neuro and behavioral processes characterizing the trajectories of IUGR infants-to-toddlers.

Intrauterine Growth Restriction (IUGR)

Among adversities occurring along the gestation, IUGR describes a pregnancy complication where an heterogeneous group of nutritional anomalies leads to stressful growth processes for the fetus. As a result of such deviation in the quality of antenatal environment, IUGR is defined by the inability of the fetus to achieve its genetic growth potential in utero (ACOG, 2013). IUGR complicates 5% to 7% of pregnancies, is comorbid with preterm birth and accounts for up to 50% of fetal deaths (Zamarian, Cruz, & Nardozza, 2018). Antenatal parameters (i.e., growth and blood velocity) have been identified to monitor fetal development and detect restriction, and classifications have been proposed based on morphometric measurements of the fetal head/abdomen growth (symmetric vs asymmetric) or IUGR onset (early vs late pregnancy). However, IUGR is still orphan of an standard operationalized definition (Gordijn et al., 2016) and in clinical practice a fetal weight estimation (EFW) below the 10^{th} percentile remains the most commonly accepted condition for identifying IUGR fetuses. Also, several studies still rely on the birth weight classification (BW < 10^{th} centile for gestational age at delivery) of Small for Gestational Age (SGA) (Battaglia & Lubchenco, 1967), which unfortunately is just a neonatal rough proxy of the quality of fetal growth and of growth restriction (Peixoto, Lopes, & Júnior, 2019). For all these reasons, IUGR represents the most common and complex problem of modern obstetrics, where the understanding of different aspects is still evolving.

During the antenatal life, maternal, placental and fetal factors interact to promote embryo and fetal growth (Pollack & Divon, 1992; Shah & Kingdom, 2011). The primary cause of IUGR is widely considered to be placental insufficiency; namely, the placental inability to support fetal growth by suppling adequate nutrients, resulting in chronic hypoxia and reduced nutriment delivery (Figueras & Gardosi, 2011). Multiple mechanisms are suddenly adopted by the fetus to face the nutriment deficiency. Indeed, IUGR reflects the

complex processes of interaction between the fetus and its intrauterine environment in order to adapt to such deprived nutritional conditions (Neerhof & Thaete, 2008). A first mechanism is a progressive slowdown in antenatal growth, very often resulting in EFW and then BW below the 10th or even the 3rd centile for gestational age. Other adaptions include increased red cell production during hypoxia, metabolic downregulation of growth processes with blood diversion and redistribution to vital organs (Antonow-Schlorke et al., 2011; Neerhof & Thaete, 2008). This last mechanism, often described as "*Brain Sparing*", is a compensatory process implemented to allow delivery of most nutrients to the major organs (i.e. adrenal glands, heart and brain, protecting their growth relative to other organs) (Garg et al., 2013). The clinical phenotypes of this fetal process are classified into symmetrical and asymmetrical IUGR. Namely, if the insult leading to IUGR occurs early in pregnancy (i.e., before the first trimester), head and brain growth are affected to a similar degree to the body; thus, these infants are classified as symmetrically growth restricted. In contrast, later insult leads to head sparing and results in asymmetrical IUGR, with presumed brain sparing (Shah & Kingdom, 2011). Despite being a neuroprotective response, under persistent insult brain sparing does not ensure normal brain development (Miller, Huppi, & Mallard, 2016) and brain abnormalities have been observed in association with IUGR, reflecting spread in the timing and severity of in utero compromise as well as the co-occurrence with preterm delivery and/or other co-existing complications. Indeed, an additional elective mechanism that fetus adopts to prevent damage from an impoverished or harmful antenatal environment is shortening its gestation (Gluckman & Hanson, 2006). IUGR is likely observed in the context of prematurity and preterm delivery could be a management option to prevent from prolonged exposure to adverse environment in growth-restricted pregnancies. For instance, it is still not clear whether the intrauterine environment offers a better long-term outcome for the growth-restricted infant than extra uterine environment after 32 gestational weeks (Bassan et al.,

2011). Among others, this issue severely complicates the understanding of the specific effect of IUGR both on neonatal neurodevelopment and later widespread outcomes since prematurity surely weights on the developmental trajectories of these individuals. Indeed, birth weight, gestational age, and birth length may reflect different underlying mechanisms with interconnected or independent effects on specific neurodevelopmental and mental health outcomes (O'Donnell & Meaney, 2016). Consequently, beyond representing a major medical concern, IUGR rises fundamental questions for neurodevelopment and behavioral growth of surviving infants.

Fetal adaptations and programming effects

According to the Developmental Origins of Health and Disease hypothesis (DOHaD; Barker, 2004), the quality of fetal development shapes individual differences in the risk for chronic illness over the lifespan. The hypothesis, evolved from epidemiological studies of infant mortality and adult deaths, postulates that antenatal adversities produce programming effects through permanent changes in physiology and metabolism, such as altered fetal nutrition, increased glucocorticoid exposure, genetic and epigenetic links. Several adult health outcomes and diseases have their origin in adverse influences early in development, particularly during intrauterine life (Barker, 2004). Indeed, long-term health outcomes have been observed in former-IUGR or adults who were born very low birth weight, including: increased incidence of chronic lung disease, hypertension, and high-risk factors for coronary heart disease (Barker, Osmond, Winter, Margetts, & Simmonds, 1989; Lapillonne, 2011). More broadly, the DOHaD studies reflect on the importance of both maternal well-being in pregnancy and fetal growth for individual differences also in vulnerability to adverse mental health outcomes and spawned the idea that child neurodevelopment may have a fetal origin (Swanson & Wadhwa, 2008; Talge, Neal, Glover, & Early Stress, 2007). Gluckman and Hanson (Gluckman & Hanson, 2006) have recently extended the Barker's hypothesis,

deepening the understanding of the processes underlying such effects. Authors suggest that in response to a change in the intrauterine environment, as a nutrient restriction or high glucocorticoid release, the fetus makes immediate adaptations to improve its chances of survival. These adaptations are often reversible; however, if the environmental changes persist, as in IUGR pregnancies, the fetus is forced to make irreversible adaptations that may (or may not) be immediately beneficial, but that will manifest themselves in later life (Gluckman & Hanson, 2006). In IUGR pregnancies, the described brain sparing mechanism might reveal this kind of processes. An initial cerebral hemodynamics aimed at protecting the brain with increased oxygen supply is mainly directed to higher cognitive functions of the frontal lobes (Cohen, Baerts, & van Bel, 2015). However, in circumstances of prolonged shortage of energetic resources or other adverse events, some developmental neuronal processes might subtly shift their preference to ensure core, vital brain connectivity, even at the cost of alterations in connections associated with important aspects of cognition and behaviors (Batalle et al., 2018). As a result, the IUGR fetus rapid adaptation to the suboptimal antenatal environment ensures the in-the-moment survival but programs its long-lasting costs exposing neurocognitive development. Altered patterns of cortical development have been observed in IUGR newborns, including: significant reduction in intracranial volume and in cerebral cortical grey matter (Tolsa et al., 2004a), smaller thalamic, basal ganglia and hippocampal volumes (Bruno et al., 2017; Lodygensky et al., 2008a), and altered cortical gyrification and cortical thickness, deeper sulci in insula and left cingulate fissure (Egaña-Ugrinovic et al., 2014). These structural brain changes are persisting during the first years of life, with findings including reduced grey matter volumes in temporal, parietal, frontal and insular regions (Padilla et al., 2011), reduced grey and white matter structural complexity (Esteban et al., 2010), reduced white matter volume and myelin alterations (Padilla et al., 2011). Overall, fetal adaptations likely produce detrimental changes in neural substrates of

cognition, neurodevelopment, while stress response and fetal mechanisms program the risk of adult mental- and health diseases before birth. Consequently, a critical question arising that need to be addressed is if (and the extent to which) these processes can be even accelerated or hopefully abated by subsequent events in postnatal life.

Environmental susceptibility

IUGR fetal growth summarizes a set of antenatal adaptations to adverse conditions, where protecting efforts toward vital organs occur at the expense of containing the fetus from reaching its genetic potential. This sort of tightrope walking can have multiple postnatal outcomes ranging from the devastating effects of fetal and neonatal death to severe-to-mild forms of neural impairment toward healthier developmental courses. In order to understand the complexity of such developmental possibilities for IUGR infants, it might be useful to reconceptualize the antenatal vulnerability as a form of increased adaptability to unpredictable characteristics of the environment. Set in this context, fetal development, and thus IUGR atypical one, has been described as a "meta-plastic state" (O'Donnell & Meaney, 2016). Namely, the antenatal adverse experience vouchsafes surviving IUGR infants an augmented susceptibility to postnatal environment, as a result of a successful adaptability to the unstable fetal environmental conditions (O'Donnell & Meaney, 2016). In other words: the influence of intrauterine factors on later development are conditional on the postnatal environment. Studies evidence that socioeconomic status moderates the effects of intrauterine growth restriction on child irritable and impulsive behaviors (Kelly, Nazroo, McMunn, Boreham, & Marmot, 2001), and the association between low birth weight and ADHD symptoms is constrained by contextual factors, as urban vs. suburban communities (Bohnert & Breslau, 2008). Also, conditional associations have been reported for low birth weight and biomarkers of depression and psychiatric disorders, depending on gender and postnatal received parental care (Buss et al., 2007). Among environmental factors, parental care and parent-child

interactions are surely the most proximal variables for child development (Belsky & Fearon, 2002; De Wolff & Van Ijzendoorn, 1997). So far, only one study investigated susceptibility in IUGR development targeting the quality of maternal care (Nichols, Jaekel, Bartmann, & Wolke, 2017). Authors speculate that through ontogenetic adaptations of the central nervous system and hypothalamic-pituitary-axis under antenatal adversities, these individuals learnt from the fetal stage to respond and adapt to certain environmental challenges (Nichols et al., 2017). The extreme value of this study is of showing the long-lasting positive effect of maternal sensitivity in childcare on IUGR adult outcomes, dismantling the traditional view of IUGR as only vulnerable for worse outcomes. Instead, such enhanced sensitivity to environment might be the key to understand how developmental routes can diverge among IUGR individuals and within the same child among developmental domains.

In addition, when describing the relationship between antenatal influences and child development, it should not be overshadowed that beyond receiving environmental influences, infant's characteristics exert active role on development. Growth vulnerabilities, as IUGR, prematurity and low birth weight, pose challenges for parental care. Indeed, vulnerable infants display ambiguous signals in interactions, making it difficult for parents to understand the intentions behind their signals and the meaning of their behaviors. For instance, they smile and look at their mothers' face less than normal birth weight matched newborns, they are less rhythmic and synchronous, more passive in daily interactions (Feldman & Eidelman, 2006), and they show higher levels of negative affect (Watt, 1987; Watt & Strongman, 1985b); thus, appearing less rewarding interactive partners. Complementarily, studies underline that IUGR infants display basic difficulties in orientating to social and non-social environment (Watt, 1990) and tend to look at people less frequently than age-matched healthy infants. As a consequence, studies are needed to ascertain bidirectional effects of antenatal IUGR adversity

on both infant's characteristics and parental care, but also exploring the potential role of infant environment exploiting IUGR susceptibility.

Nature and nurture in child development

Transactional and translational approaches to child development

Trying to understand human development, both in healthy and at-risk conditions, a conceptual reorientation has been operated in the last thirty years to overcome unidirectional approaches focused on the role of either biological (Nature) or social (Nurture) influences. Transactional models of child development (Sameroff & Chandler, 1975; Sameroff & Mackenzie, 2003) and current neurobiological approaches (Feldman & Eidelman, 2009) have highlighted that genetic and environmental influences alone explain low variability in child development and that the latter is likely compounded of processes of non-linear course where gene and environment are bound to each other. Such approaches catalyzed the interests toward an image of child development as resulting from dialectical relationships between biological and environmental factors occurring along time and across multiple levels. The great assumption behind these formulations is that child development is built by different processes rooted in continuous and multidirectional exchanges taking place along time (Sameroff, 2010). The transactional nature of these processes refers to the interdependent effects of child and environment, where the development emerges as a product of the continuous dynamic interactions of the child and the range of experiences provided by the environmental stimulation (Sameroff & Chandler, 1975). For instance, child development is embedded in a parent-child relationship, which is embedded in a family system, which is embedded in a community and then in a social context. Hence, the context provides multiple sources and variety of stimulation that can widen or narrow the individual experience (Sameroff, 2010), but also, proximity as well as the relationship and influences between these factors and the child move across time so that not only the different systems belonging to the

environment affect child development, but also child characteristics continuously shape the environment. As a result, discontinuity is observed in development every time the individual changes his/her organization in response to the continuous interexchange between the organism and the environment. Indeed, if both individual and context remain the same their relationship tends to show continuity but, since they display continuous transactions, this will result in discontinuities and thus in non-linear developmental trajectories. This last point evidences that catch-down and catch-up in several functions are common in development and their adaptive or maladaptive outcomes might depend on the relationship of the function with individual/environmental constrains. Over and beyond this important point, discontinuity is a highly relevant clinical information, since it postulates that there are continuous opportunities to change life course and multiple ports-of-entry for interventions.

Understanding such processes that explain the interconnectedness between the individual and the context, and thus healthy development and socio-emotional functioning, is pivotal, but far from easy. Indeed, teasing apart the developmental routes toward health or disorders requires to bring together many pieces of information deriving from multiple levels of analysis (Curtis & Cicchetti, 2003). Cicchetti (Cicchetti & Cannon, 1999; Masten & Cicchetti, 2010) described these processes as *developmental cascades*; that is, the cumulative consequences for development of the many interactions and transactions occurring in a developing system result in spreading effects across levels, among domains and across systems and/or generations. The effects setting a cascade might be direct and/or indirect and affect multiple pathways, but the consequences are not transient; that means, the cascade alters development (Masten & Cicchetti, 2010). Arising from these perspectives, recently emerged is the contribution of the Translational Neuroscience Framework (Wiggins & Monk, 2013), aimed at describing the cascade of effects occurring across multiple levels of analysis and interesting biobehavioral development. The model postulates that genetic materials

provide a base for a cascade of effects through affecting neurons maturation and brain structure; however, a biological capacity requires cascades to express and that addresses the major source for discontinuity in child development and heterogeneity among developmental trajectories. Indeed, perinatal neuroimaging markers of later outcome still have surprisingly low predictive power (Batalle et al., 2018), confirming that a biology-oriented perspective alone is insufficient to describe development. Additionally, this neuroscience framework adds the recognition that both biological influences expressed in brain development exert their effect on child environment, but also that environment might change brain function as well, so that brain development results as guided by genes but sculpted by the environment. This coordinated development occurring along time over a protractive period provides the architecture for the expansion of behavioral and cognitive abilities, especially rapid in the first years (Johnson, 2001).

Overall, these frameworks give the opportunity and the duty to nestle child development into the dynamic, time-, place-, and context-dependent interplay between biological and behavioral processes occurring in fetal, neonatal and infant life. As the framework is comprehensive, the field for studying is broad: we narrow our exploration to the transition from birth to toddlerhood, which is a key developmental period for the extreme brain, behavior and environmental plasticity.

Within a developmental cascade: fall by fall

We now know that human newborns begin their journey in the world already well equipped with basic competencies for learning from and be responsive to the environment. These competences, boosted through daily experience, contribute to the healthy development. Most of such basic abilities, making newborns and infants capable of adaptation by identifying and elicit behavioral responses from relatedness, arise from a genetic

predisposition which expressions are embedded in the specific developmental context (Meltzoff & Moore, 1983; Morton & Johnson, 1991). This broadly continuous, intertwined exchange between these two extents begin even before birth, during antenatal life, and has its first expression in fetal brain development. Along gestation, the assembly of basic brain architecture, as the generation of most cortical neurons (first and second trimester), and the establishment, development and consolidation in connectivity (third trimester) occur; that is, the brain growth shows critical period for most of the important developmental processes. Changes in timing and/or quality of antenatal environment nurturing such processes can become progressively magnified over time, producing long-lasting consequences for structural and functional brain organization that are likely to set the origin for neurodevelopmental disorders (Buss, Entringer, Swanson, & Wadhwa, 2012; Miller et al., 2016). So, brain development around the time of birth appears as a receptor of the intertwined gene/environment antenatal exchanges and may operate as a first valve regulating the expression of the healthy or altered genetic/environmental, prenatal-to-neonatal development. This issue thrived fascinating questions studying the developing brain to detect early biomarkers and to develop proper neuroprotective strategies. Those approaches implicitly base on probabilistic models of development and assume that having a clear understanding of the developing brain is the first step to exploit its plasticity.

After birth, brain continues showing increased plasticity by being extremely susceptible to the quality of the environmental context. Refinement in brain connectivity and function characterize the first two years of post-natal life (Innocenti & Price, 2005) and literature extensively documented *critical periods* (when the exposure to some environmental stimuli is required for typical brain development) and *sensitive periods* (when an environmental effect expresses its maximum impact) for several sensory modalities (Maurer, Lewis, Brent, & Levin, 1999; Werker & Vouloumanos, 2001). To describe the complexity of such interaction

in the real life of a developing system, Greenough proposed the concept of "experience-expectant" and "experience-dependent" brain development (Greenough, Black, & Wallace, 1993). Brain represents a structural substrate for expectations, whereas the quality of environment gives the daily experience. An example of such developmental escalation relevant for child behavior and socio-cognitive development is observed in infant face processing (Johnson, 1991; Morton & Johnson, 1991). Among neural competences displayed by newborn and infants, the ability to recognize and direct the attention to faces appear as highly relevant. Indeed, the human face provides the infant with a wealth of socially and affectively relevant information for survival and world meaning and humans appear to be inherently interested in faces, displaying from early stages a strong interest in facial-like figures (Valenza, Simion, Cassia, & Umiltà, 1996). Face perception is critical in the development of higher level social and cognitive functions (Parker & Nelson, 2005), since early disruption or delay in this low-level process can negatively impact infant's ability to interact with the social environment (Elsabbagh et al., 2015) and disturb natural mutuality in social interaction (Wan et al., 2013). Huge part of early interactive exchanges rely on the use of face and facial expression are early used to understand others emotion and thought, to make others understand themselves, and to share emotional states (Adolphs, 1999; Beebe et al., 2010, 2016). Therefore, main results of such continuous brain-environment exchange are easily and early observable in newborn and infant social behaviors. The behavioral domain (newborn' to child's) is a setting for daily multimodal learnings and is a second valve expressing the experience-expectant and experience-dependent interaction of brain development (bringing for its part the fetal gene/environment structural and functional contribution), with the post-natal environmental stimulation. A breakthrough is that infant behavior is also an extremely timely sentinel marker of healthy development. Indeed, early signs of behavioral problems screen for later neurodevelopment and behavioral problems in

childhood, which are important predictors for long term mental health outcomes (Moffitt et al., 2011). Also, most of the current developmental psychopathology is behaviorally diagnosed.

Different early stressors and risk factors, such as prolonged institutionalization or risk for autism, are likely to affect these infant bio-behavioral social competencies (Nelson & McCleery, 2008) and behavioral pathways to psychopathology have been described in humans experiencing early adverse experience hitting the quality of received care. For instance, adults who received early psychosocial deprivation and/or survived early stressful experiences, such as child abuse present increased risk for mental health outcomes (i.e., PTSD and depression) (Koenen, Moffitt, Poulton, Martin, & Caspi, 2007). At this point, adaptive rather than maladaptive outcomes of brain plasticity and infant's behavior interconnections appear to count on the quality of the proximal environmental experience too. Narrowing the field of environmental experience, parenting and parental care appear to have the most nurturing and in turn potentially devastating effects on brain-behavior development and extensive research has demonstrated that responsive relationships with primary caregivers play a critical role in healthy social-emotional development (Feldman, 2012; Tronick, 2007). In the specific context of growth vulnerability, the scarce or atypical communicative signals on infant's side, as reported for IUGR and growth vulnerable infants (Miles & Holditch-Davis, 1995; Montirosso et al., 2017), could activate compensatory behaviors in parents. These parenting responses, perhaps aimed at being highly adaptive, can eventually result into intrusive and non-attuned behaviors (Howe, Sheu, Hsu, Wang, & Wang, 2016). Indeed, beyond regulating infant's brain-behavior experience of the social world, parenting is a plastic system susceptible of influences of infant's characteristics. A step beyond for developmental cascades is that such environmental (parental) plasticity represents for clinical psychology a doorway for early interventions. In this sense, meta-analytic evidence have shown the

effectiveness of parental interventions, in enhancing infant socio-emotional development through parental sensitivity and attachment security (Bakermans-Kranenburg, Van Ijzendoorn, & Juffer, 2003; Fukkink, 2008).

Overall, the child's brain-behavior vulnerability might negatively impact parenting and the establishment of a healthy, safe, and nurturing parent–child relationship; on the other hand sustained parenting and the quality of parent-child interactions can potentially buffer the negative effect of infant scarce competencies in social experience (Baker, Fenning, Crnic, Baker, & Blacher, 2007). Nestling infant development in a comprehensive research perspective targeting the transactional and multilevel socio-emotional and cognitive mechanisms that rise neuro and behavioral symptoms in childhood is a fascinating journey and a clinical challenge.

Vision and structure of the work

Considering the evidence provided by IUGR studies on fetal programming and susceptibility to postnatal environment, and in the light of a theoretical approach founded in the transactional and translational models of development, the present work is aimed at investigating the role of Intrauterine Growth Restriction as antenatal risk factor for neurodevelopment and behavioral, especially socio-emotional, outcomes.

Such aim requires bearings. Three pillars sustain the reasoning of this work and will be reflected by its structure. First, like prematurity, IUGR is a risk factor and not a disease. To move toward a clinical comprehension of the multiple developmental trajectories, it is mandatory to interconnect several mechanisms intervening with cumulative or progressive effects, showing domain specific as well as widespread effects and leading to negative or positive consequences. At this scope, we aimed at providing a thoughtful integration of domains (i.e., brain development, neurodevelopment, affective-relational functioning), levels (i.e., brain structure, function, behaviors) and research methods (neuroimaging, ecological

observation). Secondly, as child development is a dynamic system characterized by processes of transactional nature (Sameroff, 2010), we direct the attention to the interdependency between the multiple levels. Indeed, a biological adaptive response (.i.e., occurring at a fetal stage) potentially presents long-lasting costs on the organization of cognitive and/or behavioral domains. But also, considering that producing an in-the-moment environmental change (i.e., in infant's interactive behaviors) might spread positive and potentially reverse effects across levels (i.e., brain function, socio-emotional growth). Lastly, time is a central concept for a developing system. Plasticity is a first reason coming to the mind, timely interventions is a second. We focus on the transition from birth up to toddlerhood, which is a key developmental period for brain, behavior and interactions investigating development along different time-windows (from birth up to toddlerhood) and in longitudinal research designs as stratagem to begin drawing a puzzle of stability and changes in IUGR trajectories, both in the direction of exploiting biobehavioral plasticity and detect clinically informative processes for designing suitable interventions.

Overall, the contributions presented in the following chapters are integrated in a multidisciplinary, multimethod approach to answer one single question: ***understand whether and how (through which processes) child development after IUGR is exposed***. The complexity of the aim has a twofold scope. First, we aim to increase the theoretical comprehension of IUGR as antenatal adversity marking child development. Providing an answer to this question will move toward a second objective to understand and intervene on variables constraining such vulnerability. As the two sides of the same coin, the two cannot be conceived separately. Rather, the head (theory) informs the tail (clinical practice), and in turn the latter will refine reasoning behind the first. Indeed, our hope is for future researchers and professionals to explore neighboring biobehavioral processes of development and to understand how empirically driven interventions in the complex realm of child development

might affect the biobehavioral expression of antenatal adverse experience of IUGR individuals.

Overview of the chapters

Following this formulation, the contributions presented are articulated in a hierarchical structure. A first session, I Part of the thesis focuses on IUGR across the gestational age spectrum at delivery as risk factor for neurodevelopment, specifically for cognitive outcomes. Literature is huge on this topic but often confounded by the factors surrounding IUGR, as prematurity and low birth weight, making it difficult to disentangle its specificity from a more generic effect of a perinatal fragility. Through a comprehensive meta-analytic approach, Chapter 1 attempts to ascertain the direct effect of IUGR in preterm and term-born individuals on infant-to-child cognitive functioning.

Once clarified the trajectories for IUGR neurodevelopment, we narrow the point of observation to the first two years of infant's life. The II Part is devoted at exploring putative neurophysiological and behavioral mechanisms accounting for an IUGR cascade on the developmental outcomes. This part is composed by three chapters. Chapter 2 is a cohort study investigating IUGR structural brain growth, in terms of cortical gray matter volumes around the time of birth as anatomical base for neurodevelopmental outcomes. Chapter 3 describes the research perspective and protocol of a longitudinal study exploring brain function, in terms of electrical activity during a face processing task, as underpinning infant's behaviors in social interaction and toddlerhood socio-cognitive outcomes. Chapter 4 is a preliminary case-control report from the previous longitudinal study reporting on IUGR early interactive behaviors along the first year of life; this chapter also offers a shift in the focus highlighting the role of parenting in IUGR development.

Finally, last part of the thesis, the III Part, is dedicated to translating the theoretical evidence into clinical perspectives for intervention. Timely and effective programs are a

clinical urgency. In developing interventions is extremely important to embrace a multifaceted approach considering the infant and caregiver as a mutually influencing complex and interrelated system. Chapter 5 is a single-case study describing a video-feedback intervention designed to suit a pediatric setting and aimed at sustaining parenting and foster infant's mental health. Its application with a growth vulnerably newborn is intended to exploit infants' environmental susceptibility to gain as much as possible from a sensitive and mentalizing parenting hopefully compensating for a suspected biological vulnerability in social behaviors. Beyond being the conclusive study of this thesis, it is intended as a starting point to suggest potential routes for constraining or even reverse processes interesting the presented developmental cascade.

Part 1. Growth restriction and the risk for neurodevelopment

THE ROLE OF ANTENATAL ADVERSITIES ON CHILD COGNITIVE OUTCOMES

CHAPTER 1: Sacchi C., Marino C., Visentin S., Vieno A., Nosarti C., Simonelli A. (in preparation). *The effects of Intrauterine Growth Restriction and Small for Gestational Age on cognitive development in preterm and term-born children. A meta-analysis*

CHAPTER 1

The effects of Intrauterine Growth Restriction and Small for Gestational Age on cognitive development in preterm and term-born children. A meta-analysis

ABSTRACT

Is Intrauterine Growth Restriction associated with worse cognitive outcome during childhood?

In this chapter we examine the cognitive outcome of preterm and term-born IUGR and SGA children compared to Appropriate for Gestational Age peers over the first 12 years of life.

We present a meta-analytic study on full intelligent quotient (IQ) or mental/cognitive scale in IUGR and/or SGA samples, compared to control groups of Appropriate for Gestational Age (AGA). PRISMA guidelines were followed, standardized mean difference (SMD) and Odd Ratio (OR) were calculated and data from individual studies were pooled by applying random-effect models.

Based on 83 studies, the meta-analysis proves that across childhood, IUGR and SGA children score significantly lower than their AGA peers on cognitive evaluations. Associations are consistent for preterm (SMD = - 0.34, 95% CI: - 0.47, - 0.201) and term-born children (SMD = - 0.40, 95% CI: - 0.51, - 0.29), with higher overall effect sizes reported for term-born IUGR-AGA groups comparison. Additionally, analysis reveals significant increased risk for borderline intellectual functioning in IUGR and SGA preterm children (OR = 1.61, 95% CI, 1.42 to 1.82) compared to AGA peers.

Growth vulnerability assessed antenatal (IUGR) and by the time of birth (SGA) are associated with lower cognitive development with small to medium effects. For better outcomes in these children, it would be beneficial constant improvements in antenatal diagnosis and timely interventions boosting cognitive functioning.

INTRODUCTION

Intrauterine Growth Restriction (IUGR) is a leading cause of newborn deaths, responsible for 26% and 53% of preterm and term-born still-births, respectively (Baschat & Galan, 2018; Rogers & Piecuch, 2009). It refers to an impoverished fetal growth resulting from fetal, maternal or placental causes (i.e., congenital or chromosomal anomalies, infections, malnutrition, vascular disorders) setting a detrimental cascade where, oxygen reduction (up to hypoxemia) and nutritional deficiencies lead to cardiovascular deterioration, extreme blood flow resistance and decreased fetal growth rate (Miller et al., 2016). In response such antenatal environment, the fetus attempts to prevent damages by slowing down its growth; however, the adaptive responses to cope with in-utero malnutrition have long-lasting costs predisposing to adverse developmental and health-related outcomes throughout post-natal life (Chatmethakul & Roghair, 2019). Developing brain exhibits plasticity and susceptibility to antenatal insults, showing structural and functional alterations (Rees, Harding, & Walker, 2011), exposing to later developmental problems (Baschat, 2014; Kok et al., 2007). In particular, IUGR surviving infants are affected by a range of poorer developmental outcomes encompassing cognitive, socio-emotional, and behavioral domains (Murray et al., 2015).

Most of the time, IUGR fetuses are delivered Small for their Gestational Age (SGA), a neonatal outcome classification describing newborns with birth weight below the 10^{th} percentile for gestational age. Despite SGA is a likely outcome of IUGR, and SGA and IUGR usually overlap, it is important to disentangle the definitions for the two conditions: whereas IUGR evidences signs of fetal distress, SGA classification only provides a measure of size not providing a direct measure of antenatal growth quality. That is, SGA status is not enough to identify an antenatal process of growth restriction; indeed, SGA children are commonly described as former constitutionally small fetuses (Nardozza et al., 2017). However, even

said that birth weight could be a weak indicator of antenatal environmental quality, fetal programming studies mostly rely on the use of birth weight in determining antenatal mechanisms of programming. In particular, associations between low birth weight and executive functions, attention and cognitive deficits have been found (Løhaugen et al., 2013). So far there is no evidence that being SGA does not mean experiencing a delayed or attuned form of IUGR or even different kind of antenatal environmental alteration; therefore, pathological origin of SGA cannot be excluded (Simões, Cruz-Lemini, Bargalló, Gratacós, & Sanz-Cortés, 2015).

An additional problematic aspect in this field is prematurity. Indeed, a second elective mechanism that fetus adopts to prevent damage from an impoverished or harmful antenatal environment is shortening its gestation (Gluckman & Hanson, 2006). Both IUGR and SGA conditions are likely to occur in the context of prematurity, and preterm delivery could be a management option to prevent from prolonged exposure to adverse environment in growth-restricted pregnancies. However, it is still not clear whether the intrauterine environment offers a better long-term outcome for the growth-restricted infant than extra uterine environment after 32 gestational weeks (Bassan et al., 2011). Consequently, prematurity weights on the potential effect of antenatal growth adversities on development, representing the major confounding factor for IUGR/SGA outcomes.

Growth restriction in utero, Small for Gestational Age status, and low gestational age at delivery appear as interconnected risk factors for neurodevelopment, where the specific contribution of each, as well as the additive or rather combining effects are not always easy to be isolated. Previous systematic review and meta-analysis attempted to answer the question about the role of IUGR in determining adverse neurodevelopment (Chen, Chen, Bo, & Luo, 2016; Murray et al., 2015). Despite these evidences, some key points remained unsolved as

previous studies failed to assess the differential effect of IUGR in preterm vs term-born children or neglected the potential risk for SGA samples.

The present meta-analysis investigates the effect of in utero IUGR and SGA birth classification on cognitive outcome (i.e. IQ, which is a concise indicator recognized as the gold standard measure for the evaluation of general cognitive functioning, associated with physical and mental health outcomes) and risk for intellectual functioning across infancy, childhood and middle-childhood. Specifically, aim of this study is to ascertain whether there is a significant lower cognitive outcome in IUGR and SGA individuals compared to their AGA peers. Indeed, associations will be differentially presented within the study of preterm and term-born children in order to disentangle the effects of IUGR and SGA vulnerability from the combined role of atypical growth (IUGR and SGA) and low gestation (delivery <= 37 weeks).

METHODS

A meta-analysis was conducted in close accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Search strategy

Multiple methods were used to identify potentially eligible studies. First, literature searches were conducted with the following databases: Scopus, PubMed, Web of Science, Science Direct, PsychINFO, and Eric. The search strategy used mash terms to describe IUGR and SGA outcomes and included the following keywords: ‘intrauterine growth restriction’, ‘intrauterine growth retardation’, ‘small for gestational age’ AND ‘neurodevelopment’, “neurodevelopmental outcome”, “developmental outcomes”, “cognitive development”. Last screening was performed on 27th May 2018. Research was limited to studies published after January 2000, as proxy of data collection within antenatal corticosteroid and surfactant era. Eligibility was limited to peer-review scientific papers published in English and within years

2000-2017. Review papers, conference proceedings, book chapter, thesis dissertation, case reports and all non-English materials were excluded, since mostly providing preliminary or incomplete data. Additionally, the reference sections of previous systematic reviews on this topic were searched for relevant references.

Study selection

For the scopes of this meta-analysis, inclusion criteria were defined as follows:

i) target samples consisted of IUGR and SGA children. For IUGR a study was included when presenting antenatal evidence of growth restriction, while for SGA the selection referred to birth weight (BW) classification. Antenatal assessment methods and BW cut off varied across studies and are reported in Tables 1-2-3 (Appendix, A1); *ii*) the presence of control group, defined as a sample of Appropriate for Gestational Age (AGA), presenting mean BW> 10/15th centile for gestational age, respectively matching age at delivery in the two groups of preterm and term-born children; *iii*) gestational age at birth should have been reported; studies conducted on mixed samples of preterm and term-born children were excluded; iv) the cognitive outcome was reported as a mental or cognitive subscale or full intelligent quotient (IQ) scores, or percentage of borderline intellectual functioning based on score < 1SD from mean cognitive or full IQ; *v*) the outcome assessment was based on validated standardized practitioner-based cognitive batteries; *vi*) age at outcome assessment was limited to the first 12 years of life (aged 1 month and 11.11 years).

Studies quality check

Research design has been adopted as a synthetically descriptor of the quality of the study; studies have been classified as case-control prospective, case-control retrospective studies, cohort prospective study, and cohort retrospective study.

Data managing

All studies have double screened for full-text and selected studies have been coded by CS, recording authors and year of publication, sample size, national setting, sample characteristics (diagnosis, age at outcome, type of measure for cognitive outcome), and data to compute the effect sizes. A subset of studies (N= 40, 53%) have been independently coded by author CM. In rare cases of disagreement among the coders, discrepancies were discussed until agreement was met. In case of eligible articles not reporting enough information to compute effect size, corresponding authors were contacted and asked to provide the missing information (e.g. *Mean* and /or *DS* of IQ in IUGR and SGA samples separately). We received the requested data for 1out of 12 requests.

Data are organized according to time of diagnosis (in utero IUGR vs at birth SGA) and the mean gestational age at birth (preterm vs term-born). Gestational age at birth has been considered as expressed in weeks, therefore, for studies providing gestational age in days, corresponding gestational week has been calculated. Studies on preterm children included samples of newborn with a means of <=37 weeks of gestation at delivery. Term samples were defined as having a mean gestational age at delivery of > 37 weeks. In case of presence of preterm subjects, percentage of infants delivered earlier than term should be lower than 30%.

Studies were grouped on the base of outcome: findings are analyzed separately for mean IQ and rate of borderline intellectual functioning. To avoid samples overrepresentation, potentially inflating the overall effect, when single cohort was followed up at multiple time-points, findings were selected for the time-point presenting grater sample size. Differently, in studies with follow-up assessment in both mean cognitive scores and borderline intellectual functioning domains, all data were extracted since they are analyzed separately.

STATISTICAL ANALYSES

Two separate meta-analyses were conducted on (i) studies reporting mean values of IQ for each group (effect size was computed as standardized mean difference (SMD) and (ii)

studies reporting percentages of children with borderline intellectual functioning (effect size was computed as Odd Ratio). In both cases, the target group was compared with its relative control group.

Data from individual studies were pooled by applying random effect models. Potential publication bias was evaluated in different ways: (i) first, we tested for funnel plot asymmetry; (ii) second, we checked whether additional studies needed to be imputed according to the trim and fill method. Heterogeneity was assessed by using *Q* statistics (which is distributed as χ^2 with df = *k*-1, where *k* represents the number of effect sizes; with significant *p*-value representing heterogeneity (Lipsey & Wilson, 2001); also reported is the I^2 statistic, indicating the proportion of observed variance that reflects real differences in effect size (Higgins, Thompson, Deeks, & Altman, 2003). Analyses were performed in samples of IUGR and SGA separately for preterm and term-born children. In the presence of heterogeneity moderating effects were tested with mixed-effect models; gestational age at delivery, IUGR vs SGA classification, and mean age at outcome assessment were selected as potential moderating factors. Within each meta-analysis (preterm – term-born groups), subgroup meta-analyses were conducted on IUGR and SGA subsamples. In addition, with regard to the meta-analysis using percentages of children with borderline intellectual functioning, sensitivity analyses were performed including only studies reporting cognitive impairment (i.e. cognitive outcome < 2 SD).

Data analyses were performed using the open-source software R: library *compute.es* was used to compute effect size from mean and standard deviation scores; library *metaphor* was used to run meta-analyses and library *forestplot* was used to graphically represent findings.

RESULTS

Sample of studies

Figure 1 displays the search and selection process following PRISMA guidelines. Initial pool comprised 3921 results, 2829 after duplicates removal. At first screening: 423 books, 7 dissertation thesis, 12 conference proceedings, and 63 posters and abstracts were removed. Of the remaining peer-reviewed literature, 135 items were excluded as literature review and 34 were not-English published manuscripts. At the second screening stage, items have been excluded based on title and abstract indicating no relevance for the targeted population and/or outcome; specifically, 1497 items were removed by title. A remaining set of 658 papers has been screening by abstract and 362 scientific papers have been screened by full-text and based on this other 204 items were excluded. Of a remaining set of 158 full-text, 75 were further excluded as they did not meet inclusion criteria and/or where not presenting quantitative data for data analyses.

Globally, 83 studies were comparing IUGR and SGA preterm and term-born children with their AGA peers on cognitive development: 50 studies were providing results for mean cognitive or IQ scores, and 23 studies were reporting on percentages of borderline intellectual functioning.

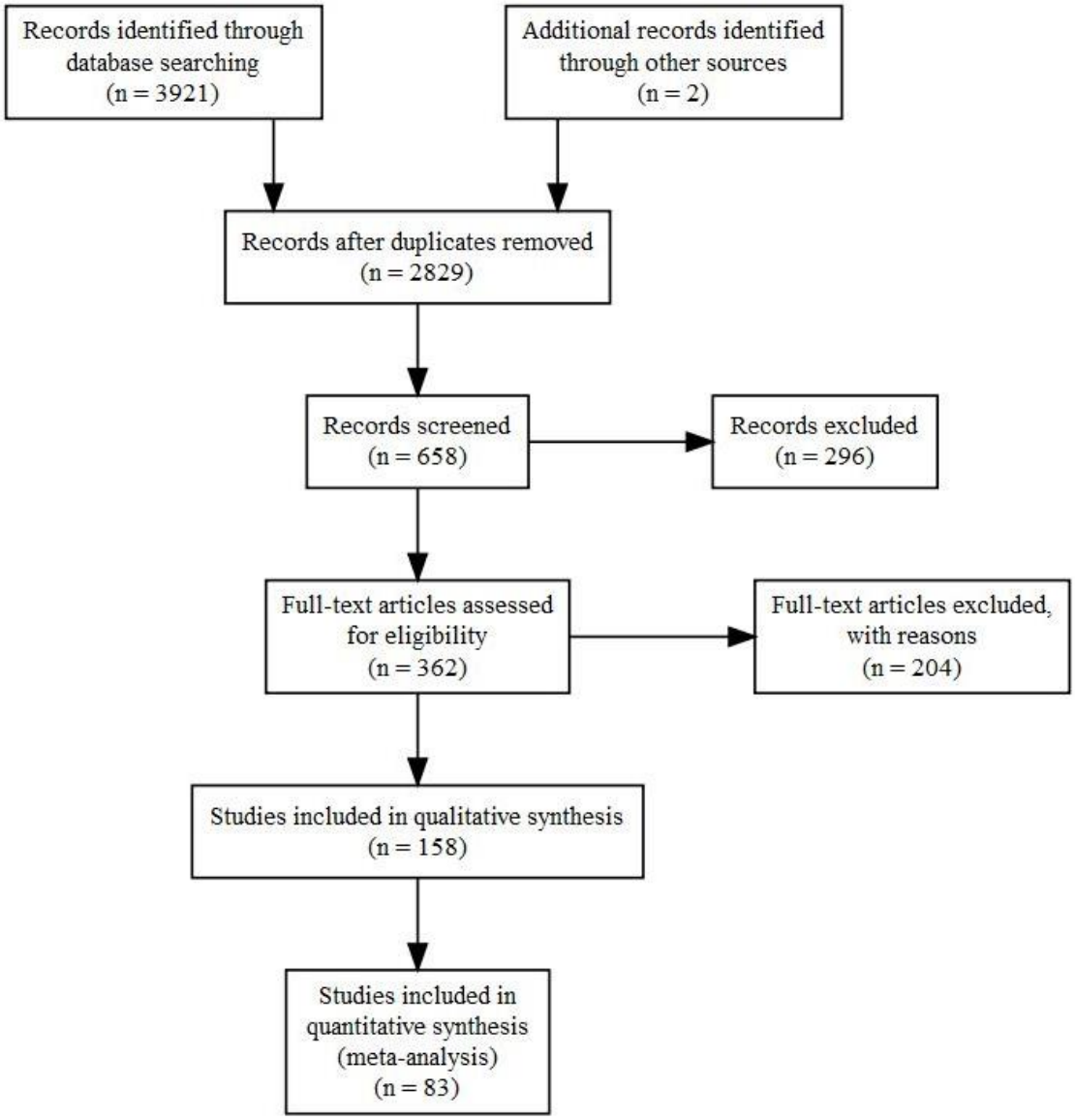


Figure 1. PRISMA flowchart for studies selection

Cognitive outcome in IUGR and SGA preterm children

Globally, the N=31 samples included in the following analysis reported data for 1088 preterm IUGR and SGA children with a mean birth weight of 974.75 grams (SD = 262.87) and gestational age (GA) of 30.51 weeks (SD = 2.82). A total of 12 samples included antenatal diagnosed IUGR, while nineteen samples were of SGA children diagnosed at birth (Appendix: A1, Table 1). Preterm IUGR and SGA children showed significantly lower scores in cognitive outcome compared to AGA peers (SMD = - 0.34, SE = 0.07, 95% CI: - 0.47; -

0.20, Z = - 4.89; p < .0001). Figure 2 reports the forest plot of this meta-analysis. Test for Funnel Plot Asymmetry indicated funnel plot symmetry ($t_{(29)}$= -1.0923, p = .28). The trim and fill method did not suggest the imputation of additional studies. Therefore, no evidence of potential publication bias was found. Test for homogeneity between studies evidences heterogeneity ($Q_{(30)}$ = 72.50, p < .001, I^2= 61.75%). Therefore, moderating effects were tested. Classification (IUGR vs SGA) was not found to play a significant moderating role ($t_{(29)}$ = .6088, p = .44). Also, gestational age at delivery did not play a significant moderating effect ($F_{(1,28)}$ = .00, p = .99), nor did the age at outcome ($F_{(1,29)}$ = 1.14, p = .30).

Subgroup analyses conducted on IUGR and SGA samples separately showed the following estimates: SMD = - .42 (SE = .13, 95% CI: - 0.68; - 0.16, Z = - 3.17; p < .001) for antenatal IUGR, and showing an estimate of SMD = - .30 (SE = .08, 95% CI: - 0.44; - 0.15, Z = - 3.90; p < .0001) for SGA; CIs overlapped indicating no significant differences.

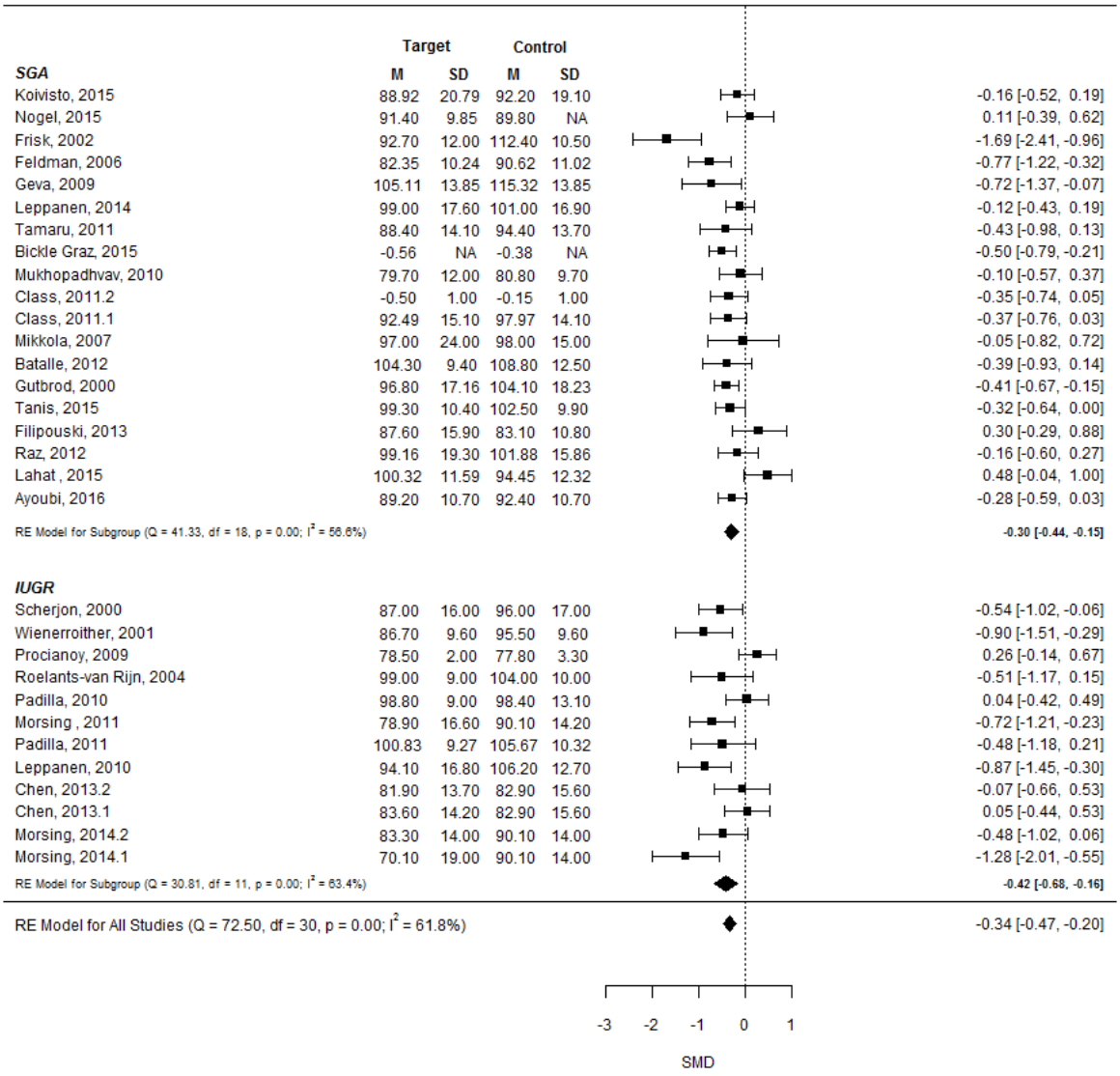


Figure 2. Forest plot for cognitive outcome in IUGR and SGA preterm individuals

Cognitive outcome in IUGR and SGA term-born children

Overall, 17 studies on 2160 term-born IUGR or SGA children were included in the following analyses, with a mean birth weight 2318.30 of grams (SD = 331.99) of and GA of 38.13 weeks (SD = 0.95). Six samples included antenatal diagnosed IUGR, whereas 16 samples were of SGA children diagnosed at birth (Appendix: A1, Table 2). Term-born IUGR and SGA children resulted as having significantly lower scores in cognitive outcome (SMD =

- 0.40, SE = 0.06, 95% CI: - 0.51; - 0.29, Z = - 7.12; p < .0001) compared to their AGA peers. Figure 3 reports forest plot of this meta-analysis. Test for Funnel Plot Asymmetry indicated no funnel plot asymmetry ($t_{(20)}$= 0.7401, p = .47). The trim and fill method did not suggest the imputation of additional studies. Test for homogeneity between studies evidences heterogeneity ($Q_{(21)}$ = 54.65, p < .001, I^2= 66.22%) and moderators were explored as potentially accounting for the heterogeneity in effect sizes. Classification (IUGR vs SGA) was found to play a moderating role close to significance ($t_{(20)}$ = 3.09, p = .08). Age at outcome did not significantly moderate the effect of IUGR and SGA on cognitive outcome ($F_{(1,20)}$ = 0.51, p = .48).

Subgroup analyses conducted on IUGR and SGA samples separately evidenced the following estimates: an high estimate (SMD = - .58, SE = .12, 95% CI: - 0.81; - 0.34, Z = - 4.81; p < .0001) for antenatal IUGR; a medium-to-high estimate (SMD = - .35, SE = .06, 95% CI: - 0.47; - 0.23, Z = - 5.75; p < .0001) for SGA.

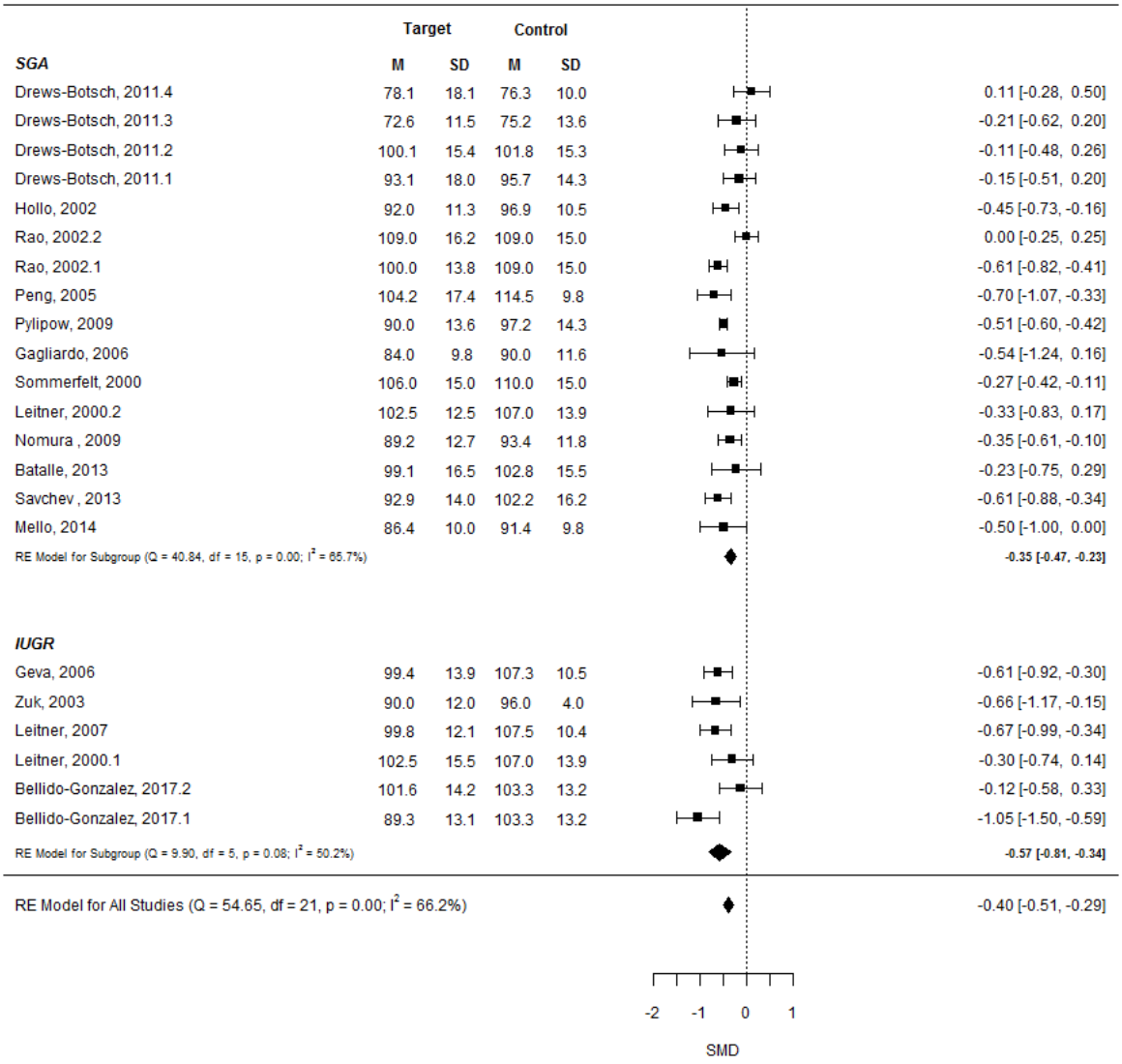


Figure 3. Forest plot for cognitive outcome in IUGR and SGA term-born individuals

Borderline intellectual functioning in IUGR and SGA children

Only 2 studies (Jelliffe-Pawlowski & Hansen, 2004; Peng et al., 2005) involved term-born SGA children and indicated a significantly higher risk for mental delay compared to their AGA peers (OR = 1.75, 95% CI, 1.50 to 2.04).

Of the 21 studies conducted on preterm samples, 6 studies included antenatal diagnosed IUGR children and 16 studies included former SGA children. Characteristics of these studies are summarized in Table 3 (Appendix A1). Globally, 1961 children (374 IUGR and 1587

SGA), with a mean birth weight of 940.44 (SD = 338.9) grams and 29.56 (SD = 2.85) gestational weeks at delivery, were assessed. IUGR and SGA preterm children were found to be at significantly higher risk for borderline intellectual functioning than AGA preterm peers (OR = 1.61, 95% CI, 1.42 to 1.82, $Z = 7.59$; $p < .001$). Figure 4 shows the forest plot of this meta-analysis.

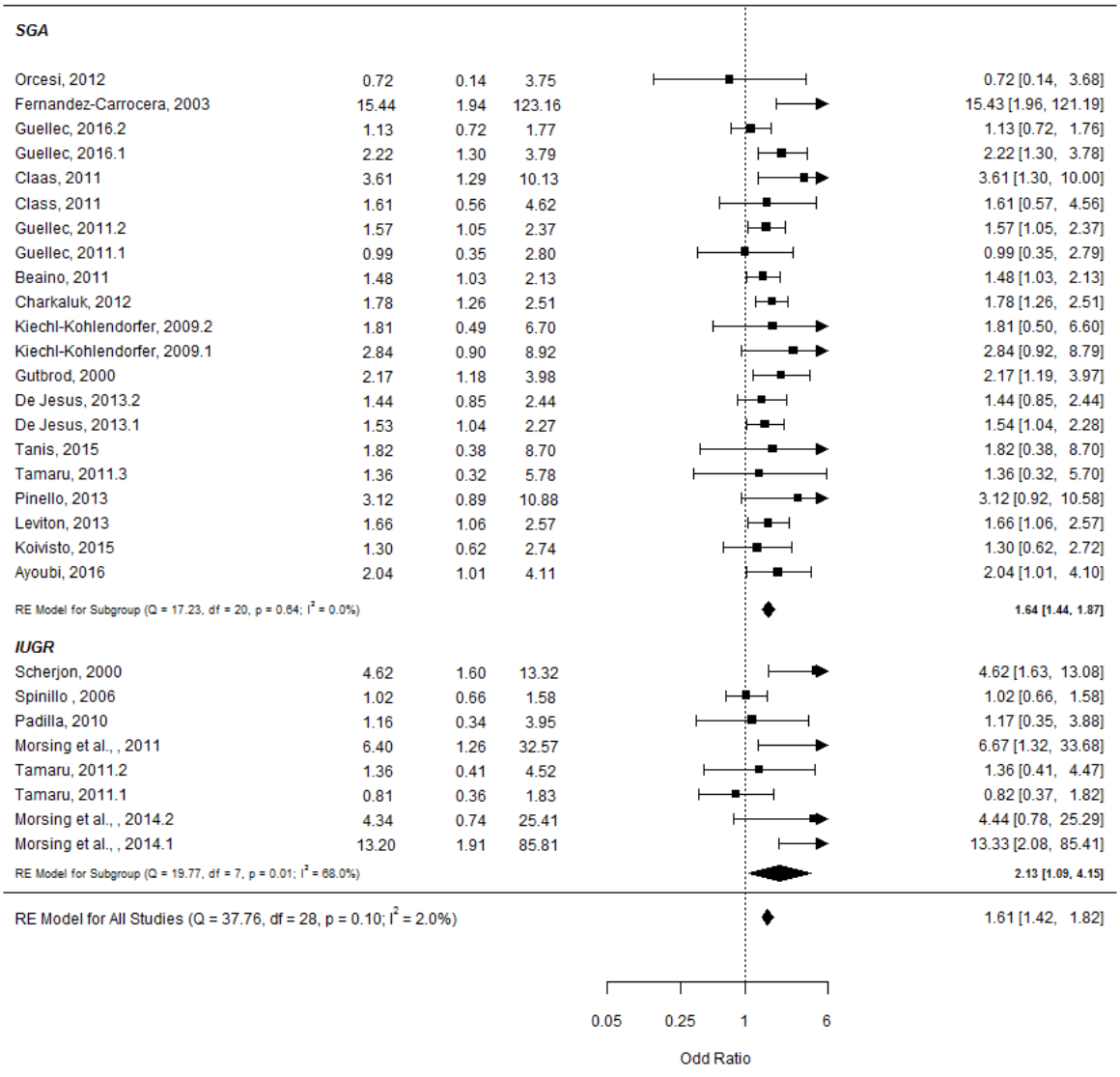


Figure 4. Forest plot for borderline intellectual functioning in IUGR and SGA preterm individuals

Test for Funnel Plot Asymmetry indicated significant funnel plot asymmetry ($t_{(27)}$= 2.4274, p = .02) and the trim and fill method suggested the imputation of five additional studies on the left side of the funnel plot (Figure 5).

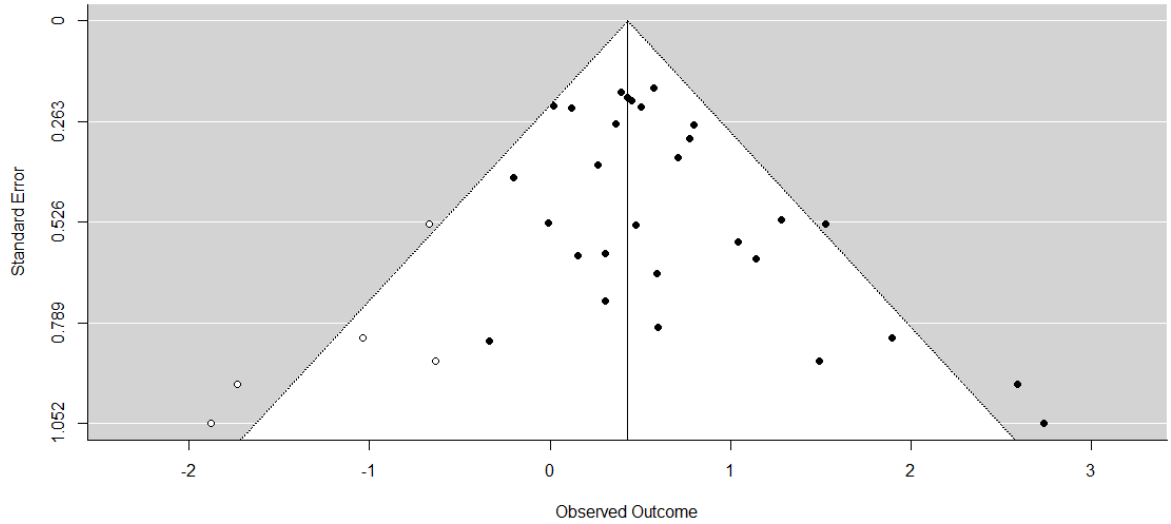


Figure 5. Funnel Plot for asymmetry in studies on borderline intellectual functioning

Test for homogeneity between studies evidences no heterogeneity ($Q_{(28)}$ = 37.76, p =.10, I^2= 2%). Meta-analyses on IUGR and SGA subgroups are presented in Figure 4. Another subgroup meta-analysis was conducted on studies (k=5) presenting data on cognitive delay in terms of cognitive outcome < 2 SD. Results revealed an higher risk for cognitive impairment for IUGR and SGA preterm children (OR = 2.77, 95% CI, 1.28 to 6.00, Z = 2.60; p < .01).

DISCUSSION

The present meta-analyses were conducted to quantify the effects of antenatal IUGR and SGA birth classification across the gestational age at delivery spectrum, separately considering the case of cognitive outcome and risk for intellectual functioning along the first 12 years of life. Based on 83 studies, robust evidence was found for cognitive vulnerability in both IUGR and SGA samples, compared to their matched for GA at delivery AGA peers.

Specifically, effects were consistent in preterm and term-born samples, across age at outcome and between the outcome domains (cognitive score and borderline intellectual functioning).

Meta-analysis on preterm group (mean GA at delivery <=37) proved that IUGR and SGA individuals have significantly lower cognitive scores compared to AGA peers, showing no heterogeneity among studies. Effects ranged from small to medium, with an overall small mean effect size. Prematurity is known as major perinatal risk factor for neurodevelopment (Allotey et al., 2018); notably, IUGR and SGA give additional risk, leading downward developmental routes of preterm children. Literature underlines huge heterogeneity in developmental outcomes of preterm children, claiming for characterization of subgroups differently exposed to negative developmental outcomes. Our findings point out that IUGR and SGA might group individuals with antenatal and perinatal experiences exposing to impoverished cognitive growth.

Meta-analysis on term-born children revealed significantly lower cognitive scores for IUGR and SGA individuals, compared with term-born AGA peers. Results show moderate variability among studies not accounted by the moderators tested. Effect size ranged from small to medium, with a small mean estimate; qualitatively, IUGR subgroup display overall higher effect sizes and higher heterogeneity among studies, whereas low variability is observed in SGA subgroup also presenting smaller SMDs across studies. These findings allow to reflect upon the importance for pediatric general health providers to early target those children around the time of birth, monitor their neurodevelopment and effectively intervene to sustaining global cognitive abilities. Indeed, term born IUGR and SGA are likely to present the lower cognitive abilities as preterm children do; however, they are very unlikely to receive post-natal follow up tailored care and habilitative trainings (Nomura et al., 2009).

Meta-analysis on borderline intellectual functioning revealed that both IUGR and SGA are at significantly increased risk compared to AGA preterm peers. Only two studies gave results on rates of borderline intellectual functioning in term born samples, highlighting this current gap in literature and hampering generalizable conclusions. Within preterm samples, IUGR and SGA children are 1.61 times more likely to score < 1SD in intelligence tests. Funnel plot revealed potential publication bias; hence warning the interpretation of these results. Sensitivity analysis showed that when considering subgroup of studies testing cognitive impairment, IUGR and SGA preterm are 2,77 times more likely to score < 2 SD then their AGA preterm peers. These results corroborate findings of the two meta-analysis presented on group comparison, highlighting that IUGR and SGA are not only associated with lower cognitive scores within a normative range but rather increase the risk for cognitive impairment confirming their remarkable role as perinatal risk factors for neurodevelopment.

Across the meta-analyses presented (on preterm cognitive outcome, term-born cognitive outcome and preterm intellectual risk), subgroup analyses consistently revealed no significant difference in estimates for IUGR and SGA subgroups. Surely, since meta-analysis only allow to methodologically framing results, we provide no answer to the theoretical question regarding constitutionality of SGA at delivery and putative etiopathological differences with antenatal IUGR. This study reports the first comprehensive evidence that SGA classification at delivery reliably detects cognitive risk across childhood in both preterm and term-born individuals. Hence, regardless being a proxy of antenatal growth, neonatal birth weight classification of Small for Gestational Age is a relevant clinical screening for cognitive vulnerability. The power of this consideration appears greater when considering that term-born children without antenatal evidence of perinatal risk are not likely to receive specific postnatal care, laying their silent vulnerability neglected. Surely, retrospective study designs or unreported antenatal diagnosis might bias our results, making it possible that at

least some IUGR individual is in the SGA group. Meta-analysis on available literature does not allow clarifying this point, making cautions the interpretation of these findings. Consequently, further research is needed on SGA children with no antenatal signs of growth restriction in order to disentangle the effect of birth smallness without atypical antenatal environment form the role of altered antenatal growth on neurodevelopment.

An additional result worthy to comment is that age at outcome does not moderate the effect of IUGR and SGA on cognitive outcome and risk for intellectual functioning. This means that the gap observed for IUGR and SGA children in respect to their preterm and term-born AGA peers mostly remains as unfilled from infancy up to middle childhood. Studies selected over-represent the first two years of cognitive development, highlighting the necessity of long-term follow up studies both for clinical intervention and for research purposes.

Interpretation, strengths and limitations

Overall, findings do reveal that both IUGR and SGA direct the cognitive trajectories of both preterm and term-born children toward negative cognitive outcomes, suggesting that antenatal and perinatal stressful growth conditions directly affect postnatal neurodevelopment. Interpretations interest the role of perinatal brain development and post-natal environment. Although not all the mechanisms underpinning IUGR are completely understood, placental insufficiency represents the main adversity in maternal environment linking fetal growth to subsequent structural and functional outcomes (Miller et al., 2016). Reduction in placental blood flow exposing to hypoxemia and undernutrition and producing a decrease in growth rate are likely to affect the important brain changes occurring along gestation, which are highly susceptible to stress exposure and impoverished environmental conditions. Frontal lobes, which are related to cognitive performances, are especially vulnerable to nutritional insults during third trimester of pregnancy (Sanz-Cortés et al., 2010).

Protective mechanisms of regional brain sparing, redirecting cardiac output to ensure the brain growth are described in IUGR fetuses (Resnik, 2002). However, human brain evolves to expect certain inputs in order to select synaptic connections (Fenoglio, Georgieff, & Elison, 2017); lacks and/or retardations in expected inputs may lead to the spectrum of observed abnormalities in brain structure (Lodygensky et al., 2008a; Tolsa et al., 2004b) and connectivity (Batalle, Eixarch, Muñoz-Moreno, et al., 2012) in both preterm and term-born IUGR infants.

In addition, studies evidenced increased environmental susceptibility in growth vulnerable individuals, suggesting that postnatal environment is crucial to constrain or rather intensify the effects of growth vulnerabilities (Nichols et al., 2017). Insight into post-natal factors contributing to subsequent outcomes of IUGR and SGA children are of high interest to improve such outcomes through the enhancement of environmental protective factors and to explore whether those children have enhanced response to cognitive trainings, hence suggesting increased plasticity to prenatal and postnatal stimulations.

The main advance given by this study is to comprehensively address the cognitive outcome of growth vulnerability experienced by true antenatal IUGR and SGA birth classification while keeping the two groups as distinguished. In addition, by including but treating separately preterm and term-born groups, this study shed light on the specific contribution added by growth vulnerabilities (IUGR and SGA) to the corresponding gestational age appropriate development. Hence, it is possible to recognize that IUGR and SGA have significant effect on term-born growth as well as in the co-occurrence of prematurity. Other strengths of this meta-analytic study include the large number of samples across countries as well as the wide span of outcome assessment.

The study also presents some limitations. First, in several researches there were lots of missing information about demographical and perinatal variables, making it difficult to study

the role of potential relevant factors such as sex, neonatal intensive care experience or socio-economic status (which is hardly comparable across states even when the information is provided). A second limitation already mentioned is the potential presence of antenatal IUGR individuals within the SGA groups. This point hampers a clear answer about potential etiopathological differences between constitutionally SGA and former-IUGR SGA. Another limitation refers to the exclusion of the so called "grey literature" and unpublished data, which might result in concerning about publication bias. However, publication bias controlling has been addressed through statistical analysis evidencing its possibility only for mental delay assessment.

Conclusion

Knowing perinatal risk factors for cognitive development would benefit clinical decision making and parent counseling in neonatal period. Data do reveal that growth vulnerability assessed antenatal (IUGR) and by the time of birth (SGA) are powerful predictors of cognitive risk both in preterm and term-born individuals. Findings shows stability in developmental trajectories, with no decrease from infancy to middle childhood in the cognitive gap observed in IUGR and SGA children compared to AGA peers. These findings suggest that, for better outcomes in IUGR and SGA children, it would be beneficial: i) constant improvements in antenatal diagnosis, in order to detect as early as possible the onset of growth restriction; ii) more detailed research designs comparing IUGR and SGA-not former IUGR children to clearly disentangle their effects on cognition; iii) specific and constant interventions boosting cognitive functioning both in preterm and term-born vulnerable IUGR and SGA children.

Summarizing, the present study represents the first and comprehensive evidence that IUGR and SGA constitute prominent risks for subsequent cognitive outcome of term-born

children, and both target preterm children for specific additional cognitive risk across childhood.

Part 2. A developmental cascade

BIOBEHAVIORAL PROCESSES INTERESTING IUGR DEVELOPMENTAL OUTCOMES

CHAPTER 2: Sacchi C., Falconer S., O'Muircheartaigh J., Batalle D., Simonelli A., Cesano M., Counsell S., Kennea N., Edwards A.D., Nosarti C. (in preparation). *Intrauterine Growth Restriction in very preterm infants affects grey matter volumes and subsequent cognitive and behavioral outcomes.*

CHAPTER 3: Sacchi C, De Carli P., Mento G., Farroni T., Visentin S., Simonelli A. (2018). Socioemotional and- cognitive development in Intrauterine Growth Restricted (IUGR) and typical development infants: early interactive patterns and underlying neural correlates. Rationale and methods of the study. *Frontiers in Behavioral Neuroscience.* 12, 315.

CHAPTER 4: Sacchi C., Visentin S., De Carli P., Furlan A., Simonelli A., (in preparation). *Interactive behaviors and early neurodevelopmental outcomes in infants with Intrauterine Growth Restriction. Preliminary report on the first year of liv*e.

CHAPTER 2

Intrauterine Growth Restriction in very preterm infants affects grey matter volumes and subsequent cognitive and behavioral outcomes

ABSTRACT

Does Intrauterine Growth Restriction (IUGR) add further neurodevelopmental risk to that posed by very preterm birth alone?

In this chapter we explore whether Intrauterine Growth Restriction (IUGR) adds further risk of alterations in brain development and of adverse childhood outcomes of VPT infants.

We present a longitudinal cohort study on VPT infants (GA < 33 weeks); participants (N=314) were recruited at birth and followed-up (N = 284, 90% of initial cohort) to 22 months corrected age. Structural T2 images were acquired at term equivalent, cognitive development at 22 months was assessed with the Bayley Scales for Infant Development and behavioral problems rated with the Modified-CHecklist for Autism in Toddlers (MCHAT).

At 40 weeks term-equivalent, IUGR (N = 49) infants display increased grey matter volumes in fronto-striatal, fronto-parietal and frontal clusters and decreased volume in Emotion Processing cluster compared to AGA VPT (N=265) peers. At 22 months, IUGR (N= 45) perform significantly lower on cognitive (88.78 ± 10.88 vs 94.25 ± 13.31) and motor (91.71 ± 11.69 vs 96.46 ± 11.62) tests compared to AGA VPT (N = 238) toddlers. They are also more likely to score positive on the M-CHAT (OR = 2.12, 95%CI – 1.11 to 4.05).

IUGR is associated with extensive volumetric brain differences at term equivalent age and with poorer cognitive and behavioral outcomes at 22 months. These findings have implications for identifying prenatal factors impacting VPT brain development and devise neuroprotective strategies to constrain the effects of IUGR.

INTRODUCTION

In 2015, the Global Burden of Disease Study estimated that preterm birth (<37 weeks of gestation) was the most common cause of death and disability in children under the age of 5 years (Almeida, Capucho, Duque, Machado, & Rodrigues, 2016). Live preterm births are increasing, with rates currently estimated by the World Health Organization as ranging between 5% and 18% of all births. With the increase of survival and the backward shift of human viability to 23-24 weeks of gestation, ex-preterm individuals often display neurological, behavioral and cognitive comorbidities throughout their life. The umbrella term "very preterm phenotype" has in fact been proposed to encompass cognitive impairments, attention deficits, socio-emotional difficulties, and internalizing problems associated with preterm birth (Johnson & Marlow, 2011). However, the developmental trajectories of preterm born children are heterogeneous, hence the need to understand the early risks for adverse outcomes prior to their phenotypical presentation in order to devise and implement early targeted interventions (Batalle et al., 2018).

Intrauterine Growth Restriction (IUGR) is a leading cause of perinatal mortality (Murray et al., 2015), responsible for 26 and 53% of preterm and term-born still-births, respectively (Bashat & Galan, 2018). IUGR represents the process of antenatal adaptation to suboptimal in-utero environmental conditions leading to reduced growth. This is a likely outcome of placental insufficiency and results from fetal protective attempts to face the reduction of placental blood flow increasing the risk of hypoxemia and undernutrition (Baschat, 2014). Such adverse environmental conditions may result in fundamental neural changes, with severe consequences for the developing brain (Rees et al., 2011). Surviving IUGR infants display a range of long-lasting neurodevelopmental problems, encompassing cognitive, socio-emotional and behavioral domains.

During fetal life, the developing brain exhibits its greatest plasticity, flexibility, and vulnerability to nutritional insults. Magnetic Resonance Imaging (MRI) has been instrumental in characterizing neuroanatomical brain alterations associated with IUGR at different stages of development. In utero, IUGR fetuses display altered patterns of cortical development, including deeper sulci in insula and left cingulate fissure (Egaña-Ugrinovic, Sanz-Cortes, Figueras, Bargalló, & Gratacós, 2013). Preterm IUGR new-borns show significant reduction in intracranial volume and in cerebral cortical grey matter (Tolsa et al., 2004a), smaller thalamic, basal ganglia and hippocampal volumes (Bruno et al., 2017; Lodygensky et al., 2008a), and altered cortical gyrification and cortical thickness compared to appropriate for gestational age (AGA) preterm peers (Dubois et al., 2008). Structural brain changes persist during the first years of life, with findings including reduced grey matter volumes in temporal, parietal, frontal and insular regions (Padilla et al., 2011), reduced grey and white matter structural complexity (Esteban et al., 2010), reduced white matter volume and myelin alterations (Padilla et al., 2011). IUGR children display brain connectivity alterations, especially in motor and cortico-striatal-thalamic networks (Fischi-Gómez et al., 2015), while in adulthood alterations in white matter microstructure have been reported (Eikenes et al., 2012; Fischi-Gómez et al., 2015). Such structural brain alterations might represent the progression of a cascade of detrimental effects associated with impoverished neurodevelopment.

This study aims to investigate the association between IUGR, brain development at term equivalent age (e.g., 40 weeks), and childhood outcomes following very preterm birth. Firstly, we compare structural brain differences between very preterm IUGR and AGA infants; secondly, we compare cognitive and behavioral outcomes between very preterm IUGR and AGA toddlers (mean age 22 months); and thirdly, we explore the association between structural brain alterations and toddlers' cognitive and behavioral outcomes.

METHODS

Study population

Participants were 511 very preterm (VPT) born toddlers enrolled into the longitudinal Evaluation of Preterm Imaging Study (e-Prime Eudra: CT 2009-011602-42; Edwards et al., 2018). Participants were recruited at birth in 2010-2013 from hospitals within the North and Southwest London Perinatal Network. Infants were included in the study if born before 33 weeks' gestation and their mother was over 16 years of age and not a hospital inpatient. Exclusion criteria included the presence of: major congenital malformation, prior magnetic resonance imaging (MRI), metallic implants, parents unable to speak English, or if the infant was subject to child protection proceedings.

IUGR was identified postnatally by reviewing medical discharge records. To ensure the presence of alterations in the antenatal environment IUGR definition was limited to: antenatal presence of abnormalities in fetal scans and/or doppler ultrasound velocimetry described as absent and/or reversed end diastolic flow, clinical evaluation showing high risk factors for IUGR, such as maternal preeclampsia or placental insufficiency, combined with very low estimated fetal weight and/or reported signs of cerebral redistribution; reported asymmetrical fetal growth. Appropriate for gestational age (AGA) was defined as birth weight > 10th centile for gestational age.

Infants received MRI at term-equivalent age, 40 weeks. At 22 months of age all toddlers were invited for neurodevelopmental assessment. Written informed consent was obtained from new-borns' carer(s) following procedures approved by the National Research Ethics Committee (14/LO/0677). Research described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Procedure

Perinatal clinical and socio-demographic data. Perinatal clinical and socio-demographic data were collected with permission from the Standardized Electronic Neonatal Database. They included gestational age at birth, sex, days of mechanical ventilation, days of parenteral nutrition, mother's age and Index of Multiple Deprivation (IMD) score, which provide a proxy for family socio-economic status.

MRI acquisition and analysis. A Philips 3 Tesla (Philips Medical Systems, Best, The Netherlands) system sited on the neonatal intensive care unit fitted with an eight-channel phased array head coil was used to acquire T2-weighted images (TR 8,670 ms; TE 160 ms; flip angle 90°; slice thickness 2 mm; in plane resolution 0.86 × 0.86 mm). An experienced neonatal radiologist qualitatively rated the MRI scan of each infant and assigned an overall global score that described the clinical severity of brain abnormalities. Scores ranged from 2-0; 2 = major lesion, defined as cystic periventricular leukomalacia, >10 punctate white matter lesions, grade 3 or 4 germinal matrix haemorrhage; 1 = minor lesion, defined as all any other lesions; 0 = no lesion.

A week-appropriate atlas was created combining cortical parcellations from the UNC infant brain atlas (82 cortical areas, Shi et al., 2011) and subcortical grey matter parcellations from an automated neonatal specific segmentation tool (Makropoulos et al., 2016, 2014). The final atlas consisted of 92 regions. For each subject, the mean Jacobian value for each region was extracted. The Jacobian determinant is a relative measure that refers to the volume in the original image in relation to the volume in the warped image. Jacobian determinant values express the rate of each brain region's compression to fit the space of a reference image; that means greater Jacobian determinant's values correspond to smaller brain regions compared to the template (i.e. a Jacobian value of 0.5 refers to the region having been compressed by a factor of 2 from its original size in the --in image when warped into the space of the --ref image).

Principal component analysis (PCA) was performed on the 92 brain regions using the Varimax method of rotation. Visual inspection of the scree plot (i.e., eigenvalues associated with each factor) was used to determine the number of factors to retain and a loading factor of =<0.40 was used to determine the brain regions that made up a specific component (hereby referred to as "volumetric component"); negative loading reflects a negative relation of the regional Jacobian determinant to the "volumetric component".

Cognitive outcome. The Bayley Scales for Infant Development—Third Version (BSID—III; Bayley, 2006) were used to evaluate cognitive, language and motor development. Each of the three scales provides a raw score, and a scaled score (M = 10, SD = 3). Cognitive, language and motor scales can be combined to obtain a composite score with a mean value of 100 and a standard deviation of 15. Composite scores lower than 85 are considered as reflecting "developmental delay" (Albers & Grieve, 2007).

Behavioral outcome. Behavioral outcome was assessed with the Modified-Checklist for Autism in Toddlers (M-CHAT; Robins, Fein, & Barton, 1999), which consists of a series of 23 "yes/no" parent-rated questions about children's behavior. Positive screening is given when 2 of 6 critical items (namely, items: 2, 7, 9, 13-15) or 3 of any 23 items are rated as positive ("yes").

STATISTICAL ANALYSES

To compare brain "volumetric components" between IUGR and AGA VPT new-borns, multivariate analysis of variance (MANOVA) was performed on estimated factors scores from PCA, controlling for sex, gestational age at delivery (weeks) and IMD score. Supplemental MANOVA was performed to observe differences between IUGR and AGA VTP infants across all 92 brain regions (i.e., before PCA); summary results are presented in Appendix (A2, Table 2). Linear regression was performed to test the effect of IUGR on cognitive, motor and language outcomes, controlling for sex, gestational age at delivery

(weeks) and socio-economic status (i.e., IMD score). Logistic regression was performed to test the effect of IUGR on M-CHAT positive screening, accounting for the abovementioned confounding variables. Lastly, brain "volumetric components" extracted from PCA were used in linear and logistic regression to test for their association with cognitive, motor and behavioral outcomes, controlling for sex, gestational age at delivery (weeks) and IMD score.

RESULTS

The original sample consisted of 511 VPT new-borns. An experienced neonatal radiologist qualitatively rated the MRI scan of each infant and assigned an overall global score that described the clinical severity of brain abnormalities. Scores ranged from 0-2 describing no lesions, minor and major lesions; 157 VPT were excluded for presence of minor and major lesions in MRI scan at 40 weeks term-equivalent. Minor lesions included isolated subependymal cysts, grade one germinal matrix haemorrhage, less than ten punctate lesions that did not involve the cortico-spinal tract, mild ventricular dilatation, and solitary punctate cerebellar haemorrhage. Major lesions included 2-4 GMH, cystic periventricular leukomalacia, multiple cerebellar haemorrhage, multiple punctate lesions including those involving the CST, or a combination of minor lesions. Of the remaining 354 new-borns, 32 VPT were excluded from the present study because they had a BW < 10^{th} centile in the absence of any reported signs of antenatal growth restriction. Other 8 participants were excluded as they had cerebral palsy (Gross Motor Function Classification System score > 2). Antenatal characteristics and perinatal outcomes of the study groups are reported in Table 1.

Table 1. Antenatal Characteristics and Perinatal Outcomes of the Study Groups

	IUGR VPT (*n* = 49)	AGA VPT (*n* = 265)	*p values*
Antenatal characteristics			
Maternal age (years)	31.13 ± 6.11	32.64 ± 5.77	.115

Maternal hypertension (years)	4 (8.1%)	15 (6.5%)	.727
Index of Multiple Deprivation	20.95 ± 11.84	19.54 ± 11.96	.452
Perinatal outcomes			
Multiple pregnancy	10 (21%)	88 (35.4%)	.103
Birth weight	1046.06 ± 263.36	1412.52 ± 395.28	< .001
BW centile	5.62 ± 6.58	46.83 ± 22.75	< .001
Head circumference	28.19 ± 3.00	29.29 ± 3.06	.027
Gestational age at delivery	30.35 ± 1.75	29.84 ± 2.28	.083
Sex (male)	27 (56%)	133 (50%)	.538
Ventilation (days)	2.55 ± 5.41	2.24 ± 4.75	.720
Parenteral nutrition (days)	9.25 ± 8.49	7.23 ± 10.51	.154

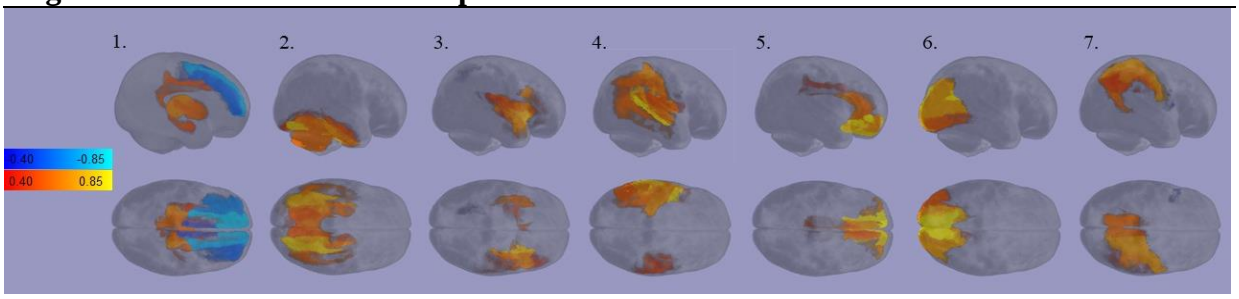
Note. Data are given as n (%), mean ± SD
p-values are calculated using Student's t-test, Pearson's chi-square test.
IUGR = intrauterine growth restriction;
AGA = appropriate for gestational age;
VPT = very preterm

Intrauterine Growth Restriction and brain developments at 40 weeks term-equivalent

Principal component analysis on the 92 Jacobian determinants yielded a 7-factors solution, accounting for 54.3% of cumulative variance. The first component identifies a "Thalamo-Cortical component" made up by superior and middle frontal gyrus, supplementary motor area, median and posterior cingulate, Heschl gyrus, thalamus and pallidum. The second component is interpreted as an "Emotion Processing" cluster including hippocampus and para-hippocampal gyrus, amygdala, fusiform gyrus, inferior temporal gyrus and cerebellum. The third component consists of inferior frontal gyrus, Rolandic operculum, insula, superior parietal gyrus, caudate nucleus, putamen and superior temporal gyrus and describes a "Fronto-striatal" cluster. The fourth component includes inferior frontal gyrus,

Rolandic operculum, inferior parietal gyrus, supramarginal gyrus, angular gyrus, superior and middle temporal gyrus and represents a “Fronto-Parietal-Temporal” component. The fifth component describes a “Frontal” component including superior and middle frontal gyrus, rectus gyrus and anterior cingulate. The sixth component represents an “Occipital” component including lingual gyrus, calcarine fissure, cuneus, superior, medial and inferior occipital gyrus. Last component includes inferior frontal gyrus, postcentral gyrus, superior parietal gyrus, angular gyrus, precuneus, and paracentral lobule and describes a “Fronto-Temporal-Parietal” cluster. The 7 PCA volumetric components are presented in Figure 1.

Figure 1. **PCA 7 volumetric components**



Note. colored regions represent Jacobian determinants with standardized factor loadings > ± .40. The following components are shown:1. Thalamo-Cortical; 2. Emotion Processing; 3. Fronto-Striatal; 4. Fronto-Parietal-Temporal; 5. Frontal; 6. Occipital; 7. Fronto-Temporal-Parietal.

Eigenvalues and standardized Factor loadings of the 7-factors solution are reported in Appendix (A2, Table 1).

Table 2 shows PCA factor scores of IUGR VPT new-born compared to AGA peers; a graphical representation is provided in Appendix (A2, Figure 1). Results of MANOVA showed a significant main effect of IUGR on brain “volumetric components” at 40 weeks term-equivalent after controlling for sex, gestational age at delivery and IMD score ($F(7, 302) = 5.97$, $p < .001$). IUGR compared to AGA infants had smaller emotion processing component volume ($b = 0.79$, $SE = 0.15$, $t(308) = 5.31$, $p < .001$), larger fronto-striatal component volume ($b = - 0.34$, $SE = 0.15$, $t(308) = - 2.25$, $p = . 044$), larger fronto-parietal

component volume (b = - 0.35, SE = 0.15, $t(308) = -2.33$, $p = .044$), and frontal component volume (b = - 0.36, SE = 0.16, t(308) = -2.27, $p = .044$).

Table 2. "Volumetric components" in IUGR and AGA VPT groups.

	IUGR VPT (n = 49)	AGA VPT (n = 265)	*p values*	ES [95% CI]
Thalamo-Cortical	0.037 ± 0.927	- 0.007 ± 1.014	.776	*d* = - .05 [- 0.35 – 0.26]
Emotion Processing	0.593 ± 1.092	- 0.109 ± 0.944	< .001	*d* = - .73 [-1.04 – -0.42]
Fronto-Striatal	- 0.236 ± 0.923	0.043 ± 1.009	.127	*d* = .28 [- 0.03 – -.059]
Fronto-Parietal	- 0.343 ± 1.191	0.063 ± 0.949	.030	*d* = .41 [0.10 – 0.72]
Frontal	- 0.299 ± 0.926	0.055 ± 1.004	.052	*d* = .36 [0.05 – 0.66]
Occipital	- 0.106 ± 1.027	0.019 ± 0.996	.589	*d* = .13 [- 0.18 – 0.43]
Fronto-Temporal -Parietal	0.064 ± 0.965	- 0.012 ± 1.007	.728	*d* = - .08 [- 0.38 – 0.23]

Note. Data are given as mean ± SD
p-values are adjusted for FDR (Benjamini & Hochberg, 1995)
IUGR = intrauterine growth restriction;
AGA = appropriate for gestational age;
VPT = very preterm
ES – effect size
CI = confidence interval
d = Cohen's d

Supplemental analyses revealed several volumetric differences between IUGR and AGA VPT new-borns in in the 92 brain regions ($F(92, 217) = 2.08$, $p < .001$); these results are reported in Appendix (A2, Table 2).

Intrauterine Growth Restriction and developmental outcomes at 22 months

At 22 months of age IUGR VTP toddlers had lower BSID – III scores (composite cognitive, motor and language) compared to those who were born appropriate for gestational age. They were also more likely to score positively on the M-CHAT (Table 3). After adjusting for sex, gestational age at birth and Multiple Deprivation Index score, the effect of IUGR only remained significant for cognition ($b = -5.27$, $SE = 1.99$, $t(279) = -2.64$, $p = .015$) and motor outcome ($b = -4.80$, $SE = 1.85$, $t(279) = -2.60$, $p = .015$); whereas no effect was found for language outcome ($b = -4.80$, $SE = 2.60$, $t(279) = -1.86$, $p = .065$). Between-group differences in terms of M-CHAT positive screening remained evident after controlling for the same confounders ($b = 0.74$, $SE = 0.34$, $z = 2.18$, $p = .027$).

Table 3. Cognitive, Motor, Language and Behavioral development for IUGR vs AGA subgroups at 22 months of life

	IUGR VPT (*n* = 45)	AGA VPT (*n* = 238)	*p values*	ES [95% CI]
BSID – III Cognitive scale	88.78 ± 10.88	94.25 ± 13.31	.019	*d* = .42 [0.10 – 0.74]
BSID – III Motor scale	91.71 ± 11.69	96.46 ± 11.62	.019	*d* = .41 [0.09 – 0.73]
BSID – III Language scale	87.00 ± 15.90	92.62 ± 17.10	.042	*d* = .33 [0.01 – 0.65]
M-CHAT	20 (43.48)	64 (26.67)	.024	OR = 2.12 [1.11 – 4.05]

Note. Data are given as n (%), mean ± SD
p-values are adjusted for FDR (Benjamini & Hochberg, 1995)
IUGR = intrauterine growth restriction;
AGA = appropriate for gestational age;
VPT = very preterm
ES – effect size
CI = confidence interval
d = Cohen's d
OR = Odd Ratio

Grey matter alterations at 40 weeks and developmental outcomes at 22 months

The results of linear and logistic regressions to explore, in the whole sample, the association between grey matter "volumetric components" and cognitive, motor and behavioral outcomes, accounting for sex, IMD score and gestational age at delivery revealed the following. Lower cognitive scores were associated with decreased values (i.e. larger volumes) in two components: frontal (b = 1.54, SE = 0.72, $t(279)$ = 2.14, p = .033) and occipital (b = 1.52, SE = 0.73, $t(279)$ = 2.09, p = .037). Lower motor scores were associated with decreased values in the fronto-temporal-parietal component (b = 1.44, SE = 0.69, $t(279)$ = 2.08, p = .038). No significant association was found for "volumetric components" and positive M-CHAT screening.

DISCUSSION

Results of this longitudinal study, in a large sample of individuals who were born very preterm, showed that IUGR (compared to AGA) was associated with extensive volumetric brain differences at term equivalent age and with poorer cognitive and behavioral outcomes at 22 months. Such structural brain alterations might represent the beginning of a cascade of atypical developmental patterns leading to the long-term sequelae associated with IUGR. These findings demonstrate that antenatal life is a sensitive and critical period for neurodevelopment, highlighting the strong and long-lasting mark that biological stress, such as growth restriction, has on cognitive, motor and behavioral growth, beyond the well-known effect of prematurity (Allotey et al., 2018). It is therefore critical to closely monitoring the postnatal neurodevelopment of IUGR individuals and devise and implement early targeted interventions aimed at supporting children's cognitive development.

At 40 weeks term-equivalent age, we noticed small to medium differences in four out of seven "volumetric components" yielded by PCA between the IUGR and the AGA subgroups. IUGR infants had smaller gray matter (GM) volume in an emotion processing component (i.e. hippocampus, amygdala, parahippocampal gyrus, fusiform gyrus, inferior temporal gyrus, and cerebellum) and larger grey matter volume in a fronto-striatal component (i.e. inferior frontal gyrus, Rolandic operculum, olfactory cortex, insula, superior parietal gyrus, caudate nucleus, putamen), a fronto-parietal (inferior frontal gyrus, Rolandic operculum, inferior parietal gyrus, supramarginal gyrus, angular gyrus, superior and middle temporal gyrus) and a frontal component (superior and middle frontal gyrus, rectus gyrus and anterior cingulate). These findings are in line with results of previous studies that showed that brain alterations associated with IUGR prenatally and in the first years of life particularly affected frontal and limbic regions (Batalle, Eixarch, Figueras, et al., 2012; Lodygensky et al., 2008b; Padilla et al., 2011, 2014). Volumetric reduction in limbic regions, especially

amygdala and hippocampus, might result from fetal exposure to glucocorticoid levels heightened under conditions of maternal stress and/or placental disfunctions (Lupien, McEwen, Gunnar, & Heim, 2009; O'Donnell & Meaney, 2016). Conversely, the fronto-striatal volumetric increase we report in the IUGR group might reflect neuroprotective *brain sparing* processes observed in IUGR pregnancies, which focus on delivering most nutrients to the major organs (i.e., adrenal glands, heart and brain), thus promoting their growth relative to other organs (Garg et al., 2013). Such *brain sparing* processes include oxygen supply that initially prioritise the higher cognitive functions of the frontal lobes (Cohen et al., 2015).

IUGR toddlers at 22-months had poorer cognitive, language and motor outcomes compared to their AGA peers, with effect sizes compatible with small to medium effects and consistent with current meta-analytic findings on cognitive outcome (Chapter 1). When taking possible confounders into account, language scores were no longer lower in the IUGR group, possibly highlighting the importance of post-natal environmental factors (i.e. socio-economic status) on such domain (Schwab & Lew-Williams, 2016). The effect of IUGR on neurodevelopment is reported in the literature across the gestational age spectrum and at different stages of development (Chen et al., 2016; Murray et al., 2015). In this study, we showed that already at 22 months of life IUGR toddlers have lower general cognitive functioning scores compared to AGA VPT peers. Results of other studies demonstrated that several neurodevelopmental functions continue to be compromised in IUGR samples later in development (Bellido-Gonzalez & Diaz-Lopez, 2018; Geva et al., 2009; Kallankari, Kaukola, Olsén, Ojaniemi, & Hallman, 2015). Further efforts should be directed to follow-up these children, monitoring whether the early cognitive disadvantage reflects later specific cognitive problems (i.e. working memory, executive functions) or generic cognitive vulnerability.

Regarding behavioral problems, we found that IUGR VTP toddlers were more likely to score positively on an autism screening questionnaire (i.e., M-CHAT) compared to AGA VPT toddlers (43% vs 27%). These results are in line with M-CHAT positive screening reported in 41% of extremely low birth weight children (Dudova et al., 2014) and 31% of IUGR VPT (<34 GA) 12 month old toddlers (Padilla, 2017). Mechanisms potentially explaining the association between IUGR and behavioral outcomes might involve the interdependent roles of metabolic alterations such as reduced Insulin-like growth factor (Steinman & Mankuta, 2013), maternal well-being during pregnancy and hypothalamic-pituitary-adrenal (HPA) axis development (Huang, 2011; O'Donnell, O'Connor, & Glover, 2009), and rapid brain changes in utero (Roza et al., 2008). The HPA axis and the sympathetic system are regulated by stress and variation in antenatal nutritional availability, which characterizes IUGR fetal growth (Figueras & Gardosi, 2011). Such factors are likely to affect behavioral maturation via the programming effects of stress mediators, such as glucocorticoids, that regulate the neural system underlying cognitive-emotional function and conduct problems (O'Connor, Heron, Golding, Glover, & Team, 2003; O'Donnell et al., 2012). Moreover, the fetal changes in blood flow (i.e., increasing in the middle and anterior cerebral arteries) described as *brain sparing* effects, have been associated with behavioral and emotional problems (Roza et al., 2008). This suggests that in case of prolonged fetal hypoxia, the cognitive and behavioral functions that are initially spared might lose their priority in favour of visual and motor functions (Hernandez-Andrade, Figueroa-Diesel, Jansson, Rangel-Nava, & Gratacos, 2008).

When exploring the association between brain volumes at term-equivalent age and cognitive, motor and behavioral outcomes at 22 months in the whole sample, we found that larger frontal and occipital component volumes were associated with poorer cognitive outcomes, although in this study these volumes did not quantitatively differ between the

IUGR and the AGA groups. We also found that larger fronto-temporal-parietal component volume was associated with worse motor function at 22 months. These results may not have a clear-cut explanation, as our previous work in the same participant sample (without differentiating between IUGR and AGA VPT infants) showed a positive correlation between brain volume and cognitive and motor outcomes (Ball et al., 2017). Recent findings have demonstrated an asynchrony of maturation across cortical regions in the infant brain during the first months of life, with advanced maturation of primary cortices compared with associative cortices (Lebenberg et al., 2019). As the current study did not include a control sample of typically developing 40 week old infants born at term, and as the immediate post-natal period is a relatively unexplored phase of development given the logistic difficulties of performing MRI in healthy babies, we propose to interpret our indexes of grey matter volume (i.e., component weights derived from Jacobian determinants) as a deviation from the group norm. Therefore, those children with frontal, occipital and fronto-temporal-parietal component values that most differed from those observed in the reference image were also those who had worse cognitive outcomes at 22 months.

As the relationship between brain and cognitive maturation is age-dependent (Razlighi et al., 2016), we speculate that the brain volumetric alterations in emotion processing component observed here at term-equivalent age in IUGR infants might affect the development of emotional skills that will emerge only later in childhood. Studies on IUGR individuals highlighted reduced social responsiveness and poor use of environmental stimuli, with decreased behavioral preference for social stimuli and interactive partners (Feldman & Eidelman, 2006; Mello, Gagliardo, & Goncalves, 2014; Padilla et al., 2011). Potential mechanisms underpinning infants' responsiveness to social environment involve different operations, such as emotional and face processing (Taylor-Colls & Pasco Fearon, 2015), that

are underpinned by several brain regions including the prefrontal cortex, amygdala, hippocampus and fusiform gyrus (Frith & Frith, 2003).

Altogether, our findings demonstrate that the antenatal stress experienced by growth restricted fetuses results in volumetric brain alterations in VPT individuals around the time of birth. This might have implications for identifying time-dependent prenatal factors impacting brain development and in particular an atypical development of IUGR individuals' 'emotional brain' that is associated with both cognitive and behavioral risk. Taking together the imaging results at term equivalent age and at and the cognitive and behavioral outcomes at 22 months, this study supports a model of fetal neurodevelopment whereby the quality of antenatal life, in addition to length of gestation, operates at different levels shaping brain and behavioral growth.

This study has several limitations. Firstly, the lack of inclusion of a term-born control group did not allow us to compare the brain and behavioral correlates of IUGR between very preterm and term born individuals. Secondly, the small sample size of our IUGR group might have limited the statistical power to detect associations between volumetric alterations and cognitive and behavioral outcomes. Thirdly, volumetric studies have limited predictive power to detect later neurocognitive or psychiatric outcomes (Batalle et al., 2018); while advanced diffusion and functional MRI offers the opportunity to improve significantly on routine neuroimaging and to define underlying neuroanatomical features associated with adverse outcomes (Kawahara et al., 2017; Salvan et al., 2017).

Along with limitations, our study has several strengths. Firstly, we were able to study subgroups of VPT individuals based on the quality of their prenatal experience. Secondly, when investigating structural brain development at term equivalent age, we used a whole-brain data driven approach. Finally, as far as we are aware, this is the first study assessing

whole brain volumes around the time of birth in IUGR VPT individuals with antenatal signs of growth restriction.

Conclusion

After considerable advances in fetal medicine and perinatal care, we are still striving to understand the pathological mechanisms leading to the heterogeneous outcomes observed in former VPT individuals. This study demonstrated that IUGR might confer a neurodevelopmental risk that is greater than that posed by VPT alone, where the stress of the environment experienced antenatally alters brain growth and global development early in life. However, several studies have also showed that a compromised fetal development might represent a "meta-plastic" state, where the influence of intrauterine factors on neurodevelopment can be modified by several postnatal factors, such as parental care, mother-child attachment, and socioeconomic status (O'Donnell & Meaney, 2016).

This suggests that, for instance, that antenatal neuroprotective strategies could be aimed at constraining the effects of atypical brain growth on later outcomes and postnatal interventions could target factors such as parenting (Nichols et al., 2017; Sacchi, De Carli, Mento, et al., 2018) in order to attenuate the impact of antenatal biological vulnerability in IUGR toddlers.

CHAPTER 3

Socio-emotional and cognitive development in Intrauterine Growth Restricted and typical development infants: early interactive patterns and underlying neural correlates

ABSTRACT

The neural and behavioral mechanisms of Iintrauterine Growth Restricted newborns engagement with social stimuli are unexplored, as well as their potential role in shaping socio-cognitive development.

In this chapter we present the research project of a longitudinal case-control study investigating mother-infant interactions and infant's event-related potential (ERP) components of face processing (infant N170, P400, Negative central) in 4 and 9 months IUGR infants as potential markers of cognitive and behavioral outcomes.

Thirty-eight IUGR participants will be recruited after receiving the antenatal diagnosis. Healthy infants will be enrolled as the control group. Behavioral responsiveness will be assessed via Emotional Availability Scales (EASs). Infants' scalp recorded cortical activity in response to social and non-social stimuli will be investigated using a high-density EEG system (EGI Geodesic system). Neurodevelopment will be measured at 12 months of child's life, using Bayley Scales for Infant Development (BSID), while presence of emotional-behavioral problems will be rated via Child Behavior Checklist (CBCL).

A significant association between neural response to social stimuli and infants' responsiveness to maternal stimulation during interactions is expected, with impoverished performances in IUGR infants, compared to healthy peers.

The chapter describe the rationale and methods of the study with the intent of enhancing understanding on the potential neural mechanisms underpinning the interactive patterns and socio-cognitive development in IUGR infants. Besides, the study will help in focusing on the role of postnatal environment in buffering the vulnerability experienced by children delayed in their fetal growth.

INTRODUCTION

Intrauterine Growth Restriction (IUGR) is defined as a fetal growth retardation, resulting in an estimated fetal weight (postnatally confirmed by birth weight) on the lowest 10th percentile for gestational age (Alfirevic & Neilson, 1993). By affecting 5% to 7% of pregnancies, IUGR is the second leading cause of perinatal mortality and morbidity worldwide, representing a major public health problem (Murray et al., 2015). A fetal growth unable to reach its genetic potential is a risk factor for later neurodevelopmental outcomes (Baschat, 2011; Kok et al., 2007). In fact, functional impairments have been observed at birth and early in life; specifically, immature attention-interaction scores and impaired visual recognition memory performances are described in 7 months old infants (Gotlieb, Biasini, & Bray, 1988; Tolsa et al., 2004a), while at 1 year of life, significantly lower scores on Bayley Scales are reported (Batalle et al., 2013; Fernandez-Carrocera et al., 2003). Moreover, growth-restricted infants show poor use of environmental stimuli, reduced social responsiveness, more insulated cry states, and poor motor performance as compared with normal birth weight infants (Padilla et al., 2011). Persisting and long-term outcomes are also observed, with cognitive impairments (e.g. executive functioning; Geva, Eshel, Leitner, Fattal-Valevski, & Harel, 2006) and behavioral problems described in childhood (Sung, Vohr, & Oh, 1993); motor problems, learning difficulties and lower academic achievements during school age period (Esteban et al., 2010; Yael Leitner et al., 2007), as well as increased risk for neurodevelopmental disorders, such as ADHD (Heinonen et al., 2013). Apart from evidence of neurodevelopmental and cognitive outcomes, socio-emotional development still appears as unexplored in the developmental context of growth restriction, although few signs of early atypical social interactions are described (Feldman & Eidelman, 2009; Watt, 1990), as well as

later poor socio-cognitive performances at school age and mood disorders (Fischi-Gómez et al., 2015).

Literature evidenced several structural and functional brain abnormalities potentially linking fetal growth rate to the detrimental neurodevelopmental and socio-cognitive outcomes. Indeed, IUGR infants show reduced brain volumes as well as delayed and diminished myelination (Dubois et al., 2008; Padilla et al., 2011; Ramenghi et al., 2011). The alterations seem to persist in long term deficits, since motor and cortico-striatal-thalamic networks impairments are observed in 6 years old IUGR children, and delayed myelination as well as disrupted white matter integrity last up to adulthood (Fischi-Gómez et al., 2015). Despite this evidence, the early neural mechanisms sustaining the socio-emotional competencies and the socio-cognitive development in IUGR infants are still underexplored. However, it is of the highest importance to provide comprehension on early markers, both in terms of behavioral and brain mechanisms, of the developmental cascade that begins with early fetal abnormal experience and might potentially result in socio-emotional difficulties and neurodevelopmental outcomes observed later in life. Indeed, in a preventive perspective, targeting a potential early vulnerability in IUGR development, particularly when born at term, could be highly convenient and rewarding. Despite literature extensively reports altered quality in antenatal environment, quite few studies investigated IUGR developmental trajectories, thus neglecting the opportunity to tailor interventions on these infants and to develop ad-hoc follow up mental health care. In addition, the urgency for identifying potential targets for interventions should consider a multifaceted approach, where infant and caregiver are parts of a mutually influencing complex and interrelated system (Sacchi, De Carli, Vieno, et al., 2018). Taking into account infant and mother's variables, different potential mechanisms to target could arise from this study. First, detecting vulnerability in processing social stimuli might guide behavioral intervention sustaining parenting abilities to use multi-

modal channels of stimulations during interactions. Second, fostering a protective effect of parenting behavior on brain functionality would potentially have an effect on infant socio emotional development, hopefully compensating for the suspected reduced early communication abilities of IUGR infants. Third, a longitudinal investigation would allow to study different potential windows of plasticity both for typical and atypical development. This could lead to more focused interventions aware of the most susceptible periods and the most rewarding processes to target.

With this theoretical and clinical perspective in mind, we propose a longitudinal investigation of two interrelated mechanisms that might be detected across the first year of life as early markers of potential atypical socio-emotional and cognitive outcomes of IUGR developmental trajectories: infant behavioral responsiveness in social interaction and infant early neural face processing.

Infant behavioral responsiveness in social interaction

Within the first year of life, typically developing infants display an amazingly sophisticated set of social behaviors, which foster learning processes in a broad collection of developmental domains (McDonald & Perdue, 2018). These socio-emotional competencies involve the abilities to interact, communicate and deal with emotions, which are primarily experienced in early interactive exchanges with the mother (Bowlby, 1978). Within this affectionate bond, the child receives not only protection, care and the recognition of his/her needs, but also an encompassing environment for physical, cognitive, social and affective development (Britto et al., 2017). Indeed, the mutuality of exchanges between mother and child represents not only a source of stimuli for the child but also an environment sensitive to activities and modifications (van den Bloom & Hoeksma, 1994). In the case of atypical development, infant characteristics can deeply expose the quality of mother child interactions (Kiff, Lengua, & Zalewski, 2011). Indeed, the few available studies evidenced that IUGR

infants are likely to display difficulties in orientating to social and non-social environment (Watt, 1990) and tend to look at people less frequently than age-matched healthy infants; also, higher levels of negative affect are reported, evidencing an early vulnerability in communication skills (Watt, 1987; Watt & Strongman, 1985a). As regards, interactive abilities, the very limited findings on IUGR or Small for Gestational Age (SGA) children suggest those infants are more passive during mother-child interactive exchanges, smiling and looking at their mothers' face less than normal birth weight matched newborns, being less rhythmic and synchronous in daily interactions (Feldman & Eidelman, 2006), and thus appearing as less rewarding interactive partners. A similar interactive pattern is displayed in preterm infants and their mothers, where a scarcity of communicative signals on infant's side could activate some compensatory behaviors in parents (Miles & Holditch-Davis, 1995; Montirosso et al., 2017). This parenting response can be highly adaptive but can eventually result into intrusive and non-attuned behaviors (Howe et al., 2016). Therefore, on the one hand, atypical development in the domain of diminished early communicative abilities can disrupt mother child exchanges leading to an additional impoverishment of infant's environment. On the other hand, the quality of mother-child interactions can potentially buffer the negative effect of infant scarce interactive abilities on child development (Baker et al., 2007). In fact, some evidences show the moderating role of maternal sensitivity on infant developmental trajectories. More specifically, recent evidences show the role of mother child interactions on infant's brain functionality, confirming the relevance of considering mother and child as a broad interrelated system where infant development takes place.

Infant neural face processing

Among early neural competences displayed by newborn and infants, the ability to recognize and direct the attention to faces appear as highly relevant for socio-cognitive development. Face perception represents an experience-expectant and activity-dependent

function (Nelson, 2001; Young, Luyster, Fox, Zeanah, & Nelson, 2017); that is critical in the development of higher level social cognitive functions (Parker & Nelson, 2005). Indeed, the human face provides the infant with a wealth of socially and affectively relevant information and humans appear to be inherently interested in faces, displaying from infancy a strong interest in facial-like figures (Johnson, 1991; Morton & Johnson, 1991). Early disruption or delay in this low-level process can negatively impact infant's ability to interact with the social environment (Elsabbagh et al., 2015) and disturb natural mutuality in social interaction with potential detrimental effects for child development (Wan et al., 2013). Indeed, huge part of early interactive exchanges rely on the use of face and facial expression are early used to understand others emotion and thought, to make others understand themselves, and to share emotional states (Beebe et al., 2010, 2016). Studies observed that different early stressors and risk factors, such as prolonged institutionalization or risk for autism, are likely to affect this infant capacity that is a considered a strong candidate for being one of the mechanisms of the association between early stress and socio-emotional difficulties (Nelson & McCleery, 2008). More specifically, Parker and colleagues (2005) found that the amplitude of the ERP responses to familiar and unknown faces were lower in institutionalized children, while Swingler and colleagues (2010) found ERP latencies to be associated with infant behavioral response to maternal separation. Mesquita and colleagues (2015) showed altered ERP components magnitude in response to faces in children with atypical social behaviors and recently (Kungl, Bovenschen, & Spangler, 2017) found an association between attachment security and face brain responses. In addition, recent studies show that in healthy children the quality of the maternal environment is related to the magnitude of ERP components in response to emotional faces (Carlsson, Lagercrantz, Olson, Printz, & Bartocci, 2008; Taylor-Colls & Pasco Fearon, 2015), confirming the association between early interactive experience and brain development of face perception. As a consequence, it is possible that an early

dysfunction of the relevant circuitry of neural face processing could affect the quality of the interactions, and probably also decrease the quality of the child environment, contributing to activate a negative developmental pathway. Up to date limited information is available on how infants process and respond to social stimuli in early at-risk conditions. In particular, no study investigated whether early human face processing is susceptible to antenatal growth and/or might be affected by fetal growth restriction. Indeed, in the study of IUGR, researches are needed in order to ensure that facial processing is not compromised by their antenatal adversities slowing down the fetal growth. In fact, in the light of studies on clinical groups (Nelson & McCleery, 2008; Parker & Nelson, 2005), it appears as of highest clinical importance to understand the role of early adversities on neural face processing and how altered face processing could be conceived as early marched on possible risk on socio-emotional development.

With the aim of bridging the above-described research focuses and objectives, the present study protocol attempts to open a new research perspective on early development of IUGR infants, following their interactive and neural developmental pathways across the first year of life. By comparing IUGR with healthy children we study the effect of antenatal adversity on brain functionality and interactive abilities. Specifically, aim of the study will be to investigate whether growth restriction significantly affect socio-cognitive developmental at 12 months both directly and thought the mediation of behavioral and neural response to social stimuli as displayed at 4 and 9 months. In particular, mediation hypotheses cover the following pathways:

- *Infant behavioral responsiveness in social interaction:* since studies on IUGR population support IUGR infants' greater passivity, communicative difficulties in early mother-child exchanges and an early disinclination to be engaged by human faces, we investigate a group difference (IUGR – Control), expecting IUGR lower levels of responsivity

to maternal stimulation during free-play exchanges. Worse communicative abilities in the IUGR group can lead to an impoverished environment for the infant and therefore fewer opportunities for stimulation and learning. In turn, this could affect the cognitive development and therefore could represent a mechanism linking the stress experienced during intrauterine life to later adaptation.

- *Infant neural social processing*: Many evidences showed that neural competence in face processing is significantly altered in clinical populations, advocating a likely role of this neural domain in sustaining and worsening the effects of early stress on child development. Since research on IUGR show their difficulties in engaging with faces and social situations, we suggest a potential role for face processing neural correlates in the association between antenatal growth restriction and cognitive outcomes. Therefore, we aim to explore the role of the scalp-recorded cortical activity, in terms of event-related potentials (ERPs), in response to social and non-social stimuli in IUGR and non IUGR infants. The following ERP components will be selected in accordance with current evidence of the literature on infants' face processing-i.e., the infant N170 at around 290 msec after the stimulus onset and P400 (de Haan, Johnson, & Halit, 2003; De Haan & Nelson, 1999; Moulson, Westerlund, Fox, Zeanah, & Nelson, 2009), and emotional/attentional processing-i.e., Nc (Moulson et al., 2009; Taylor-Colls & Pasco Fearon, 2015). Indeed, by considering several ERP components, the potential role of intrauterine growth adversity on social processing will be linked to specific features of neural processing. Specifically, we expect to find reduced amplitude (N170, Nc) and latency (P400) in the IUGR group. In addition, we hypothesized that these alterations in brain functionality in response to human faces can represent an early marker of the later cognitive deficit of IUGR infants, therefore suggesting a mediation effect.

Then, cortical response to social stimuli will be investigated as possible underpinnings of reduced responsiveness to maternal environment in IUGR infants, compared to matched healthy controls. Therefore, positive correlations will be expected, highlighting this link.

Last, along with the mediation roles expected for child behavioral and neural social responsivity, maternal environment, in terms of sensitivity, will be investigated at an explorative level as exerting a moderating role in the association between infant responsivity on cognitive and behavioral development assessed at 12^{th} months. Indeed, although no specific evidence suggests that maternal sensitivity can modulate the developmental trajectories in IUGR samples, this effect has been shown in other at risk population such as premature infants. Therefore, we aim at considering moderator effects in order to detect potential buffering or detrimental roles of maternal environment in infants experiencing fetal stress.

Overall, research design and hypotheses are graphically summarized in Figure 1 (Appendix: A3).

METHODS

Participants

For the IUGR group, 38 pregnant women will be recruited at the Department of Women's and Child's Health, University of Padova (Italy). Healthy control pregnant mothers (N = 38) will be recruited from birth-preparation courses of the Obstetrics and Gynecological Clinic of Padua Hospital. All pregnant women are orally presented with a longitudinal study on the role of Intrauterine Growth Restriction on child socio-emotional development by a Gynecologist and a Psychologist, while waiting their visit or the birth-preparation class. For mothers with pregnancy complicated by IUGR; research will be proposed at the first obstetrical visit following diagnosis. All mothers interested in the study will receive a detailed informative module, describing stages and tasks on the study. In particular, they will be

informed on the study length and procedures; absence of risk for both behavioral and EEG assessment is declared, and a potential tolerable level of discomfort is reported for the EEG cup wearing procedure. Participants will also be informed on the possibility to withdraw their participation at any time without giving an explanation and that their decision would not affect future healthcare encounters. In accordance with the Declaration of Helsinki, prior to first assessment, parents agreeing to be involved in the present study will sign written informed consent. Mothers will sign an informed consent as participants; while two other different consent forms are required to be signed by both parents for infant's participation, namely in the behavioral and neuroimaging assessments. The present study received ethical approval from the Ethic Committee of the University of Padua (protocol reference number: 2293). The sample size was determined by a power analysis performed in order to ensure power equal to .80 to detect an intermediate effect (Chapter 1: Cohen's d = .57) of being IUGR on the Bailey scores at 12 months (difference between two independent means, G*Power 3.1.9.2). The power for test each specific hypothesis is presented in the Data Analysis section.

Participants will be mother-infant dyads who received in utero IUGR diagnosis (verified by Doppler ultrasound and estimated birth weight below the 10th percentile of growth), confirmed by birth weight below the 10th percentile of growth curve. Infants exclusion criteria will be: genetic disorders, unrelated comorbidities, presence of fetal infections, congenital malformations (i.e., congenital heart disease), metabolic and chromosomal disorders at birth, as well as infant neurological pathologies, brain abnormalities, or preterm delivery (<37^{th} gestational week). Mothers' exclusion criteria will be IUGR diagnosis before the 7th month of pregnancy and complicated pregnancies, non-Italian nationality, mother age<18 years, psychiatric disorders' risk as defined by clinical

score (namely a Global Symptom Index > 65) in the Symptom Checklist 90- Revised (Derogatis, 1975), neurocognitive disorders, drug addiction, single mothers.

Procedure

This project describes a longitudinal research, articulated in four stages over the first year of the child's life. During recruitment at the pregnancy stage demographical information will be collected through a detailed paper-and-pencil evaluation. Indeed, an ad-hoc socio-demographic assessment has been designed in order to collect comprehensive information about maternal age, cohabitation, marital status, education, work, parity and presence of previous abortion or at-risk pregnancies.

In addition, psycho-social and clinical-psychological status of the mother and of the whole family system will be assessed, by applying the following self-report questionnaires: Childhood Trauma Questionnaire – Short Form (Bernstein et al., 2003; Sacchi, Vieno, & Simonelli, 2017); Parental Bonding Instrument (PBI; Parker, 1989; Scinto, Marinangeli, Kalyvoka, Daneluzzo, & Rossi, 1999); Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004; Sighinolfi, Pala, Chiri, Marchetti, & Sica, 2010); State Trait Anxiety Inventory (STAI; Spielberger, 1983; Giardinelli et al., 2012); Beck Depression Inventory (BDI-II; Beck, Steer, Ball, & Ranieri, 1996; Sica & Ghisi, 2007).

After recruitment and the first assessment during pregnancy taking place at the Hospital, all participants agreeing to take part into the study will be telephonically contacted at the 4th month of child's life for behavioral and neuroimaging assessment. In particular, mother-child couples will be invited to visit the Department of Developmental Psychology and Socialization at the University of Padova. At 4 and 9 months, assessment procedure will involve free play interactions and EEG recording at the Inter-departmental High-density EEG lab; while at 12 months, developmental outcomes will be measured with children assessed on

cognitive development by a structured procedure performed by trained psychologist, and emotional-behavioral problems rated by mothers.

Cognitive and socio-emotional development at 12 months of life

Cognitive assessment will be performed at 12 months of child's life using Bayley Scales for Infant and Toddler Development – Third Version (BSID – III; Bayley, 2006; Gasparini et al., 2017); which evaluates five different domains: cognitive, language, motor, socio-emotional behavior and adaptive behavior. Evaluation of the first three domains consist of a direct observation of the child performance on different task, while socio-emotional and adaptive behaviors are parent rated. For direct assessment, each item is assessed on a dichotomous scale, with 1 given to child's ability to perform the targeted behavior and 0 to the absence of such behavior. After 5 consecutive missing behaviors the scale's administration is interrupted. Cognitive scale is composed by 91 items assessing: sensorimotor development, exploration and manipulation, object relatedness, concept formation, and memory. Language scale is composed by 49 items referring to receptive communication (i.e., pre-verbal behavior, vocabulary development, morphological development, understanding morphological markers, social referencing and verbal comprehension), and 48 items assessing pre-verbal communications (i.e., vocabulary development and morpho-syntactic development). Motor scale examines fine motor and gross motor domains. In particular, fine motor subtest is composed by 66 items about: prehension, perceptual-motor integration, motor planning and speed, visual tracking, reaching, object grasping, object manipulation, functional hand skills, responses to tactile information. Gross motor subtest refers to 72 items covering movement of the limbs and torso, static positioning (e.g., sitting, standing), dynamic movement (including locomotion and coordination), balance, and motor planning.

Socioemotional scale represents and adaptation from the Greenspan social-emotional growth chart (Greenspan, 2004) assessing child self-regulation, communicating needs, the ability to establish relationship and the use of emotions for interactive purposes or to solve problems. Last, Adaptive Behavior assessment refers to child's social, motor, pre-academics, home living, self-care, self-direction, community use, leisure, communication, health and safety skills.

Each of the five scales provide a raw score, and a scaled score (M=10, SD=3). For Cognitive, language and motor scales also allow to compute composite scores, referred to a mean value of 100 and a standard deviation of 15. Composite scores lower than 85 were considered as abnormal performances (Albers & Grieve, 2007). Examinations will be performed by a trained psychologist with enduring experience in the BSID-III.

Socio-emotional development will be parent rated via Child Behavior Checklist ½ - 5 (CBCL ½ - 5; Achenbach & Rescorla, 2000; Frigerio et al., 2006), a checklist of 113 questions, scored on a three-point Likert scale (0 = Not True, 1 = Somewhat or Sometimes True, 2 = Very True or Often True, based on the past 6 months). CBCL provides scores for eight syndromes, three broadband domains (Internalizing, Externalizing, and Total Problems), and six DSM-oriented scales. Although CBCL was originally designed for child assessment from 18 months of age, previous studies showed its good psychometrical properties with 12 months infant and encouraged its downward extension (Ramchandani et al., 2013; Van Zeijl, Mesman, Stolk, et al., 2006; Van Zeijl, Mesman, Van IJzendoorn, et al., 2006).

Child responsiveness and maternal sensitivity

Mother-child interactions will be video-recorded during free-play interactive exchanges lasting about 15 minutes. At this purpose, a quiet and silent room will be equipped with a kid rug, pillows and age-appropriate toys; namely: rattles, puppies, and soft activity books for 4 months infants; pop-up surprise box, soft telephone, blocks box, activity book, and rock-a-

stuck for 9 months. Mothers will be instructed to freely interact with their baby as they are used to do at home; they are kindly asked to remain within camera focus, unless their baby show signs of distress and need to calm them down.

Emotional Availability Scales (Biringen, 2008) will be applied to code interactive behaviors following the coding system of the EA Third Edition. EAS constitutes of four parental dimensions: adult sensitivity, adult structuring, adult non-intrusiveness, adult non-hostility; and two child scales: child responsiveness and child involvement. Each EA dimension produces score on a 7-point scale, where higher ratings stand for more optimal features. Values between 5 and 7 are representative of an emotionally available dyad and considered index of a healthy relationship. Scores around 4 indicate complicated emotional availability, that is behaviors that are appropriate in some ways but that are not optimal. Scores around 3 indicate less optimal aspects while the range between 1 and 2 concerns more problematic behaviors (Biringen, 2008). According to EAS Third Edition, the six scales can also be scored on 7 subscales each; this allows to observe and detect specific behaviors composing the six macro-categories. Among the six dimensions, Adult sensitivity and Child responsiveness will be selected for the purposes of the present study. Indeed, maternal sensitivity represents an early indicator of the quality of infant's postnatal social environment. Child responsiveness will be selected as behavioral correlates of child's early responsiveness to social stimuli, investigated as cortical response. Video-recorded interactions will be coded by two independent judges, trained on the EAS system, who will be blind with respect to objectives and design of the study.

EEG Recording, signal processing and ERP components selection

Infants' cortical activity will be continuously recorded using a Geodesic EEG system (EGI) through a pre-cabled high-density 128-channel HydroCel Geodesic Sensor Net (HCGSN-128) referenced to the vertex. While infants are placed on their mother's legs in

front of a screen at about 50 cm of distance, brain activity will be registered, through the use of the elastic sensor nets fitting each participant's head size. Each electrode channel of the net is enveloped by a sponge and protected by a soft, plastic pedestal; this guarantee participants' skin contact is only with sponge and plastic parts. Before assembly, Sensor Net is immersed in a shampoo, potassium chloride and distilled water solution for five minutes. After disassembly, all the non-disposable material used during the experiment (net, electrodes), is always disinfected before a subsequent re-use.

The electrophysiological data collection will last about 30 min per each infant, including equipment assembly and disassembly; also, to maximize infant comfort, skin pressure points and overturned sensors are checked before data acquisition, in accordance with EGI recommendations. While seating on mothers' legs in the overshadowed room, both social and non-social stimuli will be presented. Specifically, the experimental paradigm employed will be adapted from a previous study (Mento & Valenza, 2016), and will involve the use of real female faces as social stimuli. Images of unfamiliar toys will be selected as the visual non-social stimuli. A total of 100 trials per condition will be delivered. During the procedure, infants' behavior will be continuously monitored via a video camera, in order to allow the experimenter to decide when deliver on the screen attention-getter audio-visual stimuli (cartoon scenes) as soon as infants attention on the screen will be loose. The electrical signal will be filtered with a 0.1- to 100-Hz band-pass with a sampling rate of 500 Hz.

Consistent with previous studies on face and emotion processing in infants (de Haan et al., 2003; De Haan & Nelson, 1999; Guy, Zieber, & Richards, 2016; Taylor-Colls & Pasco Fearon, 2015), component timings will be selected as follows: the infant N170 component will be selected as the early correlate of specialized face processing in infants (infant 170), reflecting structural features of face processing. This component has been consistently shown to exhibit greater amplitude in response to faces as compared to visual noise in 3 month-old

infants (Halit, Csibra, Volein, & Johnson, 2004) and also to familial vs non-familial faces at 9 months (Scott, Shannon, & Nelson, 2006). The infant N170 will be expected to peak negative in amplitude 290-350 ms after stimulus onset in posterior electrodes (de Haan et al., 2003). Second, the P400 will be considered as involved in high-order face processing; the P400 represents a positive component peaking between 390 and 450 ms after stimulus onset and maximal over occipital electrodes (de Haan et al., 2003). Last, the "Negative central", Nc component will be considered as relevant components of late face-processing (de Haan et al., 2003). The Nc will be defined as the negative EEG deflection occurring between 350 and 750 ms after stimulus onset over frontal and central midline electrodes (Guy et al., 2016). The Nc component is thought to reflect the activation of attentional processing linked to the appraisal of the motivational significance of emotional expressions (Taylor-Colls & Pasco Fearon, 2015).

The EEG recordings will be processed offline using MATLAB toolboxes EEGLAB and ERPLAB. EEG signal will be segmented into epochs beginning 100 ms before stimulus

onset and ending 800 ms after. Prior to epoching procedure, videos will be visually inspected off-line in order to reject EEG segments where participants did not look at the screen. In order to identify, reject or correct bad channels, artifacts, eye blinks and eye movements, the Independent Component Analyses (Stone, 2002) will be applied on individual epoched EEG dataset. As the last step, data will be averaged and re-referenced to average reference. Only participants showing a minimum of 30 artifact-free trials per condition will be included in the grand average.

STATISTICAL ANALYSES

To answer the first research question about the social stimuli processing in IUGR infants in terms of amplitude and latency of ERP components, analysis will involve repeated measure models, with group (IUGR vs Controls) as between factor and developmental stage

(4-9 months) and stimuli condition (social vs non-social) as within factors. No previous study is available to obtain an estimate of the target effect size; however, we can refer to Parker and Nelson (2005) work on institutionalized children compared with non-institutionalized children to obtain an estimation of the effect of clinical conditions on ERP components in response to human faces. Even if it is unlikely that a perinatal condition such being IUGR is comparable with a complex relational stressor as being raised in an institution, this study can provide a rough estimation of the effect involved in the present protocol. Indeed, they found differences in N170, Nc, PSW and P250 amplitude between groups that range from intermediate to large. In the present study, considering the planned sample size, we should be able to obtain a .98 power to detect a small effect (repeated measures ANOVA within-between interaction, G*Power 3.1.9.2, Faul et al., 2009), which seems satisfactory in relation to the previous findings.

Second, to test the mediation effect of both neural response to social stimuli and behavioral child responsiveness on cognitive and neurodevelopment outcomes, Hayes approach will be followed (Hayes, 2013). As already noted, the power to detect a direct an intermediate effect of IUGR condition on 12 months outcome is above .80 (Difference between two independent means, G*Power 3.1.9.2). For what concerns indirect effects, mediation models have usually larger effect sizes than main effects (Kenny & Judd, 2014). Last, at a more explorative level a path analysis will be conducted to study the moderation role of maternal sensitivity in the previous mediation models. In particular, the moderation effect on the direct association between IUGR condition and later outcome as well as on the association between IUGR condition and child responsiveness will be explored.

EXPECTED RESULTS

For the developmental outcomes at 12 months, in line with previous studies (Batalle et al., 2013; Fernandez-Carrocera et al., 2003), we expect poorer cognitive and behavioral

performances in IUGR infants, compared to control peers, as result of both a direct effect of being IUGR and a mediation of neural and behavioral responding to social stimuli.

On the behavioral domain, lower levels of child responsiveness during mother-child interactions are expected within the IUGR group, evidencing poorer behavioral responses to social stimuli, in accordance with evidence of IUGR greater passivity during social exchanges (Feldman & Eidelman, 2006). Then, significant positive correlations between ERPs amplitude for social stimuli and behavioral responsiveness to maternal stimulations are expected across groups, suggesting that early face processing might be conceived as a neural correlate of child responsiveness during mother-child interactive exchanges.

As regards the investigation of the neural mechanisms sustaining infants processing of social stimuli, temporal resolution given by the application of the EEG will allow to test the potential effect of being IUGR on different steps of face processing. Specifically, differences in infant N170 amplitude will allow to detect a potential role of being IUGR on basic structural features of face processing, while differences in P400 latency between groups, expected in the direction of longer latency for IUGR performances, will allow to detect an atypical IUGR processing regarding more complex steps of face processing. Last, between-groups difference in the Nc component will be tested in order to highlight atypical attention engagement in IUGR infants.

Considering in details the potential differences in ERP components in response to social and non-social conditions, we first expect faces to elicit greater amplitude in infant N170 and Nc and shorter latency in P400 than toys across groups (IUGR vs Controls), in line with previous studies on infants face processing (Guy et al., 2016; Taylor-Colls & Pasco Fearon, 2015). Second, we expect that the prenatal stress experienced by IUGR infants results in smaller ERPs amplitude for social stimuli in the IUGR group, similarly to other at risk populations exposed to early adverse conditions, such as institutionalized children and young

children with autism (Nelson & McCleery, 2008). Third, we expect an interaction effect Group x Condition, resulting in a reduced difference in amplitude between the social vs non-social conditions for the IUGR group. Moreover, at an explorative level, the longitudinal design of the study will offer the opportunity to investigate whether neural social processing is susceptible to different pathways of specialization across groups (IUGR vs Controls), as displayed by potential between-groups differences in neural face responses across steps (4 vs 9 months). No specific results are expected, but a tendency toward stability across stages of the hypothesized detrimental effect of prenatal stress on neural face processing would suggest the presence of an atypical developmental trajectory for the IUGR population. On the contrary, a tendency toward a decreasing gap between groups would point toward considering face processing in IUGR as a stage-dependent mechanism limited in time, even if the potentially negative effect on long term outcomes could remain.

However, the limited knowledge in the functionality of IUGR brain in response to social stimuli does not ensure that group differences can be found in the hypothesized components or that they are located in the same brain regions of typically developed children. In this respect, subsequent exploratory analyses can enrich the quality of the investigation by means of data driven approach able to study the overall brain functionality (i.e., Maris, 2004).

Last, about the role of infants' postnatal environment, high maternal sensitivity, considered as a proxy of the overall maternal environment quality, is expected to buffer the effect of adversities in fetal growth on later developmental outcome by enhancing child's engagement and responsivity to social environment.

DISCUSSION

Recent approaches to the study of early brain development are shifting backward sensitive epochs, emphasizing the role of antenatal life and fetal growth. Framed in this context, Barker's hypothesis of fetal programming suggests that adverse influences during

intrauterine life, such as growth restriction, can result in permanent long-term changes in physiology and metabolism, increasing the risk for adult diseases and health problems (Barker, 1998). The present study pursues the objective of broadening this research field providing new insights on the interconnected role of both antenatal and postnatal life on cognitive and emotional-behavioral development. In particular, results deriving from this research project will enhance understanding on early neural mechanisms underpinning the interactive-relational patterns sustaining socio-cognitive development in infants with Intrauterine Growth Restriction. Indeed, this study represents a first contribution to understand whether antenatal stress in terms of fetal growth delay is likely to affect early neural competences of face processing and whether this capacity represents a neural correlate of altered behavioral-interactive development along the first year. In particular, the evidence of a role of intrauterine life experiences in affecting later face processing would enhance our understanding of the development of this fundamental ability and its experience-expectant and activity-dependent nature. In addition, the study will also help in clarifying the role of (prenatal and postnatal) mother-child exchanges in buffering the vulnerability experienced by children delayed in their fetal growth. Indeed, even if it is difficult to disentangle the direction of the effects, it is clinically relevant considering infant's face processing and environmental quality in the study of developmental trajectories of children experiencing early adversities, such as alterations in the antenatal growth. The present study aims to develop the perspective proposed by Taylor-Colls and Pasco Fearon (2015) on the role of parental quality on infants' neural response to emotional faces, in which further studies on clinical and at-risk populations and longitudinal designs are claimed. However, in the study of IUGR, before considering the neural response to emotional cues, a step back is needed in order to ensure that facial processing is not compromised by the antenatal adversities that slow down the fetal growth.

Therefore, the present study will provide a preliminary link, opening the way for further studies on early social processing in IUGR infants.

As a first attempt in the study of IUGR socio-emotional fragility, our protocol still presents some potential limitations. First, the aforementioned lack of knowledge on the specificity of brain functionality of IUGR infants does not ensure that ERP components can be found with the same localization and characteristics to be compared with typically developing children. Second, the selection criteria of excluding IUGR infants born before the 28 gestational week ensures a specific focus on the unique role of being IUGR as a source of antenatal stress, apart from the stress and physical pain experienced by premature infants after birth (Montirosso, Giusti, De Carli, Tronick, & Borgatti, 2018). However, future studies could explore potential differences between term IUGR and preterm IUGR, in order to disentangle the specific contribution of ante and post-natal stress in infant development. Third, IUGR disorder could result associated with highly severe maternal conditions during pregnancy such as infections, toxins, prescriptions drugs, substances abuse, that affect both intrauterine and postnatal environment (Brancato & Cannizzaro, 2018). In the present protocol, severe maternal conditions were excluded in order to study the specific effect of being IUGR, but future investigations with a similar methodology could consider whether IUGR is one of the mechanisms involved in the child detrimental outcomes of these maternal conditions.

Conclusion

In conclusion, very few is known on the effect of antenatal growth on socioemotional development during early infancy. Studies investigating early pattern of social processing (Tronick & Beeghly, 2011), both in terms of neural and behavioral features in clinical or at-risk groups, have the potential to early inform on underpinning mechanisms exposing vulnerable infants to different developmental pathways (Fumagalli et al., 2018). Overall, the clinical relevance of the present research protocol lays in designing a longitudinal research

perspective where, despite the laboratory setting, the selected tasks rely on processes (i.e., face perception and mother child interactions) relatively ecological for infants. More importantly, infants neural and behavioral competences are combined to at least partially switch on a light on one of the potential pathways through which antenatal adversities translate into development fragilities, before fragility becomes a clinical outcome. Addressing this question has the clinical relevance to translate results into applicative guidelines in order to potentially generate effective and empirically-driven interventions in early infancy. Indeed, considering possible difficulties of IUGR infants in face processing and behavioral interactions might help in developing early ad-hoc interventions aimed at supporting mothers in sensitive and multimodal communications, thus hopefully constraining the effect of infant's social processing deficits on later socio-emotional development. Last, a second-order implication of the present protocol is that it might be generalizable to several developmental risks' population deriving from decreased or altered antenatal growth trajectories (i.e. prematurity, congenital heart disease; maternal substance abuse) in order to identify differential trajectories starting form specific etiopathological conditions, or rather common mechanisms predisposing to multiple outcomes.

CHAPTER 4

Interactive behaviors and early neurodevelopmental outcomes in infants with Intrauterine Growth Restriction. Preliminary report on the first year of live

ABSTRACT

The effect of Intrauterine Growth Restriction on socio-emotional development is overshadowed, despite literature prove the role of early socio-emotional growth in healthy child development.

In this chapter we report on a longitudinal assessment of term-born IUGR mother-infant interactive exchanges along the first year of life and their potential role in one-year cognitive outcome.

Seven IUGR infants completed the longitudinal assessment waves and are compared to Appropriate for Gestational Age peers. Interactive behaviors at 4 and 9 months were observed via Emotional Availability Scales (EASs), whereas cognitive outcome was rated at 12 months of child's life, using Bayley Scales for Infant Development (BSID-III).

We provide descriptive results highlighting decreased levels of maternal structuring at 4 months and infants' responsiveness at nine months as characterizing IUGR dyads. No other differences interesting infant's and maternal interactive behaviors emerged. At 12 months, significant differences are observed in cognitive and motor performances. No significant associations emerge between infant and mother early interactive behaviors and 12 months cognitive outcomes.

Overall, both mother and infants' early interactive characteristics show to be negatively marked by IUGR in different time-points along the first 12 months of life. The study suggests clinical interventions fostering infant's social engagement might take place in the very first months of life, before the expression of a behavioral interactive disadvantage.

INTRODUCTION

Intrauterine Growth Restriction (IUGR) describes a heterogeneous group of anomalies in antenatal environment characterizing the inability of the fetus to achieve its growth potential in utero (ACOG, 2013). IUGR represents a major problem for fetal medicine, complicating 5% to 7% of pregnancies and accounting for up to 50% of fetal deaths (Zamarian et al., 2018). As a significant medical concern, IUGR received massive attention and a burden of studies evidenced its significant role in risking neurodevelopment (Chapter 1 for a review). However, IUGR is extremely underexplored as affecting socio-emotional trajectories of surviving infants, despite literature proved the role of infants' socio-emotional growth on later healthy child development (Felfe & Lalive, 2018; Nelson et al., 2007). Early socio-emotional development involves infant's abilities to interact, communicate and deal with emotions; these competencies arise from the synergic contribution of biologically rooted individual characteristics (Bates, Kohnstamm, & Rothbart, 1989), the quality of infant-caregiver relationship (Bretherton, Munholland, Cassidy, & Shaver, 2008) and the role of proximal-to-distal social factors. The bases for socio-emotional development are observable soon after birth (Meltzoff & Moore, 1977), when newborns begin to display a repertoire of active, stimulus-seeking (i.e., rooting, sucking, orienting and visual scanning) and responsive behaviors (i.e., widened and brightened eyes, changes in respiration, decrease in random movements, and facial expressions). These patterns equip the infant to rapidly engage with the human partner, that in turn, nourishes the expression and flourishment of such abilities through daily interactive exchanges (Tronick, 1989). So far, extensive research proved the role of infants' socio-emotional growth on later healthy development (Felfe & Lalive, 2018; Nelson et al., 2007) and demonstrated that responsive relationships with primary caregivers provide the architecture for the infant's whole experience of the world, playing a leading role

in healthy socio-emotional development (Beebe, 1986; Beebe et al., 2010; Feldman, 2012; Tronick, 2007).

Atypical contexts of development, both provided by maternal and/or infant at-risk characteristics (Porreca et al., 2018; Salo et al., 2009; Wan et al., 2013), deeply expose the quality of such experiences (Kiff et al., 2011). As regards infant's atypical characteristics, studies on preterm samples observed a scarcity of infant's communicative signals that challenge parents' understanding of infant behaviors and might activate compensatory responses (Miles & Holditch-Davis, 1995; Montirosso et al., 2017). These parenting behaviors can be highly adaptive but can eventually result into intrusive and non-attuned behaviors (Howe et al., 2016). Despite a lack of studies specifically focused on mother-infant interactions, a few data on IUGR and Small for Gestational Age (SGA) infants have pointed out early signs of atypical socio-emotional competences. Compared to normal birth weight peers, IUGR and SGA newborns showed more insulted cry states, poor use of environmental stimuli (Figueras et al., 2008), higher negative affects and difficulties in orientating to social and non-social environment (Watt, 1989). Also, from toddlerhood, significant delays have been observed in adaptive behaviors and social interactions domains (El Ayoubi et al., 2016; Padilla et al., 2011). Specifically focusing on interactive exchanges, only one study reported patterns of passivity and ambiguous signals in SGA infants, suggesting for the parents potential difficulties in understanding infants' reactions and behaviors (Feldman & Eidelman, 2006). In addition, the distressing information about abnormal fetal and offspring size (Geva, Eshel, Leitner, Valevski, & Harel, 2006) might impact parental attitudes toward child care. Both these parental representations and the infant's atypical contribution to the early interactive exchange, in terms of diminished and ambiguous communicative abilities, can disrupt early emotional exchanges that build the quality of the mother-infant relationship (Tarabulsy, Tessier, & Kappas, 1996).

Transactional models of development have highlighted how child development emerges from a continuous and bidirectional interaction between both biological and environmental forces (Sameroff & Mackenzie, 2003). In the specific context of IUGR early socio-emotional growth, the biological vulnerability might be expressed though impoverished infant's socio-emotional behaviors (Baker et al., 2007). In fact, consistently with this hypothesis, a previous study found a vulnerability in the brain areas specifically deputed to emotion processing (Chapter 2). Also, IUGR might negatively impact parenting: a potential sense of inadequacy to provide the fetus with a growth-promoting inner environment might affect maternal emotional state, and thus her engagement with an IUGR baby and the establishment of a healthy, safe, and nurturing parent–child relationship. On the other hand, parenting and the quality of parent-infant interactions can potentially moderate the negative effect of infant scarce interactive abilities due to IUGR and therefore affect long-term outcomes (Nichols et al., 2017). Indeed, in the study of fetal influences on neurodevelopment, the antenatal process of growth restriction has been described as potentially enhancing IUGR surviving infants susceptibility to postnatal environmental factors (i.e., family socioeconomic status, parental care in childhood) (O'Donnell & Meaney, 2016). Consequently, along with studies exploring the underlying neurobiological mechanisms accounting for decreased neurodevelopmental outcomes in IUGR infants and toddlers (Chapter 2 and 3), it is of clinical relevance to monitor the quality of IUGR infants' early engagement with post-natal environment and the intertwined relationship of parental and infant interactive characteristics.

To our knowledge, the present study represents the first focusing on infant's interactive behaviors and parenting in the context of IUGR early development. Our aim is to preliminary assess maternal and infant's interactive characteristics, by comparing IUGR and Appropriate for Gestational Age (AGA) term-born mother-infant dyads during early interactive exchanges at 4 and 9 months. In addition, the study aims at investigating the effect of IUGR on cognitive

development at 12 months of age and to explore the association of early interactive competencies with such outcomes. Specifically, based on the few available findings about IUGR socio-emotional atypical behaviors (El Ayoubi et al., 2016; Padilla et al., 2011; Watt, 1989), we expect IUGR infants to display significantly lower levels of social engagement with the caregiver during early interactions. In addition, despite IUGR studies systematically lack a focus on parenting, we hypothesize less-than-optimal levels of maternal interactive characteristics during early exchanges as observed by for mother-infant interactions in other perinatal risk groups, like premature and low birth weight infants (Bozzette, 2007; Feldman & Eidelman, 2009). As regard cognitive outcomes, in line with available meta-analytic findings (Chapter 1) we expect IUGR infants to display significantly lower cognitive and motor scores. Last, as regard the association between interactive behaviors and cognitive we expect positive associations between mother-infant behavioral patterns and 12 months developmental outcomes.

METHODS

The main features of the study are summarized below. A full description of research design and methods refers to the study "*Neurobiological bases and socio-emotional development in IUGR infants*" and has been presented in Chapter 3 and research stages are graphically summarized in Figure 1 (Appendix: A3).

Participants and procedure

The study was implemented with pregnant IUGR and healthy women attending the Children and Women's Health Department Medical School (University of Padova), approached between the 28th and the 32th weeks of gestation. Women willing to participate received the completely informative material about study design and methods and were re-contacted during the post-partum period. A complete description of participants inclusion and exclusion criteria was presented in Chapter 3. Overall, from September 2017 to March 2019,

100 healthy and 31 IUGR pregnant women were contacted for the study. During pregnancy, IUGR participants diagnosis was ensured by ultrasound tests while at birth premature newborns were excluded. About 58 healthy and 17 IUGR pregnant women were eligible for the postnatal assessment waves. The procedures took place at the Laboratories of the Department of Developmental Psychology and Socialization at the University of Padova. At 4 and 9month it involved the assessment of mother-infant interactions, though video-recording of brief free play ecologic exchanges. At 12 months, developmental outcomes have been assessed during structured procedure performed by trained psychologist.

Measures

Interactive dimensions

Emotional Availability Scales (EAS; Biringen, 2008) have been applied to code interactive exchanges following the coding system of four parental dimensions: adult sensitivity, adult structuring, adult non-intrusiveness, adult non-hostility; and two child scales: child responsiveness and child involvement. Each EA dimension produces a score on a 7-point scale (1 – 7), where higher ratings stand for more optimal features.

Developmental outcomes

Bayley Scales for Infant and Toddler Development – Third Version (BSID – III; Bayley, 2006) were performed at 12 months of child's life to assess for cognitive development. BSID-III evaluates five different domains: cognitive, language, motor, socio-emotional behavior and adaptive behavior. The scales produce standardized scores with a mean of 100 and a standard deviation of 15. Scores lower than 85 were considered as abnormal performances (Albers & Grieve, 2007).

STATISTICAL ANALYSES

To compare interactive variables at 4 and 9 months of age between IUGR and AGA term-born infants, Student's *t*-test were performed on the four parental (Sensitivity, Structuring, Non-Intrusiveness, Non-Hostility) and two infant (Responsiveness, Involvement) scales of the Emotion Availability Scales (EAS). To test for the effect of IUGR on cognitive, motor and language outcomes at twelve months of age, linear regression were performed controlling for sex and gestational age at delivery (weeks). Last, in the whole group of infants, linear regression analyses were performed to test the association between mother and infants' interactive behaviors and cognitive outcomes.

RESULTS

Demographic and perinatal data

Antenatal characteristics and perinatal outcomes of the study groups at pregnancy stage are reported in Table 1.

Table 1. Antenatal characteristics and perinatal outcomes of the study groups

	IUGR (*n* = 29)	AGA (*n* = 100)	*p values*
Antenatal characteristics			
Maternal age (years)	33.60 ± 6.52	34.08 ± 5.07	.738
Perinatal outcomes			
Birth weight	2569.74 ± 356.60	3420.81 ±450.12	< .001
Length	46.56 ± 1.98	49.15 ± 1.72	< .001
Gestational age at delivery	38.99 ± 1.18	39.65 ± 1.30	.074
Sex (male)	7 (29%)	50 (54%)	.050

Note. Data are given as n (%), mean ± SD
p-values are calculated using Student's t-test, Pearson's chi-square test
IUGR = intrauterine growth restriction; AGA = appropriate for gestational age

Group differences in interactive behaviors

Group differences between IUGR and AGA term-born infants in mother and infant's interactive dimensions at 4 and 9 months of age are presented in Table 2.

Table 2. Mother and infants' interactive dimensions in IUGR and AGA groups

	4 months			*9 months*		
	IUGR (*n* = 7)	AGA (*n* = 23)	*p values*	IUGR (*n* = 7)	AGA (*n* = 13)	*p values*
Maternal dimensions						
Sensitivity	4.79 ± 0.76	4.90 ± 0.91	.675	4.55 ± 0.71	4.62 ± 0.42	.702
Structuring	4.07 ± 0.61	4.98 ± 0.94	< .001	3.93 ± 0.35	4.15 ± 0.32	.178
Non-intrusiveness	4.71 ± 0.95	5.17 ± 1.08	.302	4.07 ± 0.79	4.35 ± .055	.432
Non-hostility	6.14 ± 0.38	6.34 ± 0.78	.411	6.14 ± 1.07	6.5 ± 0.64	.441
Infant dimensions						
Responsiveness	4.07 ± 0.84	4.55 ± 1.02	.206	4.00 ± 0.76	4.94 ± 0.99	.032
Involvement	3.07 ± 0.93	3.66 ± 1.22	.171	3.21 ± 0.76	3.80 ± 0.78	.121

Note. Data are given as mean ± SD
p-values are calculated using Student's t-test
IUGR = intrauterine growth restriction; AGA = appropriate for gestational age

Group differences in developmental outcomes

At 12 months of age IUGR infants had significant lower BSID – III scores (composite cognitive, motor and language) compared to AGA term-born peers (Table 3). After adjusting for sex and gestational age at birth the effect of IUGR only remained significant for motor outcome (b = - 19.20, SE = 8.03, $t(14)$ = - 2.39, p = .032).

Table 3. Cognitive, motor, language outcomes for IUGR vs AGA infants at 12 months of life

	IUGR (*n* = 6)	AGA (*n* = 16)	*p values*
BSID – III Cognitive scale	97.50 ± 7.58	107.5 ± 12.78	.040
BSID – III Motor scale	85.00 ± 6.00	101.88 ± 14.15	< .001
BSID – III Language scale	92.67 ± 10.33	91.13 ± 14.59	.787

Note. Data are given as n (%), mean ± SD
p-values are calculated using Student's t-test
IUGR = intrauterine growth restriction; AGA = appropriate for gestational age

Whole group association between interactive behaviors and infant cognitive outcomes

The preliminary results of linear regression testing for the association between mother and infant's interactive behaviors and cognitive outcomes at 12 months of life reveal the follow. No significant association were found between mother and infant's behaviors at 4 and 9 months and cognitive and language outcomes at 12 months of age. Infant's responsiveness at 9 months of age was marginally associated with motor outcome (b = 7.18, SE = 3.40, t(14) = 1.92, p = .069). Additionally, exploratory analysis testing interactions between interactive abilities and group (IUGR vs AGA) have been conducted leading to non-significant results. However, considered the very limited sample size, no conclusion can be drawn by these results.

DISCUSSION

The present study examined maternal and infant interactive characteristics during early exchanges at 4 and 9 months in a group of antenatal diagnosed term-born IUGR infants, compared to AGA peers and investigated the association of such patterns with the infants developmental outcomes. The results of the video-analysis of mother-infants interactions along the first year of life showed few differences between IUGR and AGA groups. As regard infant's behaviors, decreased levels of responsiveness are observed at nine months in the IUGR group; whereas no earlier differences at 4 months emerged. No significant differences were found in infant involvement neither at 4 nor at 9 months in infant involvement, a variable describing child willingness to actively engage the partner during the interaction. Infant's responsiveness variable taps infant affect and behavioral regulation during the interaction along with the willingness to be engaged following the suggestion provided by the interactive partner. The diminished responsiveness observed for the IUGR group at 9 months is in line with previous evidence of atypical interactive abilities in IUGR infants reporting signs of greater passivity and decreased sensitivity to social stimulation (El Ayoubi et al., 2016; Feldman & Eidelman, 2006; Watt, 1990). Also, huge part of early interactive

exchanges rely on the ability to interpret and perform facial expressions that are early used to understand others emotion and thought, to make others understand themselves, and to share emotional states (Beebe et al., 2010, 2016; Meltzoff & Moore, 1977). Consequently, a diminished interactive responsiveness in IUGR infants might derive from a poorer ability to deal with and respond to visual social stimuli, probably rooted in a fragile neural base for face-, emotion- processing (Chapter 2).

The gap observed in responsivity between the two groups of infants emerged relatively late during first year of life, suggesting that early patterns of interactions are not observably compromised by IUGR. A possible interpretation of this finding refers to the dialectical relationship between biological and environmental factors occurring along time and across multiple levels. IUGR biological vulnerability prompts a trajectory that results in atypical development after a relatively prolonged exposure to the environment. Indeed, IUGR infants seem stuck to simple interactive strategies for affective and behavioral regulation and responsibility to interactive signals. Such limited patterns might remain in a range of normality during first months of life; whereas they display their negative effect further on, when environmental stimulations and interactive requests increase in complexity. This sort of catch-down in IUGR social behaviors might point out the opportunity and the responsibility for clinical interventions to foster infant's social engagement along the very first months of life, before the expression of the behavioral disadvantage.

As regards maternal interactive characteristics, at 4 months IUGR mothers scored significantly lower in structuring the interaction with their infants. No other differences emerged at four and nine months. This result might reflect an initial difficulty in IUGR mothers in understanding infant's need and signals. Such difficulty is translated during the interaction into incoherent and excessive but not attuned attempts to scaffold infant's experience, characterized by frequent, uncoordinated and ineffective attempts. This result

appears in line with previous findings reported for preterm mothers suggesting compensatory processes in preterm parenting behaviors (Montirosso et al., 2017). Indeed, along time IUGR mothers might learn to better identify and recognize their infant's communications and this would result into more optimal and attuned structuring competencies.

Observing mother and infant IUGR interactive patterns in a dyadic lens, we can attempt to describe some transactional processes. Indeed, IUGR mothers seem to face very initial difficulties in providing optimal scaffolding to their infant's social behaviors. We speculate that such difficulties might be due to IUGR biological vulnerability expressed in early ambiguous signs. On contrary, IUGR infants seem to face more challenges in responsivity later in the 1st year of life, when their biological fragility made them less able to reach autonomy, regulation and adequate exploration. It might be possible that early maternal difficulties in structuring interactive exchanges produces less attuned and synchronized stimulation that in turn makes infant's environment more challenging and thus potentially enhancing infant vulnerability.

As regards developmental outcomes at 12 months of age, despite the very limited sample size, preliminary results show significant differences in both cognitive and motor domains at 12 months of age, indicating that IUGR is related to less than optimal cognitive and motor development, compared to the ones of term-born AGA peers. These findings are in line with current meta-analytic evidence on term-born IUGR neurodevelopmental outcomes (Chapter 1) and results on very preterm IUGR toddlers (Chapter 2). Specifically, we confirm that cognitive and motor trajectories of IUGR and AGA term-born individuals diverge very early in life, whereas language development is more preserved by the effect of IUGR. Considering the whole-group association between early interactive behaviors and cognitive outcomes, our results found no significant associations. Infant's responsiveness at 9 months only displays a close-to-significant effect on motor development; perhaps pointing a direction

on the role of behavioral interactive regulation in sustaining motor growth (Sacchi, De Carli, Vieno, et al., 2018). Within the affectionate bond with the caregiver, the infant receives not only protection, care and the recognition of his/her needs, but also an encompassing environment for physical, cognitive, social and affective exploration (Britto et al., 2017).

Limitations

The study has limitations. First, the very limited sample size requires results to be replicated in larger groups. This will also allow to control the associations for the effect of different covariates and to better explore the intertwined relationship between maternal and infant's interactive influences. Indeed, larger sample would allow to test for moderating effects, exploring whether the quality of mother-child interactions can potentially buffer the negative effect of infant scarce interactive abilities on child development (Baker et al., 2007). Also, longer time frame to study the association with cognitive outcomes as well as with other developmental domains, such as behavioral and emotional problems, should be encouraged. Given the high rate of IUGR pregnancies and the lack of studies on socio-emotional competencies, our work is an important first step in understanding the social-emotional, and parenting environment of these children. A great advantage is given by a direct observation of interactive patterns in two repeated time-points; however, wider assessment of parenting in term of well-being, mental health state, and maternal representation, and the inclusion of variables describing infant's familial and social context would allow to a more detailed understanding of IUGR-environment interaction.

Conclusion

Globally, the present study describes the relevance of evaluating infants' characteristics and the caregiving context in the specific expression of early interactions. Contributing to the clinical literature on IUGR postnatal development, these results indicate that both mother and infants' early interactive characteristics show to negatively mark IUGR infant's development

in different time-points along the first 12 months of life. Therefore, these interactive patterns need to be further investigated to strengthen the transactional view of infants socio-emotional development as emerging from both parental and infants relational characteristics (Leve & Cicchetti, 2016). Our findings also suggest that negative developmental outcomes observed in IUGR children, especially in motor domain may be ameliorated through enhanced infant's social responsiveness with the caregiver (Sacchi, De Carli, Vieno, et al., 2018). This study points out that plasticity windows for clinical interventions fostering IUGR infant's social engagement might take place in the very first months of life, before the expression of a behavioral interactive disadvantage. This kind of observations could lead to more focused interventions aware of the most susceptible periods (first months of life) and processes (responsiveness) to target. In addition, parenting interventions pursuing the aim of being effective for infant's development, should not overshadow the importance of parental subjectivity (Feldman, 2012). Indeed, without providing mothers with rewarding alternative interactive experiences and satisfactory strategies to engage infant, no change in mother-infant patterns is thinkable. Therefore, clinical interventions should first embrace parental difficulties in handling their parental role and infant's atypical characteristics; also, they need to support maternal multimodal communications relying on less frustrating and challenging channels.

Part 3. The intervention

TRANSLATING BIOBEHAVIORAL VULNERABILITY INTO PORT-OF-ENTRY FOR CLINICAL INTERVENTIONS

CHAPTER 5: Sacchi C, Facchini S., Downing G., Simonelli A., (submitted). *Framing pediatric care into a relational perspective with the Primary Care-Video Intervention Therapy. A case study*

CHAPTER 5

Framing Pediatric Care into a relational perspective with the Primary Care-Video Intervention Therapy. A case study

ABSTRACT

Infant growth vulnerabilities (e.g. Intrauterine Growth Restriction and Small for Gestational Age) pose the goal to not overlook subtle susceptibilities and their impact on the parent-infant relationship.

In this chapter we present a clinical application of a video-feedback intervention program to support parenting, the Primary Care-Video Intervention Therapy (PC-VIT), specifically developed to fit pediatric care characteristics and delivered to a family with a SGA newborn.

This case-study presents the principal steps of the intervention with the family of an SGA infant from birth up to toddlerhood.

Preliminary findings show that parenting is challenged by SGA vulnerability increasing worries about infant growth, with such worries becoming particularly salient along the weaning process. Findings support that PC-VIT suits the pediatric setting, allowing parents to explore their worries and suggest that video-feedback interventions can give an innovative answer to the need for support in families with growth-vulnerable infants.

The study shows the powerful opportunity to limiting the impact of infant growth vulnerability on parent-child relationship and socio-emotional development and the importance of promoting an integrated approach to child development in the early primary care contexts of intervention. Embracing mental-health and parenting-related issues in the pediatric settings would be extremely beneficial for those infants experiencing slight developmental fragilities.

INTRODUCTION

Small for gestational age (SGA) is a birth outcome classification describing newborns delivered at a birth weight below the 10th centile for gestational age in their normal distribution reference curve. In the absence of preterm delivery, SGA newborns do not experience high perinatal risk; hence, they are very unlikely to receive postnatal care. Despite this, SGA infants show a subclinical vulnerability that might progress into negative health, and mental-health outcomes (Simões et al., 2015). Also, being born SGA constitutes a risk factor for neurodevelopmental impairments, emotional-behavioral problems, and several health diseases later in life (Puga et al., 2012).

Parenting in such atypical growth contexts is challenging (Sacchi, De Carli, Mento, et al., 2018). A potential sense of inadequacy to provide the fetus with a growth-promoting inner environment might affect the mother's emotional state and engagement with the baby. Those parents are confronted with distressing information about fetal and offspring size, impacting the attitudes and behaviors toward child care (Geva, Eshel, Leitner, Valevski, et al., 2006). Also, growth-vulnerable infants display ambiguous signals, making it difficult for parents to understand the intentions behind their signals and the meaning of their behaviors (Feldman & Eidelman, 2006). Indeed, both greater maternal intrusiveness and increased infant passivity during interactive exchanges are reported in SGA mother–infant dyads (Feldman & Eidelman, 2006). Both parental difficulties and the child's vulnerability might negatively impact the establishment of a healthy, safe, and nurturing parent–child relationship. Considering that there is no initial need for clinical interventions with SGA babies, for pediatric general health providers, their early vulnerability still poses the challenge to properly sustain the growth, without overlooking their subtle susceptibility and its impact on the parent–infant relationship.

The pediatric setting excels in being a suitable context to address relational and developmental issues surrounding atypical and stressful growth. For pediatricians, an infant's physical growth represents a primary index of health, and its assessment constitutes an essential part of pediatric care (Singhal, 2017). Furthermore, well-baby visits allow pediatricians to regularly monitor infants' development, along with the family environment. Pediatricians visit infants and their families earlier and more often than any other health professionals, with the great advantage that parents value that relationship and feel comfortable in openly discussing their concerns. Therefore, primary care represents the first setting to provide an integrated view of child development and to implement effective strategies to nurture healthy parent–child relationships. Pediatricians should embrace the huge responsibility of identifying, supporting, and helping parents to recognize these moments and to develop tailored strategies for facing them.

Among several techniques adoptable within a pediatric setting, video feedback (VF) represents a cutting-edge approach. VF is a powerful tool increasingly used across a number of therapeutic modalities (Steele et al., 2014); evidence of effectiveness in early mother–child intervention is largely documented (Fukkink, 2008). Indeed, parents' experience of observing themselves in the video aids achieve a more realistic perspective on their relationship with their child (Leyton et al., 2019). In particular, they become more aware of their own reactions and are supported in better hypothesizing the motivational roots behind the child's behaviors.

Video Feedback in Primary Care

The application of a video intervention method in primary care is completely innovative. Early interactive exchanges observed during a pediatric consultation provide a wealth of relevant cues about child development and the parent–child relationship, hence furnishing several possibilities of intervention. Starting from this clinical observation, the

primary care-video intervention therapy (PC-VIT; Facchini et al., 2016, 2018) program was developed to suit the characteristics of a pediatric setting.

PC-VIT represents the adaptation of video intervention therapy (VIT; Downing, Bürgin, Reck, & Ziegenhain, 2008). VIT is a mentalization-based cognitive-behavioral methodology; beyond to classical behavior-oriented techniques, it draws on mentalizing eliciting and other techniques developed within VIT itself (Crugnola, Ierardi, Albizzati, & Downing, 2016; Downing et al., 2008). Mentalization refers to the capacity to understand oneself and others in light of mental states (Fonagy, 2018). In the specific context of parenting, it represents the parental attitude of making sense of the child's behaviors as an expression of internal emotional and mental states. It is a powerful predictor of infant–parent attachment security because parents are more likely to respond sensitively to a child's signals when they can understand the meaning and intentions of the child's behaviors (Slade et al., 2019). This parental capacity to treat the child as a psychological agent positively impacts the child's socio-cognitive development, stimulating his or her own mentalizing capacity, autonomy, and self-regulation (Sharp & Fonagy, 2008).

CASE ILLUSTRATION

The present case study illustrates the application of the innovative protocol of VF intervention, PC-VIT (Facchini et al., 2016, 2018), across the first year of a child's life with the family of an SGA infant. The case reports on a family belonging to a non-referred healthy group of primiparous parent–infant dyads attending a pediatric primary care community center, located in Pordenone, in the north of Italy. Both parents had an upper-intermediate level of education and were working full-time. Pregnancy was healthy and delivery was spontaneous at 41+5 gestational weeks. The baby was born weighing 3,130 g (below the 10^{th} centile for gestational age). During the first year, growth was constant, but weight and length ranged from the 3^{rd} to the 10^{th} centile for gestational age. The parents came to the first visit

reporting high levels of anxiety and worry concerning their son's physical growth and his several episodes of crying and psychomotor agitation. A pediatrician trained on VIT by Dr. George Downing delivered the intervention focusing on sustaining healthy parent–child interactions and driving parents to positive attitudes toward the child's physical and mental growth. PC-VIT has been applied to address parental worries concerning a child's weight and growth. Also, the aim of the intervention was to sustain parents in the emergence of their new parental abilities; specifically, parents were encouraged and modelled to develop metalizing attitudes toward their child's behaviors.

Primary Care-Video Intervention Therapy

PC-VIT is proposed during the first pediatric visit, between 15 and 30 days after birth; parents are invited to receive VF consultations about physical and mental health along the typical content of well-baby visits. During subsequent health report sessions, parents and infants are recorded for about five minutes during face-to-face interaction. Shortly after registration, the pediatrician reviews and comments on the video together with the parents. A specificity of PC-VIT is that each session is focused on a specific developmental milestone (see Table 1), which is translated into different stratagems proposed for family interaction. Indeed, VF is focused on the specific developmental challenges faced by the family at each specific time point or anticipating upcoming ones.

Table 1. **PC-VIT Structure**

PC-VIT Session	**Theme**	**Task**
1 month	Touch & Cry	Free contact
3 months	Affective matching/Descriptive language	Face to face
6 months	Feeding	Eating together

8 months	Separation & Autonomy	Separation procedure
12 months	Reading	Reading together
18 months	Limit setting	Don't care procedure

Note. PC-VIT = primary care-video intervention therapy.

The general structure of each PC-VIT visit is summarized in Table 1. First, the pediatrician shows a selected part of the video (Step 1). Second, parents are encouraged to share what caught their attention (Step 2). Then, the pediatrician points out a series of positive interactive moments visible in the video and shares the reasons for regarding them as positive. Also, the pediatrician and parents reflect together on one or more new actions that can be implemented at home to translate positive moments into routinely nurturing exchanges (Step 3). Last, the pediatrician summarizes the main points elaborated in the session (Step 4).

Table 2. **PC-VIT in the Pediatric Visit Framework**

Medical examination	15–20 minutes	**Step 1.** Look at the video clip together for the first time
Video recording	5 minutes	**Step 2.** Ask parents for their reaction
PC-VIT	30 minutes	**Step 3.** Show an appropriate positive interaction
Wrap up	5–10 minutes	**Step 4.** Work on that interaction

Note. PC-VIT = primary care-video intervention therapy

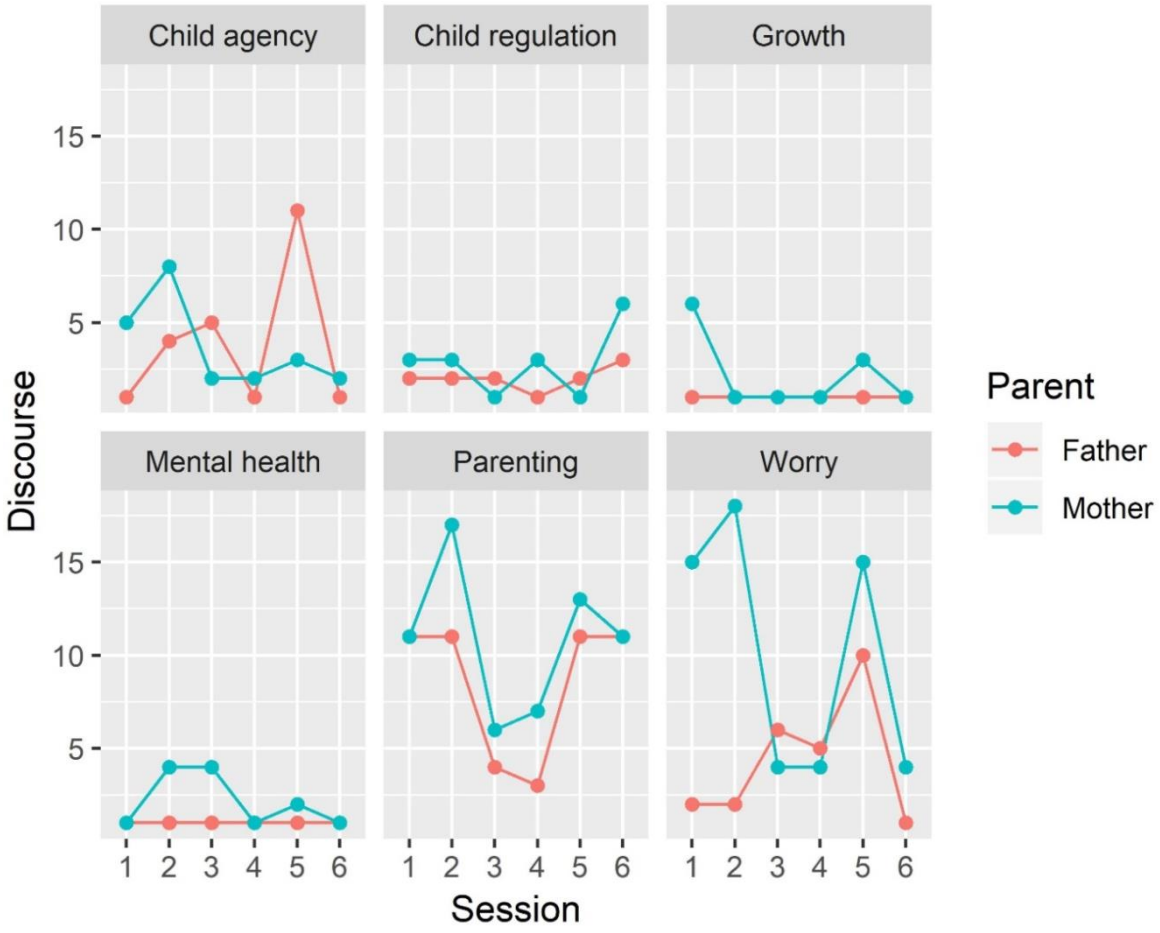
CASE OUTCOMES

Development of Parental Discourse

To provide an overview of potential changes in parental narrations throughout the intervention, we longitudinally analyzed the quantity of parental discourse during the PC-VIT

sessions. Parental narratives constitute a powerful indicator of their thoughts, worries, and emotional states. Also, they provide the possibility to explore parental engagement in the intervention in terms of increased versus decreased verbal production. To investigate patterns of parental discourse, we first identified specific thematic areas referring to the following: (a) general themes of pediatric visits and (b) principal targets of PC-VIT. In particular, the first area defines the infant's physical growth (e.g., "I used to breastfeed every three hours"; "I should remember vitamin D"). The second area identifies discourse on "mental health and developmental skills" (e.g., "He turns, we find him in all positions on the bed"). Then, we selected four areas to describe the main goals of PC-VIT. Namely, two areas fit discourse related to parenting (e.g., "We're parents, so we try! … everything is still new for us"; "We have the task of encouraging his personality") and parental worries related to the child's

growth (e.g., “We panicked because the banana’s slice was too big”; “Is it true that his weight at six months should be double of his birth weight?”). The last two areas focus on parental discourse identifying the child as a psychological agent; we called them child’s agency (e.g., “I see, he tries to communicate his needs”; “He is very exacting”) and child regulatory abilities (e.g., “He wants the body contact to calm down”; “For some days he has been waking up uneasily, I wonder if it might be the teeth”). Each PC-VIT session was transcribed verbatim. Then, both maternal and paternal narratives were manually gathered according to the six categories. We performed preliminary analyses to quantify the amount of text



produced by each parent across each thematic area and along the six PC-VIT sessions. Figure 1 graphically depicts the rate of change across time in quantity of parental discourse from the first well-baby visit, in the postpartum period, to the 18th month of the child’s life.

Through visual inspection, one can observe that areas eliciting most maternal and paternal expression refer to parenting, parental worry, and child's agency. In particular, "parenting" and "parental worry" texts were present from the beginning of the intervention. This highlights that the pediatrician setting represents an appropriate context for housing parenting-related content, which is already available in the minds of the newborn's parents. On the contrary, overall, less discourse was produced referring to the child's physical growth.

Figure 1. Trends in parental discourse across sessions for selected thematic areas

That might be due to the structure of a PC-VIT session, where in the first part of the visit, the child's medical examination takes place. Generally, the parents used that moment for requests and clarifications related to their son's development. Regarding, discourse development along the intervention, maternal worry about her child's growth was highly reported in the first 3 months of the child's life; then, after a decrease in the third and fourth sessions, it increased again at 12 months. This pattern might reflect an initial process of mutual discovery between the mother and her baby, whereas at 1 year of age, the child's acquisition of new abilities of walking might bring new worries about the child's autonomy. Another interesting point is that progressively, the parents reflected one another in the quantity of their discourse related to parental worries. Namely, across sessions, higher father involvement emerged, whereas maternal verbal production decreased, so that from the third session, the parents displayed a very similar pattern of discourse remaining stable for the rest of the intervention. Perhaps, the positive experience offered by the relational setting of the intervention might foster a mutual involvement in the child's development, which might be translated into higher levels of father involvement in childcare and in daily mother–father exchanges at home. Indeed, parents might become more likely to share parental duties and responsibilities of parenting, and this new shared weight of what is likely to present concern

and worry supports the co-construction of solid parenting abilities. Another interesting outcome that emerged through our observation of parental narratives was the possibility for the parents to reflect about their son as an interactive agent. Notably, the parental focus on the child's agency appeared to be present from the first session, whereas attention to the child's emotion and state regulation appeared to emerge in parents' discourses around the fifth session. As expected, parental mentalization of the child's internal states required more effort than a focus on the child's behavior. This increased attention to the child's regulation around the sixth month of the child's life might represent that along the intervention, a shift of focus from behaviors to the child's internal states took place.

Clinical Vignette: Eating Together (Third Session)

To give the readers a close view of PC-VIT, we present a clinical vignette to directly observe the application of PC-VIT principles within a single session. Parental worries about the growth are likely to become particularly salient along the weaning process, where parents of SGA infants might underestimate the infant's competencies. Weaning truly matters to parents in general, representing a turning point in a child's nutrition and autonomy. This is likely to be even truer for parents of children with growth vulnerability. We present the third pediatric session (around the 6^{th} month of life). Generally, at this time point, parents are asked to feed their baby with a banana as the interactive stratagem that elicits discussion about feeding and weaning. As follows, we provide some extracts of the VF session to observe the interactive dynamics between the pediatrician and parents during VF.

In this first extract, the pediatrician explores parental feedback about the video (Step 2). He provides an emotionally available relational context allowing the mother to report on her worries and sustains maternal comments on the infant's activity:

Pediatrician: *So, we saw this little part [of the video], what do you think?*

Dad: *That he is very active*

Mom: *uhm . . . (punted)*

Pediatrician: *(smile at the mother) . . . try not to focus on the piece of banana . . . [the pediatrician refers to previous mother's comments on the fear of suffocation]*

Mom: *He acts, he's interested, he wants to experience something new, he wants to touch it*

Pediatrician: *Yes! There you see this, how he puts his hands, he wants to try, to smell. Beyond the fear, which is a very common fear most of parents have . . . this fear might limit your possibility to look at how your child is growing up. As we said, you can start placing some smashed food on the table or on the plate and then you increase, you will, you will be reassured seeing that he is capable . . . he is programmed for this!*

Then, the pediatrician comments on the feeding interaction with parents (Step 3). He starts pointing out the infant's interest and agency toward this new experience. By showing the child's abilities, he aims at promoting a more positive and less worried point of observation. Also, he accepts and validate the parents' worries, giving reassurance.

Pediatrician: Here, look at how interested he is! Did you see how he hooked [the banana slice]?

Mom: *We panicked a bit, the slice was too big!*

Pediatrician: *Okay it's normal . . . Look here, is he nibbling it?*

Mom: *Yes, yes!*

Pediatrician: *Ok, here he brings the banana, can you see? Did you see that he feeds? Oh, how interested he is in this new thing! Well, what we have here? He takes [the banana], so he has his own initiative too, he puts a little of control in this thing, unlike [what he can do with] the teaspoon*

Dad: *Yes, there he is passive*

Pediatrician: *With the teaspoon it's just right to the mouth and stop! That's also okay, but it might not be just that! Here (indicating the monitor with the baby holding the banana) he sees it, it has a color, a smell, he takes it, he hunts it. So, these two things can go a bit together: a little you two taking control, a little he does*

Mom: *Maybe, to relieve this anxiety a bit . . . we can star with a small piece of banana! Here, I had a little bit of anxiety, but for example last night it was a smaller piece and I felt calmer, I crushed it a bit*

Dad (to the mother): *I see, this is my concern too. But if the doctor says no, I think there is no danger*

Pediatrician: *No, absolutely. Not with such soft things*

Then, the pediatrician suggests replicating the interactive experience of feeding and eating at home (Step 3) and gives some general advice.

Pediatrician: *Also, eating together is a great idea, because he learns a lot by looking. If he is the only one who eats, and only eats with the spoon, he learns a little: just to receive the spoon.*

Dad: *So, you say, while we eat, can we also give him something?*

Pediatrician: *Give him some small pieces, some sauce . . .*

Dad: *Bread?*

Pediatrician: *A small piece of pasta, bread is good too, most of all I recommend variety. There are children who only eat only bread . . . but children need variety in food.*

Dad: *Ok.*

Last, the pediatrician goes back to parental worries that emerged in previous sessions and during the first part of this VF and links them with new emerging challenges for the parents: control and discipline (Step 4).

Pediatrician: *So, what do you think of him, how is he growing up? This moment of eating also reflects other areas of his growth. He is now with his own desires, initiatives, this new willingness to do something. How is this thing?*

Mom: *Oh, that show us he's growing, he changed a lot just in a month, even in few weeks!*

Dad: *He shows us that he has his own intelligence, his intent, his desires and needs, and he tries to communicate them in his own way.*

Pediatrician: *Perfect!*

Mom: *He has his own personality, which is not easy!*

Pediatrician: *What do you mean?*

Mom: *That when he wants something you can see it; he makes you understand, like he cries*

Pediatrician: *And, how do you stand with this new willingness, intentionality, which is emerging now?*

Overall, the clinical vignette highlights the positive impact that a family-oriented, mental health-focused pediatric visit can have on a vulnerable family. Observing VF during such a consultation enables to directly observe how PC-VIT works on the crucial issue of a child's vulnerability. Indeed, several difficulties can emerge during this developmental stage, with the possibility to negatively impact the parent–child relationship. Using VF at this crucial point allows direct observation of how sustaining parents fosters their abilities in recognizing their child's competences. This might reduce parental worries and potential negative practices deriving from such fears. In particular, the pediatrician used the video to show the parents their son's interest toward food/world exploration. By doing that, he shifted the parental focus from their worry of suffocation to the child's abilities. This took place in a non-judgemental and relational context, which allowed the parents to freely discuss between each other about potential alternative strategies to handle this turning point of child development.

DISCUSSION

We presented a promising application of the innovative PC-VIT, which combines a relational perspective and a specific focus on mental health and parenting with the daily

activity characterizing a pediatric setting. Findings on parental discourse highlighted that most of the parental narratives reflected the thematic areas targeted by the intervention. Namely, PC-VIT was aimed at holding parental worries about child's growth and sustaining their mentalization abilities. Parental focus on their worries enabled reflection on the opportunity in the pediatric setting to provide early effective support. Indeed, birth and the first year of life are a unique window for intervention; the survival of the baby emerges as the first parental concern, making parents extremely receptive to support and guidance. During PC-VIT, the parents also became more able to speak about their child's competences. The use of the video taught them to recognize their child's communicative skills and progressively identify his self-regulatory abilities. These competences boost a secure parent–child attachment and represents an early marker of socio-cognitive development (Eisenberg, Spinrad, & Eggum, 2010).

The use of PC-VIT appeared particularly relevant for this vulnerable family in the developmental stage of weaning. A short interactive feeding sequence was enough to activate parental worries concerning the infant's competences and emerging autonomy. The relational and non-judgemental context of PC-VIT allowed parents to share their emotional states while feeling understood, supported, and sustained in their initiatives. A specific feature of PC-VIT is the temporal contingency of video recording and VF; this short time span fosters the learning process. Parents' emotional involvement is still active during VF, which aids them to freely report on their emotional states. The pediatrician can then intervene on potential misinterpretations of a child's behavior driven by parental emotions. Replacing parental fears and sense of inadequacy with new interpretations of a child's actions can modify parental inner states underlying negative thoughts and attitudes.

Overall, PC-VIT perfectly suits the pediatric setting, allowing parents to explore thoughts, worries, and doubts about parenting challenges and their child's growth.

Preliminary findings support the encouraged shift in pediatric care toward more family-centered and mental health-focused approaches (Ordway, Webb, Sadler, & Slade, 2015). Pediatric health care providers have been called upon to develop strategies enhancing parent–child interactions (Simpson et al., 2016), and the present case study shows that VF might provide an innovative answer to this point. Indeed, PC-VIT allows the pediatrician to address a focus on familiar and relational issues surrounding each child's milestones and to promote an integrated approach to child development, where socio-emotional health is sustained along with physical growth. Also, within the routine activity, the pediatrician can prevent vulnerable infants from a clinical outcome by accompanying and sustaining their parents throughout the development fragility. Therefore, this kind of intervention meets the need for early support in families with growth-vulnerable infants, who are unlikely to receive tailored follow-up care despite their known vulnerability (Feldman & Eidelman, 2006; Sacchi, De Carli, Mento, et al., 2018).

General discussion

CONCLUSION AND FURTHER DIRECTIONS

General discussion

The work presented in this dissertation was aimed at investigating the neuro and behavioral socio-emotional courses of infants antenatal exposed to Intrauterine Growth Restriction. The main findings emerged from the empirical chapters provide support for the argument that IUGR is a significant antenatal risk factor for child neurodevelopment, especially targeting biobehavioral mechanisms of emotion and social processing. The investigative question posed in introduction was: "***whether and how (through which processes) child development after IUGR is exposed"***. Properly answering this ambitious interrogative is far beyond the possibility of a dissertation. As for infant and child development, transactional investigations and continuous, multifocal efforts are required. This dissertation wished to be a rigorous observation of certain multilevel falls describing a putative cascade of effects interesting IUGR infant-to-toddler development.

The presentation of the empirical studies followed a progression of investigations focused on birth, infancy and toddlerhood and a hierarchical structure moving from base research approaches toward clinical application. In this conclusive session we provide a concise summary of the main findings tracing the order of their relative chapters and we discuss the meaning of the results in the light of the theoretical transactional and translational models proposed in the introduction. Limitations of the work are also addressed to inform further research perspectives as well as guidelines for clinical applications.

1. The effects of Intrauterine Growth Restriction and Small for Gestational Age on cognitive development in preterm and term-born children

Chapter 1 was aimed at ascertaining and quantifying the effect of antenatal IUGR, disentangled from the effect of Small for Gestational Age (SGA) at birth and across the gestational age at delivery spectrum, on cognitive development and risk for intellectual functioning along the first 12 years of life. Based on 83 studies, the study proved that across childhood, IUGR (and SGA) are associated with lower cognitive evaluations, compared to appropriate for gestational age, showing overall small effects. Effect sizes are consistent for IUGR/SGA children born preterm and at-term, with higher overall effect sizes reported for term-born IUGR-AGA groups comparison. In addition, borderline intellectual functioning as well as risk for cognitive impairment are about twice higher in IUGR (and SGA) preterm and term-born children, evidencing the robustness of IUGR association with cognitive risk. Overall, most significant advance given by this study was to comprehensively address the childhood cognitive outcome of growth vulnerability experienced by true antenatal IUGR and SGA birth classification while keeping the two groups as distinguished. In addition, by including while treating separately preterm and term-born groups, it is possible to recognize that IUGR (and SGA) not only gives additional risk, leading downward developmental routes of preterm children, but also, it displays a specific effect on cognitive trajectories of term-born individuals.

2. Intrauterine Growth Restriction in very preterm infants affects grey matter volumes and subsequent cognitive and behavioral outcomes

The longitudinal cohort study presented in Chapter 2 was focused on brain structural growth at birth as potential differential outcome of IUGR in very preterm (VPT) newborns and early precursor of their cognitive and behavioral toddlerhood outcomes. Results showed

that extensive grey matter volumetric alterations in frontal and limbic regions are observable at 40 weeks term-equivalent age in IUGR VPT individuals, compared to AGA VPT peers. Specifically, findings highlight a medium effect on volumetric reduction in limbic/emotion processing regions (i.e., amygdala, hippocampus, fusiform gyrus, cerebellum), along a with small fronto-striatal, fronto-parietal and frontal sparing. At 22 months, poorer cognitive and behavioral outcomes are identified in IUGR toddlers; however, volumetric alterations do not exert a predictive effect on such outcomes. These findings demonstrated that, beyond the well-known effect of prematurity, also the quality of antenatal experience, compromised by IUGR, is a sensitive and critical factor for VPT neurodevelopment, with strong and long-lasting marks on brain, cognitive, motor and behavioral growth. Our results on grey matter volumes reflect later brain alterations reported for IUGR infants (Bruno et al., 2017; Lodygensky et al., 2008a), thus suggesting a potential stability in frontal and limbic abnormality.

We suggested to interpret such alterations in the light of the antenatal mechanisms of growth restriction, so that the observed regional gray matter patterns at term-equivalent might reflect brain sparing processes characterizing IUGR fetal attempts to preserve brain growth. That is, the frontal volumetric increase we report in the IUGR group might reflect neuroprotective brain sparing processes observed in IUGR pregnancies, focused on delivering most nutrients to the major organs (Garg et al., 2013) and initially prioritizing the higher cognitive functions of the frontal lobes (Cohen et al., 2015). Conversely, emotion processing brain regions, especially amygdala and hippocampus, might result constrained in their volumetric growth from fetal exposure to glucocorticoid levels heightened under conditions of pregnancy stress and/or placental dysfunctions (Lupien et al., 2009; O'Donnell & Meaney, 2016).

3. Socio-cognitive development in Intrauterine Growth Restricted and typical development infants: early interactive patterns and underlying neural correlates

Based on the results of the previous two studies, in Chapter 3 we presented the rationale and methods for a research protocol designed as longitudinal case-control study. This perspective overcame some issues hampering IUGR investigations, such as: retrospective design, concurrent effect of prematurity and uncertain antenatal diagnosis. Here, we proposed the description of infant early neural face processing and infant behavioral responsiveness in social interaction as two interconnected neural and behavioral mechanisms underpinning socio-emotional development and thus involved in later behavioral and socio-cognitive growth. Specifically, we targeted human face processing as a critical experience-expectant and activity-dependent function, crucial for infant's survival and social and cognitive functions (Parker & Nelson, 2005). Indeed, the potential underpinnings of infant responsiveness to social environment involve different neural competences, like emotional and face processing (Taylor-Colls & Pasco Fearon, 2015). Also, the mother-infant interacting exchanges rely on the use of gaze and eye-contact both for instrumental and emotional connection purposes. Research design and methods of this study highlighted the challenging aim to explore multilevel processes of transactional nature characterizing health and at-risk infant development.

4. Interactive behaviors and early neurodevelopmental outcomes in infants with Intrauterine Growth Restriction

Chapter 4 reported on term-born IUGR mother-infant interactive exchanges along the first year of life and their one-year developmental outcomes. Preliminary descriptive results highlighted that decreased levels of infants' responsiveness at nine months and of maternal structuring at 4 months characterized IUGR dyads. No other differences interesting infant's

involvement, maternal sensitivity, intrusiveness or non-hostility were identified. At 12 months, significant differences emerged in cognitive and motor performances, consistently with meta-analytic findings (Chapter 1) and VPT toddlers' outcomes (Chapter 2). Only infant responsiveness at 9 months showed a close to significance negative effect on motor outcome. Previous studies on IUGR highlighted reduced social responsiveness and poor use of environmental stimuli, with decreased behavioral preference for social stimuli and interactive partners (Feldman & Eidelman, 2006; Mello, Gagliardo, & Goncalves, 2014; Padilla et al., 2011). In the present sample, infant's interactive abilities group differences emerge relatively later, at 9 months of age, suggesting that early patterns of interactive abilities are not observably compromised by IUGR. This sort of catch-down in IUGR responsiveness might point out that IUGR biological vulnerability is sculpted through daily interactive learning processes; thus, it expresses its significant effect on infant interactive behaviors along time. Indeed, IUGR infants seem to face more challenges in responsivity later in the 1st year of life, when their biological fragility perhaps made them less able to reach autonomy, regulation and adequate exploration. Regarding IUGR mothers' interactive abilities, a diminished structuring at 4 months might highlight an increased initial difficulty in understanding infant's signals that might result into less attuned and synchronized stimulation.

Overall, both mother and infants' early interactive characteristics showed to be negatively marked by IUGR in different time-points along the first 12 months of life. Therefore, these interactive patterns need to be further investigated to strengthen the transactional view of infants socio-emotional development as emerging from both parental and infants relational characteristics (Leve & Cicchetti, 2016). Also, one of the main values of a longitudinal investigation involving several time-points of observation is that it allows the study of different potential windows of plasticity both for typical and atypical development. This study pointed out that a plasticity window for clinical interventions fostering infant's

social engagement might take place in the very first months of life, before the expression of a behavioral interactive disadvantage.

5. Framing pediatric care into a relational perspective with the Primary Care-Video Intervention Therapy

Chapter 5 presented a promising application of a video-feedback intervention designed for pediatric settings: the innovative Primary Care – Video Intervention Therapy (Facchini et al., 2016). The PC-VIT was applied to a family of a Small for Gestational Age (SGA) infant. The intervention combined a relational perspective and a specific focus on mental health and parenting with the daily pediatric care. Findings for this family, observed through clinical vignettes and the analysis of parental discourse along the intervention, highlighted that initial parental narratives reflect worries about infant's growth and the new parental role. Along sessions, the intervention sustained parental mentalization abilities. Indeed, the use of the video taught parents to recognize infant's communicative skills and progressively identify his self- and emotion regulatory abilities, so that parents became more able to speak about their son competences. These characteristics are fundamental for child development, as they boost a secure parent–child attachment and represent early markers of socio-cognitive development (Eisenberg et al., 2010). Overall, postnatal environment plays a leading role in shaping child development and studies have showed that responsive relationships with sensitive caregivers are critical for healthy socio-emotional growth (Feldman, 2012; Tronick, 2007). Therefore, timely and targeted interventions might have the chance to play antagonistic effects on growth restriction and exploit an enhanced IUGR susceptibility in parent-infant interactions for better outcomes.

DISCUSSION

Embedding IUGR child development into developmental cascades

Comprehensively, this dissertation helped to portrait an hypothetical model for IUGR early development, that we schematically presented in Figure 1. Overall, our findings attested widespread effects of growth restriction interesting brain growth, interactive behaviors and parenting (wide gray arrows), and suggested different intertwined developmental cascades characterizing IUGR development.

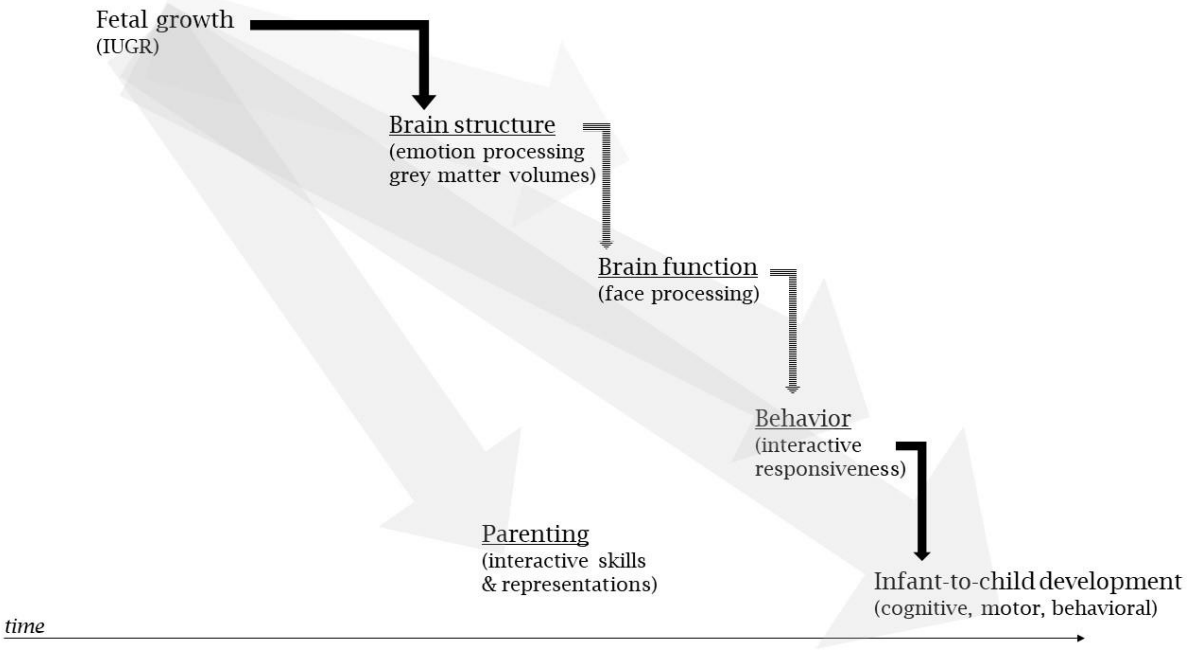


Figure 1. Hypothesized cascade model of IUGR development

Considering potential cascades of risk, this dissertation suggested that the quality of fetal growth, and particularly the adverse experience of IUGR, affects postnatal socio-emotional growth through a set of multilevel effects exposing brain and behavioral development. We postulated that brain growth around the time of birth expresses the continuous exchange between the genetic potential of the fetus and the quality of its antenatal environment. Our results proved that grey matter brain volumes around the time of birth are altered in IUGR very-preterm newborns, in term of a frontal spreading and a constrained

emotion processing structural clusters. Such patterns might tract antenatal protective attempts to preserve cognitive function (Cohen et al., 2015) at the expense of emotional brain circuits. Besides, they might serve as a neural substrate for a cascade of effects beginning under condition of subsequent processes. In this sense, we hypothesized that face processing might be one of the neural functions at the crossroad of these brain-environment extents affected by IUGR. Indeed neural face-processing is anatomically rooted in some of the regional substrates (Frith & Frith, 2003) targeted by IUGR (i.e., Amygdala, Hippocampus and Fusiform Gyrus; Chapter 2). Unfortunately, in this thesis we were not able to provide the corresponding findings allowing to parallel evidence of structural alterations with functional impairment in neural face and social processing. However, beyond infant perception of faces per se, a developing child needs neurocognitive mechanisms for understanding others' behavior (Frith, 2007) and face processing is highly relevant in the context of social exchanges to understand others emotion and thought, to make others understand themselves, and to share emotional states (Adolphs, 1999; Beebe et al., 2010, 2016). At this scope, we targeted infant behavior in early interactive contexts as observable phenotype of such altered neural emotion (and face) processing. Our preliminary results highlighted that at 9 months, infant responsiveness to maternal stimulation in ecological interactions is negatively affected by IUGR. We suggested that this IUGR scarcity in behavioral responsiveness might reflect a limited set of strategies for emotional and behavioral interactive regulation. Such limited competencies might derive from a poorer ability to deal with and respond to social stimuli, rooted in a fragile neural base for face- and emotion- processing resulting from the antenatal brain changes. Despite not leading to firm conclusions, these results also suggest that such IUGR scarcity in interactive strategies for emotional and behavioral regulation might challenge the interaction only at the increase in complexity of environmental (maternal) stimulation but not in very early (4 months) interactive exchanges. Further, such reduced behavioral responsiveness seemed to

potentially exert a negative effect on IUGR neurodevelopment at 12 months of life, at least in a motor domain.

In addition to such described developmental path, IUGR infants appear to be exposed to less-than-optimal maternal structuring during the very early interactions. A proposed nearby cascade characterizing IUGR development might, therefore, interest the quality of parenting experience. Mother and infant share from pregnancy and antenatal life both a genetic and ecological niche. First, maternal health in pregnancy, especially stress and anxiety states, might influence both the fetal growth (Federenko & Wadhwa, 2004) and the postnatal parental practices (De Carli et al., 2019). Besides, parenting might be impacted by the distressing information and medical practices surrounding fetal and perinatal management of IUGR and beyond by the challenging interactions with infant's brain-behavior socio-emotional vulnerability. New mothers undergo dynamic changes that support positive adaptation to parenting (Kim, 2016); such changes are guided by biochemical processes but are likely to be sculpted by child characteristics (Montirosso et al., 2017; Riem et al., 2017). Our preliminary findings drawn impoverished maternal behaviors in interactive exchanges with IUGR infants at 4 months, characterized by frequent, uncoordinated and ineffective interactive attempts. Such results might have caught the initial difficulty of IUGR mothers in understanding infant's needs and signals and perhaps in having realistic expectations on their infant's competencies (Chapter 5). The closer observation provided by the case-study, pointed parental (mother and father) worries about infant's autonomy and exploration abilities, especially during the weening developmental milestone. Such worried parental representations and the non-optimal interactive structuring, as well as infant early behaviors transact and might progressively intensify compromising the quality of daily interactions, and thus of parental representations and practices, and child development.

All these transactional processes characterizing mother-infant development make the system highly receptive to other environmental influences. Treatments can be considered environmental influences (Cicchetti & Gunnar, 2008). A third potential developmental cascade, we suggested in the attempt to constrain IUGR socio-emotional and affective-relational risk, interests early interventions. In a perspective of clinical psychology, parenting is an excellent port-of-entry for early interventions directed to both parental and child development (Bakermans-Kranenburg & van IJzendoorn, 2015; Fukkink, 2008). Such interventions can modify both parents' interactive patterns and the subjective experience of parenting, giving more realistic views of themselves and their child (Leyton et al., 2019). Besides, parents are a primary source of interactive regulation for infants (Sameroff, 2010). Therefore, enhancing parental experience and interactive practices might boost the development of infant's regulatory abilities. In our case-study application, we proposed a video-feedback intervention aimed at holding parental worries about growth vulnerability and enhancing mentalization abilities. Mentalization, as parental ability of making sense of the child behaviors as expressing internal emotional and mental states (Fonagy, 2018), is a powerful predictor of infant-parent attachment security. This parental capacity stimulates child's mentalization, his/her autonomy and self-regulatory abilities (Sharp & Fonagy, 2008). In our application, we observed that the intervention allowed parents to progressively decrease their worry, recognize and talk about their infant's agency and regulation. This enhanced parental ability might be translated into more sensitive and attuned interactive strategies fostering infant affective regulation. Besides, daily learning of more sophisticated regulatory abilities for affect and behaviors might have positive effects in the infant's brain development (Bick, Palmwood, Zajac, Simons, & Dozier, 2019). In this view, rigorous parenting interventions might prime a virtuous escalation from infant interactive- to self-regulation (Sameroff, 2010), with potential widespread effects on parent-child relationship,

child behavior and emotional brain function. Hopefully, such beneficial cascade might redirect the biobehavioral trajectories toward more positive outcomes.

Limitations

This dissertation brings limitations. The specific shortcomings characterizing the singles studies have been discussed within each chapter; some of them will be briefly recalled here to direct future investigations. Specifically, comorbidity with very preterm delivery and retrospective design were the main limitations of Chapter 2. The findings on structural brain development at term-equivalent age should be confirmed or confronted with evidence on term born IUGR samples. Unfortunately, large samples of healthy term-born newborns undergoing MRI scan around the time of birth are difficult to obtain, strongly limiting this encouraged direction. Easier to overcome is the use of retrospective research designs ensuring controlled sampling. Chapter 3 and 4 described a prospective research, with case-control sampling excluding comorbidity with prematurity. However, theses chapters only portrayed a research perspective and the preliminary findings significantly lack power to bring definitive results. Specifically, evidence on IUGR face-processing still need to be tested, while the sample size for behavioral results dramatically prevent from drawing clear conclusions. In this sense, these chapters mainly suggested an intriguing route of study, with preliminary findings pointing in the hypothesized direction.

Across chapters, research designs or sample size limited the possibility to explore transactional processes in term of moderating effects and to properly and systematically account for perinatal and postnatal social influences (i.e., socioeconomic status, marital status). In particular, constantly lacking is a focus on maternal well-being, in terms of anxiety, depression or stress, along pregnancy and first year of child life. Future studies are strongly encouraged to pursue this investigation; the next session will address this issue more in details. Overall, the main limitation of this thesis is the lack of an overall assessment of all the

hypothesized effects, that inhibits the opportunity to provide a comprehensive model of IUGR developmental trajectories and defy a straightforward summary of the underlying mechanisms. Complex multilevel, longitudinal designed studies are needed to properly found our hypotheses. Specifically, some of the proposed processes still need to be proved: for instance, a link between volumetric brain development and altered neural face processing has still to be explored in the context of IUGR. Also, data on the potential association between face processing and infant's behaviors are still to be processed. Last, evidence on IUGR behaviors needs to be confirmed by larger samples, as well as their association with cognitive outcomes. In this sense, the research perspective proposed should be intended as an hypothetical model of IUGR neurodevelopment and the findings provided by this thesis as arising newly formulated questions for further investigations.

Directions for research on IUGR development

Beyond the advances encouraged by the limitations of this thesis, two surrounding research focuses appear extremely relevant in the field of clinical developmental psychology for the study of IUGR development. Moving a *step back:* beyond representing a starting point for a suspected cascade of effects, IUGR is a result of the transactional processes interesting fetal development (Sankaran & Kyle, 2009). Such processes involve fetal, maternal and placental health. Potential mechanisms underpinning IUGR interest the interdependent roles of metabolic alterations due to maternal or placental insufficiency, such as reduced Insulin-like growth factor (Steinman & Mankuta, 2013), maternal well-being and fetal hypothalamic-pituitary-adrenal (HPA) axis development (Huang, 2011; O'Donnell et al., 2009). Specifically, stress, anxiety and depression in pregnancy are major risks to increase transplacental passage of glucocorticoids, which is strongly linked to fetal growth (O'Donnell et al., 2009). Indeed, maternal psychosocial stress exposure in pregnancy has been significantly associated with increased risk of adverse pregnancy and birth outcomes both in

terms of preterm delivery and low birth weight/small-for-gestational age (SGA) birth (Federenko & Wadhwa, 2004; Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999). Besides, maternal anxiety and depression during pregnancy have been also associated with more difficult/reactive offspring temperament (Davis et al., 2007; Erickson, Gartstein, & Dotson, 2017), and maternal cortisol levels in pregnancy has been observed to predict right amygdala volume in childhood (Buss, Davis, et al., 2012). Overall, further studies on maternal stress and mental health in pregnancy are encouraged to explore whether maternal adversities operate to program child brain-behavior through a carefully orchestrated chain of fetal stress-related events resulting in Intrauterine Growth Restriction. This would project the study of IUGR as turning point for an intergenerational transmission of stress reactivity and risk for psychopathology (Bowers & Yehuda, 2016; Plant, Barker, Waters, Pawlby, & Pariante, 2013).

The second research suggestion is to move a *step forward* focusing on the developmental processes characterizing adolescence. Adolescence is another crucial period of developmental plasticity (Zelazo & Carlson, 2012). Research largely documented brain plasticity especially in the communication between emotional regulation and cognitive capacity, with corresponding hierarchical developmental changes in the brain (Somerville, 2016). The social interactive abilities are crucial for adolescence; indeed, adolescent's milestones include negotiating emotional, social, physical and intellectual conflicts progressively without the buffer of a caregiver. Observing the infant fragility in emotion processing and risk for cognitive development, an intriguing research question pertains how such variables transact in those conditions of required cognitive capacity under emotionally arousing states, that particularly house adolescence. Further research is encouraged to parallel the focus of this thesis on brain, behavior and parenting exploring how IUGR biobehavioral

vulnerability in early infancy encounter the demanding tasks and biological changes of adolescence.

Overall, since the discussion of IUGR development in a socio-emotional perspective is lacking, our first attempt was to cautiously explore IUGR vulnerability to negative outcomes. An important remind for scientific research is not to bias the investigation of vulnerability neglecting the focus on resources and resilience factors. Indeed, researches should cover the wide spectrum of factors composing the definition of healthy development (Irwin, Siddiqi, & Hertzman, 2007); in particular, beyond expanding the comprehension of the negative effects of IUGR on cognitive, motor, behavioral, brain and social interaction, research should understand how IUGR impacts the perceived quality of life.

Translational implications for research and clinical practice

In a translational perspective of research, implications for this dissertation pursued widespread "effects". First, our work was intended to inform prediction. Providing key answers of the role of IUGR on child neurodevelopment allows to predict domain specific or rather more general developmental fragilities. In this sense, we observed consistent negative effects on cognition and motor domains in infancy, toddlerhood and across childhood. Also, we suggested high risk for early behavioral development. A step forward would be to detect whether IUGR risk represents a general fragility encompassing cognitive and behavioral domains or the two are domain specific co-occurring difficulties. Strongly tied to this first point is the implication for prevention. The encouraged focus on maternal well-being and stress exposure during pregnancy might serve to prevent fetal growth form adverse intrauterine and perinatal outcomes observed to trigger a postnatal cascade of effects. Third, informing diagnostics was also a hoped objective. In our research, particularly in providing meta-analytic findings, we detailed the description of Intrauterine Growth Restriction, considering the severity of antenatal compromising both in terms of co-occurrence with

prematurity and in term of antenatal vs. at birth diagnosis. Research on fetal development and characteristics of IUGR also underscored the importance of fetal age at IUGR onset, placing at 32 weeks of gestation a possible cut-off distinguishing between Early and Late IUGR phenotypes (Gordijn et al., 2016). Meta-analytic evidence should further detail the potential role of early vs late onset in the developmental trajectories of surviving infants.

Primarily, our findings were aimed at informing and suggesting empirically driven interventions to sustain IUGR socio-emotional development. The attention to specific functions, in terms of both neural and behavioral vulnerability and in specific time windows (the very first months of life) might inform clinical interventions. Also, we suggested the primary care as a first setting to house parenting-related contents, provide an integrated view of child development and implement effective strategies to nurture healthy parent–child relationships. More generally, effective and empirically driven interventions are encouraged to take place in the earliest stages of IUGR infant development, selecting biobehavioral markers of emotion processing as therapeutic targets and exploiting parenting plasticity as port-of-entry to sustain infant development.

Last, this thesis hoped to be meaningful for pediatricians and general health providers to be aware of the developmental risk of IUGR and SGA preterm and term-born individuals, as well as of their biobehavioral vulnerability in socio-emotional processing and of the challenging that parenting in these contexts undergoes. Our findings allowed to reflect upon the importance for pediatric general health providers to provide an integrated view of child development, implementing effective ad-hoc strategies to monitor neurodevelopment, sustaining global cognitive and emotional abilities and nurture healthy parent-child relationships. Along with that, the evidence of IUGR cognitive risk and fragile base for emotion processing opened to fascinating questions for all those contexts where infant and child learning processes are sustained by early regulatory abilities (Immordino-Yang,

Darling-Hammond, & Krone, 2019). Beyond the directions proposed for mother-infant relationship, our hope is also for the educational contexts to bear in mind the atypical trajectory of IUGR individuals, considering their biobehavioral plasticity, and thus the zone for proximal development, as informed by the specific socio-emotional features.

CONCLUSION

This dissertation concludes that multiple mechanisms are needed at different levels of investigation and along several time points to tease out the different outcomes of IUGR infants. Specifically, this work points to the importance of situating the study if IUGR development in an integrated and complex theoretical and methodological framework.

More broadly, the studies evidenced the importance of directing the attention to prenatal epochs of development as critical period founding the grounds for postnatal development. They suggested that antenatal adversities, as IUGR, play a role in founding developmental cascades of effects involving constant transactions between brain, behavior and the environment. Over and above the potential value of understanding IUGR early development, the research perspective and the prospective model proposed by this dissertation might be generalizable to several developmental risks' population deriving from adverse antenatal experiences (i.e., prematurity, congenital heart disease; maternal substance abuse). This would allow to identify differential trajectories starting form specific etiopathological conditions, or rather common mechanisms predisposing to multiple outcomes. From a clinical standpoint, knowing the pre- and perinatal factors and their mechanisms exposing neurodevelopment and behavioral growth would benefit timely interventions manipulating the described mechanisms of plasticity for better outcomes.

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- APPENDIX -

A1.

CHAPTER 1: The effects of Intrauterine Growth Restriction and Small for Gestational Age on cognitive development in preterm and term-born children. A meta-analysis

List of abbreviations

Diagnosis methods

BW = birth weight

EFW = estimated fetal weight

GA = gestational age

ARED = Absent or Reversed End Diastolic Flow

UA = umbilical artery

MCA = middle cerebral artery

PI = pulsatility Index

U/C ratio = umbilical artery pulsatility index (PI)/middle cerebral artery PI ratio

Outcome methods

WISC-III = Wechsler Intelligence Scale for Children – III Edition

KSPD = Kyoto Scale of Psychological Development

BSID-II = Bayley Scale for Infant Development – II Edition

RAKIT = Revised Amsterdam Children's Intelligence Test

GQ = Global Developmental Quotient corrected for age Brunet-Lezine test

CMM = Columbia mental maturity scales

K-ABC = Kaufman Assessment Battery for Children

GMDS = Griffiths Mental Development Scales

DAS II = Differential Abilities Scale

TABLE 1. Study characteristics of preterm (<37 GA) IUGR and SGA children assessed for cognitive outcome

Study	Study characteristics				Subjects				Diagnosis		Outcome assessment	
	Year	Country	Design	Sampling	IUGR/SGA	Control	GA at delivery	BW	Measure	Classification	Measure	Age (yrs)
Morsing	2014	Sweden	prospective	case-control	11	34	26.29	633	ARED + BW	antenatal IUGR	WISC-III FSIQ	6.5
Morsing	2014	Sweden	prospective	case-control	23	34	27.43	679	ARED + BW	antenatal IUGR	WISC-III FSIQ	6.5
Chen	2013	Japan	prospective	cohort	28	38	30.6	1127	EFW <10th centile by Ultrasound + Preeclampsia + BW	antenatal IUGR	BSID -II MDI	2
Chen	2013	Japan	prospective	cohort	15	38	31.3	1030	ARED + BW	antenatal IUGR	BSID -II MDI	2
Leppanen	2010	Finland	prospective	case-control	16	54	29.6	968	IUGR = abnormal UA-PI/MCA-PI ratio	antenatal IUGR	BSID -II MDI	2
Padilla	2011	Spain	prospective	cohort	18	15	32.1	1060	Abnormal Doppler blood flow in UA (PI>2 SD) + EFW + BW	antenatal IUGR	BSID III MDI	1.5
Morsing	2011	Sweden	prospective	case-control	34	34	27.04	642	ARED + BW	antenatal IUGR	WISC-III FSIQ	6.5
Padilla	2010	Spain	prospective	cohort	37	36	30.43	981	Abnormal Doppler blood flow in UA (PI>2 SD) + EFW + BW	antenatal IUGR	BSID-II MDI	1
Roelants-van Rijn	2004	Netherlands	prospective	case-control	14	26	30.1	675	abnormal UA Doppler flow patterns	antenatal IUGR	GMDS DQ	2

Appendix

Study	Study characteristics				Subjects				Diagnosis		Outcome assessment	
	Year	Country	Design	Sampling	IUGR/SGA	Control	GA at delivery	BW	Measure	Classification	Measure	Age (yrs)
Procianoy	2009	Brazil	prospective	cohort	55	41	31.7	1130	placental insufficiency from UA doppler + BW	antenatal IUGR	BSID -II MDI	0.66
Kutschera	2002	Austria	prospective	case-control	16	31	31	990	ARED in UA	antenatal IUGR	K-ABC CMS	4
Kutschera	2002	Austria	prospective	case-control	15	31	33	1190	increased PI in UA. decreased PI in MCA or increased cerbroplacental ratio	antenatal IUGR	K-ABC CMS	4
Wienerroither	2001	Austria	prospective	case-control	23	23	34.1	1258	abdominal circumference < 10^{th} centile + AREDF in UA	antenatal IUGR	K-ABC CMS	6
Scherjon	2000	Netherlands	prospective	case-control	28	45	30.86	1190	hemodynamic redistribution. ie. brain-sparing (raised U/C ratio) or not (normal U/C ratio).	antenatal IUGR	RAKIT	5
Drews-Botsch	2011	USA	prospective	case-control	86	48	32-42	2584	BW <10^{th} centile for GA	birth SGA	DASII (adaptation of BSID)	4.5
Drews-Botsch	2011	USA	prospective	case-control	67	49	32-42	2584	BW <10^{th} centile for GA	birth SGA	DASII (adaptation of BSID)	4.5
Drews-Botsch	2011	USA	prospective	case-control	63	37	32-42	2460	BW <10^{th} centile for GA	birth SGA	DASII (adaptation of BSID)	4.5
Drews-Botsch	2011	USA	prospective	case-control	89	35	32-42	2460	BW <10^{th} centile for GA	birth SGA	DASII (adaptation of BSID)	4.5

Appendix

Study		Study characteristics			Subjects				Diagnosis			Outcome assessment	
	Year	Country	Design	Sampling	IUGR/SGA	Control	GA at delivery	BW	Measure	Classification		Measure	Age (yrs)
Ayoubi	2016	France	retrospective	cohort	49	219	25.2	660.6	BW <10th centile for GA	birth	SGA	Brunet-Lezine GCDQ	2
Lahat	2015	Canada	prospective	cohort	22	44	32.36	847.05	BW <10th centile for GA	birth	SGA	WISC-R	8
Raz	2012	USA	retrospective	cohort	25	118	28.14	1075	BW <10th centile for GA	birth	SGA	WPPSI-R FSIQ	4.5
Filipouski	2013	Brazil	prospective	cohort	56	14	31.8	1209.4	BW <10th centile for GA	birth	SGA	BSID-II Cognitive	2
Tanis	2015	Netherlands	prospective	cohort	42	336	34.5	1696	BW <16th centile for GA	birth	SGA	WISC-III FSIQ	6.9
Gutbrod	2000	Germany	prospective	case-control	115	115	32.4	1232	BW <10th centile for GA	birth	SGA	GMDS	0.4
Batalle	2012	Spain	prospective	cohort	24	32	36.6	-	EFW + BW <10th centile for GA	birth	EFW + BW	BSID-III	1.75
Mikkola	2007	Finland	prospective	case-control	12	14	27.8	-	BW < SD of mean weight for GA	birth		WPPSI-R	5
Class	2011	Netherlands	retrospective	cohort	56	45	28.84	635	BW <10th centile for GA	birth	SGA	GMDS / BSID-III	2
Class	2011	Netherlands	retrospective	cohort	56	45	28.84	635	BW <10th centile for GA	birth	SGA	GMDS-BSID z score	2
Mukhopadhvav	2010	India	prospective	cohort	30	41	<34	<1500	BW <10th centile for GA	birth	SGA	DASII (adaptation of BSID)	1.5
Bickle Graz	2015	Switzerland	prospective	cohort	54	288	28.5	784	BW <10th centile for GA	birth	SGA	K-ABC CMS	5

Appendix

Study	Study characteristics				Subjects				Diagnosis			Outcome assessment	
	Year	Country	Design	Sampling	IUGR/SGA	Control	GA at delivery	BW	Measure	Classification		Measure	Age (yrs)
Tamaru	2011	Japan	retrospective	cohort	19	38	28	882.5	BW <10th centile for GA	birth	SGA	KSPD total DQ	1.5
Leppanen	2014	Sweden	prospective	cohort	59	122	30.86	1090	BW <10th centile for GA	birth	SGA	WPPSI-R FSIQ	5
Geva	2009	Israel	prospective	case-control	20	19	36.66	-	BW <5th centile for GA	birth	SGA	WPPSI	6
Feldman	2006	Israel	prospective	case-control	40	40	33.19	- 1282.05	BW <10th centile for GA	birth	SGA	BSID-II MDI	1
Frisk	2002	Canada	prospective	cohort	25	16	32	1110	BW < SD of mean weight for GA + HC	birth	SGA	WISC-III	8
Nogel	2015	Germany	retrospective	cohort	22	48	30	1024	BW or lenght <10th centile for GA	birth	SGA	BSID-II Mental Scale	2
Frisk	2002	Canada	prospective	cohort	29	16	34.4	1655	BW < SD of mean weight for GA + HC	birth	SGA	WISC-III	8
Frisk	2002	Canada	prospective	cohort	17	16	34.8	1380.3	BW < SD of mean weight for GA + HC	birth	SGA	WISC-III	8
Koivisto	2015	Finland	prospective	cohort	60	61	28.1	782.6	-	birth	SGA	WISC-III FSIQ	11.6

Note. FSIQ = full-scale intelligent quotient; MDI = mental developmental Index; DQ = developmental quotient;

TABLE 2. Study characteristics of term-born (>37 GA) IUGR and SGA children assessed for cognitive outcome

Study	Study characteristics				Subjects				Diagnosis		Outcome assessment	
	Year	Country	Design	Sampling	IUGR/SGA	Control	GA at delivery	BW	Measure	Classification	Measure	Age (yrs)
Bellido-Gonzalez	2017	Spain	retrospective	case- control	32	61	37.29	2175	abnormal MCAPI, cerebrolac.ratio and UAPI	antenatal IUGR	WISC-IV	7
Bellido-Gonzalez	2017	Spain	retrospective	case- control	27	61	37.48	2391	abnormal MCAPI	antenatal IUGR	WISC-IV	7
Leitner	2000	Israel	prospective	case- control	39	41	37.1	1770	late onset verified by Ultrasound or clinically + BW	antenatal IUGR	WPPSI	6.5
Leitner	2007	Israel	prospective	case- control	98	63	37.6	1945	Ultrasound + clinical evaluation	antenatal IUGR	Estimated IQ WISC-R	9.5
Zuk	2003	Israel	prospective	case- control	31	31	37.09	1923	third trimester serial ultrasound	antenatal IUGR	42 items:motor language and cognition	2
Geva	2006	Israel	prospective	cohort	123	63	37	1853	late onset verified by Ultrasound or clinically	antenatal IUGR	WISC	9.3
Mello	2014	Brasil	prospective	cohort	25	43	> 37	-	BW < 10^{th} centile for GA	birth SGA	BSID-II Cognitive scale	0.16
Savchev	2013	Spain	prospective	cohort	112	111	38.8	2416	BW < 10^{th} centile for GA	birth SGA	BSID-II	2
Batalle	2013	Spain	prospective	case- control	41	22	38.1	-	Estimated fetal weight (EFW) + BW < 10^{th} centile for GA	birth SGA	BSID-III	1.75

Appendix

Study	Study characteristics				Subjects				Diagnosis			Outcome assessment	
	Year	Country	Design	Sampling	IUGR/SGA	Control	GA at delivery	BW	Measure	Classification		Measure	Age (yrs)
Nomura	2009	USA	prospective	cohort	63	1372	> 33	-	BW < 10th centile for GA	birth	SGA	WISC full scale	7
Leitner	2000	Israel	prospective	case- control	25	41	38.2	2004	asymmetrical growth restriction + BW < 5th centile for GA	birth	SGA	WPPSI	6.5
Sommerfelt	2000	Norway	prospective	cohort	338	335	> 37		BW < 15th centile for GA	birth	SGA	WPPSI-R	5
Gagliardo	2006	Brasil	prospective	case- control	14	19	> 37	2370	BW < 10th centile for GA	birth	SGA	BSID-II Cognitive scale	0.16
Pylipow.	2009	USA	retrospective	cohort	503	30412	> 37	< 2211	BW < 5th centile for GA	birth	SGA	WISC	7
Peng	2005	China	prospective	case- control	68	52	39.13	2280	BW < 10th centile for GA	birth	SGA	WPPSI	5
Rao	2002	Norwway	prospective	cohort	139	299	39.5	2878	BW < 15th centile for GA	birth	SGA	WPPSI-R	5
Rao	2002	Norwway	prospective	cohort	81	299	39.6	2866	BW < 15th centile for GA	birth	SGA	WPPSI-R	5
Hollo	2002	Finland	retrospective	cohort	96	97	38.8	2452	BW < 2.5th centile for GA	birth	SGA	WISC-R	10

Note. FSIQ = full-scale intelligent quotient; MDI = mental developmental Index; DQ = developmental quotient;

TABLE 3. Study characteristics of preterm IUGR and SGA children assessed for Mental Delay

Study	Study characteristics				Subjects				Diagnosis		Outcome assessment	
	Year	Country	Design	Sampling	IUGR/SGA	Control	GA at delivery	BW	Measure	Classification	Measure	Age (yrs)
Morsing	2014	Sweden	prospective	case-control	11	34	26.29	633	ARED + BW	Antenatal IUGR	**WISC-III FSIQ < 70**	6.5
Morsing	2014	Sweden	prospective	case-control	23	34	27.43	679	ARED + BW	Antenatal IUGR	**WISC-III FSIQ < 70**	6.5
Tamaru	2011	Japan	retrospective	cohort	32	118	30.4	882.5	AREDFV in UA	Antenatal IUGR	KSPD DQ < 85	1.5
Tamaru	2011	Japan	retrospective	cohort	12	118	30.4	882.5	Ri of MCA/UA<1	Antenatal IUGR	KSPD DQ < 85	1.5
Morsing et al	2011	Sweden	prospective	case-control	34	34	27.04	642	ARED + BW	Antenatal IUGR	**WISC-III FSIQ < 70**	6.5
Padilla	2010	Spain	prospective	case-control	37	36	30.43	981	Abnormal Doppler blood flow in UA (PI>2 SD) + EFW + BW	Antenatal IUGR	BSID-II MDI < 85	1
Spinillo	2006	Italy	retrospective	cohort	197	287	< 30	< 1200	abdominal circumference < 10^{th} centile of growth curve on 2 consecutive ultrasound	Antenatal IUGR	BSID -II MDI < 85	1
Scherjon	2000	Netherlands	prospective	case-control	28	45	30.86	1190	signs of hemodynamic redistribution, ie. brain-sparing (raised U/C ratio) or not (normal U/C ratio).	Antenatal IUGR	RAKIT < 85	5

Appendix

Study	Study characteristics				Subjects				Diagnosis			Outcome assessment	
	Year	Country	Design	Sampling	IUGR/SGA	Control	GA at delivery	BW	Measure	Classification		Measure	Age (yrs)
Ayoubi	2016	France	retrospective	cohort	49	219	25.2	660.6	BW < 10th centile for GA	birth	SGA	GC DQ < 85	2
Koivisto	2015	Finland	prospective	cohort	60	61	28.1	782.6	-	birth	SGA	WISC-III FSIQ < 85	11.6
Leviton	2013	USA	retrospective	cohort	116	689	23-27	< 750	BW < 10th centile for GA	birth	SGA	**BSID-II MDI < 70**	2
Pinello	2013	Italy	prospective	case-control	17	34	32	-	BW < 10th centile for GA	birth	SGA	BSID-II < 85	1
Tamaru	2011	Japan	retrospective	cohort	8	118	30.4	882.5	BW < 10th centile for GA	birth	SGA	KSPD DQ < 85	1.5
Tanis	2015	Netherlands	prospective	cohort	42	336	34.5	1696	BW <= -1 SD for GA	birth	SGA	WISC-III FSIQ < 85	6.9
De Jesus	2013	USA	retrospective	cohort	150	1342	25	524	BW < 10th centile for GA	birth	SGA	BSID-III cogn. < 80	1.7
De Jesus	2013	USA	retrospective	cohort	150	1342	25	524	BW < 10th centile for GA	birth	SGA	**BSID-III cogn. < 70**	1.7
Gutbrod	2000	Germany	prospective	case-control	115	115	32.4	1232	BW < 10th centile for GA	birth	SGA	CMM < 1SD	4.6
Kiechl-Kohlendorfer	2009	Austria	retrospective	cohort	15	81	27.5	1073	BW < 10th centile for GA	birth	SGA	BSID-II MDI & PDI < 85	1
Kiechl-Kohlendorfer	2009	Austria	retrospective	cohort	12	97	30.5	1524	BW < 10th centile for GA	birth	SGA	BSID-II MDI & PDI < 85	1
Charkaluk	2012	France	prospective	cohort	155	883	30.02	940	BW < 10th centile for GA	birth	SGA	K-ABC MPC < 85	5
Steinish	2012	USA	prospective	case-control	106	910	23-27	< 750	BW < 10th centile for GA	birth	SGA	**BSID-II MDI < 70**	2

Appendix

Study	Study characteristics				Subjects				Diagnosis			Outcome assessment	
	Year	Country	Design	Sampling	IUGR/SGA	Control	GA at delivery	BW	Measure	Classification		Measure	Age (yrs)
Beaino	2011	France	prospective	cohort	133	1364	22-32	-	BW < 10th centile for GA	birth	SGA	K-ABC MPC < 85	5
Guellec	2011	France	prospective	case-control	16	358	24-28	-	BW < 10th centile for GA	birth	SGA	K-ABC MPC < 85	5
Guellec	2011	France	prospective	case-control	106	1055	29-32	-	BW < 10th centile for GA	birth	SGA	K-ABC MPC < 85	5
Class	2011	Netherlands	retrospective	cohort	21	80	31	649	BW < 2SD for GA	birth	SGA	RAKIT / WPPSI /SON-r < 1 z score	5.5
Claas	2011	Netherlands	retrospective	cohort	56	45	28.84	635	BW < 10th centile for GA age	birth	SGA	GMDS-BSID < 1 z score	2
Guellec	2016	France	prospective	case-control	65	476	29.9	1027.6	BW < 2SD for GA	birth	SGA	K-ABC MPC < 85	5
Guellec	2016	France	prospective	case-control	175	187	30.7	1059.4	BW < 2SD for GA	birth	SGA	K-ABC MPC < 85	5
Fernandez-Carrocera	2003	Mexico	prospective	case-control	77	77	36	1590	BW <10th centile for GA + Ponderal Index	birth	SGA	BSID MDI < 84	1
Orcesi	2012	Italy	prospective	cohort	49	107	< 31	< 1325	-	birth	SGA	GMDS < 75	2

Note. FSIQ = full-scale intelligent quotient; MDI = mental developmental Index; DQ = developmental quotient; **Bold studies** included in moderation and subgroups analyses

A2.

CHAPTER 2: Intrauterine Growth Restriction in very preterm infants affects grey matter volumes and subsequent cognitive and behavioral outcomes

Table 1. Eigenvalues and Standardized Factors Loading

		TC	EP	FS	FPT	F	O	FP
Eigenvalues		10.08	8.58	6.78	6.68	6.39	6.20	5.29
Explained variance (%)		11	9	7	7	7	7	6
Factor Loadings (> .40)								
Superior frontal gyrus	L	-0.73						
Superior frontal gyrus	R	-0.69						
Middle frontal gyrus	L	-0.62						
Middle frontal gyrus	R	-0.55						
Supplementary Motor Area	L	-0.49						
Supplementary Motor Area	R	-0.50						
Superior frontal gyrus, medial	L	-0.72						
Superior frontal gyrus, medial	R	-0.7						
Median cingulate	L	0.57						
Median cingulate	R	0.47						
Posterior cingulate	L	0.58			0.49			
Posterior cingulate	R	0.53			0.45			
Heschl gyrus	L	0.42			0.45			
Heschl gyrus	R	0.53						
Thalamus	R	0.63						
Thalamus	L	0.63						
Pallidum	R	0.56						
Pallidum	L	0.48		0.44				
Hippocampus	L	0.53	0.56					
Hippocampus	R	0.52	0.53					
Amygdala	L	0.51	0.42					
Amygdala	R	0.51	0.43	0.44				
Para Hippocampal gyrus	L		0.58					

Para Hippocampal gyrus	R	0.52				
Fusiform gyrus	L	0.71				
Fusiform gyrus	R	0.76				
Inferior temporal gyrus	L	0.58		0.41		
Inferior temporal gyrus	R	0.56				
Cerebellum	L	0.60				
Cerebellum	R	0.58				
Inferior frontal gyrus, opercular	R		0.62			
Inferior frontal gyrus, triangular	R		0.47			
Inferior frontal gyrus, orbital	R		0.44			
Rolandic Operculum	R		0.53	0.48		
Olfactory cortex	L		0.56			
Olfactory cortex	R		0.49			
Insula	L		0.58			
Insula	R		0.73			
Superior parietal gyrus	L		-0.46			0.41
Caudate nucleus	L		0.41			
Putamen	L		0.41			
Putamen	R		0.48			
Temporal pole: superior temporal gyrus	L		0.45			
Temporal pole: superior temporal gyrus	R		0.63			
Inferior frontal gyrus, orbital	L			0.49		-0.49
Rolandic Operculum	L			0.77		
Postcentral gyrus	L			0.64		
Inferior parietal gyrus	L			0.57		
Supramarginal gyrus	L			0.71		
Supramarginal gyrus	R			0.43		0.47
Angular gyrus	L			0.55		
Superior temporal gyrus	L			0.8		
Superior temporal gyrus	R		0.46	0.52		

Middle temporal gyrus	L			0.57		
Superior frontal gyrus, orbital	L				0.81	
Superior frontal gyrus, orbital	R				0.76	
Middle frontal gyrus, orbital	L				0.63	
Middle frontal gyrus, orbital	R				0.64	
Superior frontal gyrus, medial orbital	L				0.82	
Superior frontal gyrus, medial orbital	R				0.79	
Rectus gyrus	L				0.73	
Rectus gyrus	R				0.71	
Anterior cingulate	L				0.66	
Anterior cingulate	R				0.56	
Lingual gyrus	L	0.48			0.51	
Lingual gyrus	R	0.45			0.55	
Calcarine fissure	L				0.71	
Calcarine fissure	R				0.68	
Cuneus	L				0.81	
Cuneus	R				0.8	
Superior occipital gyrus	L				0.67	
Superior occipital gyrus	R				0.66	
Medial occipital gyrus	L				0.55	
Medial occipital gyrus	R				0.68	
Inferior occipital gyrus	L				0.46	
Inferior occipital gyrus	R				0.55	
Inferior frontal gyrus, triangular	L					-0.41
Postcentral gyrus	R					0.66
Superior parietal gyrus	R					0.67
Superior parietal gyrus	R					0.61
Angular gyrus	R					0.47
Precuneus	L					0.57
Precuneus	R					0.58

Paracentral lobule	L	0.44
Paracentral lobule	R	0.52

Note. TC = Thalamo-cortical component; EP = Emotion processing component; FS =Fronto-Stiatal component; FPT = Fronto-Parietal-Temporal component; F =Frontal component; O = Occipital component; FP = Fronto-Parietal component

Table 2. Jacobian determinants for IUGR and AGA VPT new-borns

Anatomical region		IUGR VPT (*n* = 49)	AGA VPT (*n* = 265)	*p*
Precentral gyrus	L	1.051 ± 0.115	1.009 ± 0.105	.034
Precentral gyrus	R	1.046 ± 0.084	1.009 ± 0.087	.032
Superior frontal gyrus	L	1.047 ± 0.114	1.022 ± 0.112	ns
Superior frontal gyrus	R	1.120 ± 0.135	1.069 ± 0.122	ns
Superior frontal gyrus, orbital	L	0.912 ± 0.083	0.931 ± 0.085	ns
Superior frontal gyrus, orbital	R	0.910 ± 0.082	0.945 ± 0.082	.017
Middle frontal gyrus	L	1.028 ± 0.082	1.013 ± 0.102	ns
Middle frontal gyrus	R	1.009 ± 0.089	1.001 ± 0.094	ns
Middle frontal gyrus, orbital	L	0.959 ± 0.100	0.913 ± 0.112	.015
Middle frontal gyrus, orbital	R	0.944 ± 0.100	0.918 ± 0.105	ns
Inferior frontal gyrus, opercular	L	1.005 ± 0.158	1.044 ± 0.142	ns
Inferior frontal gyrus, opercular	R	0.973 ± 0.082	1.000 ± 0.105	ns
Inferior frontal gyrus, triangular	L	0.969 ± 0.094	0.997 ± 0.115	ns
Inferior frontal gyrus, triangular	R	0.997 ± 0.096	1.005 ± 0.097	ns
Inferior frontal gyrus, orbital	L	1.032 ± 0.085	1.014 ± 0.094	ns
Inferior frontal gyrus, orbital	R	1.012 ± 0.080	0.994 ± 0.086	ns
Rolandic operculum	L	0.897 ± 0.126	0.950 ± 0.096	.010
Rolandic operculum	R	0.918 ± 0.096	0.967 ± 0.093	**.002**
Supplementary motor area	L	1.221 ± 0.227	1.176 ± 0.175	ns
Supplementary motor area	R	1.318 ± 0.283	1.242 ± 0.226	ns
Olfactory cortex	L	0.951 ± 0.073	0.982 ± 0.083	ns
Olfactory cortex	R	0.950 ± 0.077	0.984 ± 0.085	.014
Superior frontal gyrus, medial	L	1.120 ± 0.190	1.106 ± 0.198	ns
Superior frontal gyrus, medial	R	1.182 ± 0.262	1.170 ± 0.272	ns
Superior frontal gyrus, medial orbital	L	0.890 ± 0.100	0.930 ± 0.111	ns
Superior frontal gyrus, medial orbital	R	0.879 ± 0.103	0.920 ± 0.107	.050
Gyrus rectus	L	0.931 ± 0.094	0.977 ± 0.088	.006
Gyrus rectus	R	0.912 ± 0.099	0.971 ± 0.090	**<.001**
Insula	L	0.930 ± 0.099	0.967 ± 0.085	.051
Insula	R	0.931 ± 0.103	0.954 ± 0.086	ns
Anterior cingulate	L	0.904 ± 0.115	0.939 ± 0.124	ns
Anterior cingulate	R	0.967 ± 0.095	0.979 ± 0.106	ns
Median cingulate	L	0.884 ± 0.105	0.911 ± 0.110	ns
Median cingulate	R	0.933 ± 0.090	0.948 ± 0.106	ns
Posterior cingulate	L	0.999 ± 0.155	0.977 ± 0.141	ns
Posterior cingulate	R	1.002 ± 0.142	0.993 ± 0.143	ns
Hippocampus	L	1.020 ± 0.110	0.967 ± 0.096	**.002**
Hippocampus	R	1.020 ± 0.117	0.958 ± 0.099	**<.001**
ParaHippocampal gyrus	L	1.010 ± 0.094	0.974 ± 0.104	ns
ParaHippocampal gyrus	R	1.028 ± 0.101	0.991 ± 0.100	ns
Amygdala	L	1.002 ± 0.125	0.971 ± 0.095	ns
Amygdala	R	1.012 ± 0.119	0.977 ± 0.087	.032
Calcarine fissure	L	0.913 ± 0.129	0.930 ± 0.130	ns
Calcarine fissure	R	0.907 ± 0.145	0.918 ± 0.132	ns
Cuneus	L	0.953 ± 0.161	0.958 ± 0.137	ns

Cuneus	R	0.957 ± 0.155	0.968 ± 0.131	ns
Lingual gyrus	L	0.987 ± 0.116	0.957 ± 0.088	.028
Lingual gyrus	R	1.013 ± 0.133	0.978 ± 0.097	.018
Superior occipital gyrus	L	0.940 ± 0.118	0.952 ± 0.118	ns
Superior occipital gyrus	R	0.950 ± 0.129	0.975 ± 0.118	ns
Middle occipital gyrus	L	0.884 ± 0.104	0.889 ± 0.099	ns
Middle occipital gyrus	R	0.892 ± 0.109	0.906 ± 0.093	ns
Inferior occipital gyrus	L	0.923 ± 0.112	0.909 ± 0.092	ns
Inferior occipital gyrus	R	0.907 ± 0.131	0.920 ± 0.095	ns
Fusiform gyrus	L	0.965 ± 0.097	0.929 ± 0.082	.009
Fusiform gyrus	R	0.980 ± 0.121	0.938 ± 0.072	**.001**
Postcentral gyrus	L	0.990 ± 0.126	0.994 ± 0.103	ns
Postcentral gyrus	R	0.998 ± 0.095	0.985 ± 0.083	ns
Superior parietal gyrus	L	1.020 ± 0.145	1.047 ± 0.168	ns
Superior parietal gyrus	R	1.106 ± 0.135	1.093 ± 0.161	ns
Inferior parietal gyrus	L	0.963 ± 0.157	0.979 ± 0.128	ns
Inferior parietal gyrus	R	0.950 ± 0.104	0.949 ± 0.116	ns
Supramarginal gyrus	L	0.954 ± 0.206	0.990 ± 0.192	ns
Supramarginal gyrus	R	0.962 ± 0.117	1.014 ± 0.111	.002
Angular gyrus	L	0.953 ± 0.160	0.960 ± 0.152	ns
Angular gyrus	R	0.963 ± 0.103	0.962 ± 0.097	ns
Precuneus	L	1.020 ± 0.108	1.019 ± 0.107	ns
Precuneus	R	1.036 ± 0.140	1.033 ± 0.111	ns
Paracentral lobule	L	1.151 ± 0.263	1.080 ± 0.195	ns
Paracentral lobule	R	1.211 ± 0.319	1.130 ± 0.235	ns
Caudate nucleus	L	0.946 ± 0.071	0.972 ± 0.088	ns
Caudate nucleus	R	0.956 ± 0.076	0.967 ± 0.081	ns
Putamen	L	0.910 ± 0.134	0.930 ± 0.115	ns
Putamen	R	0.903 ± 0.144	0.912 ± 0.107	ns
Heschl gyrus	L	0.865 ± 0.118	0.907 ± 0.104	ns
Heschl gyrus	R	0.889 ± 0.092	0.917 ± 0.096	ns
Superior temporal gyrus	L	0.911 ± 0.146	0.944 ± 0.118	ns
Superior temporal gyrus	R	0.942 ± 0.085	0.977 ± 0.081	.028
Temporal pole: superior temporal gyrus	L	1.067 ± 0.145	1.058 ± 0.157	ns
Temporal pole: superior temporal gyrus	R	1.111 ± 0.123	1.099 ± 0.163	ns
Middle temporal gyrus	L	0.889 ± 0.121	0.889 ± 0.108	ns
Middle temporal gyrus	R	0.928 ± 0.083	0.93 ± 0.072	ns
Temporal pole: middle temporal gyrus	L	1.059 ± 0.141	1.077 ± 0.189	ns
Temporal pole: middle temporal gyrus	R	1.026 ± 0.124	1.049 ± 0.151	ns
Inferior temporal gyrus	L	0.949 ± 0.106	0.942 ± 0.089	ns
Inferior temporal gyrus	R	0.962 ± 0.096	0.953 ± 0.073	ns
Cerebellum	L	1.020 ± 0.125	0.980 ± 0.101	.019
Cerebellum	R	1.027 ± 0.133	0.977 ± 0.099	.008
Thalamus	L	1.007 ± 0.074	0.958 ± 0.080	**<.001**

Thalamus	R	1.015 ± 0.078	0.969 ± 0.082	**<.001**
Pallidum	L	0.882 ± 0.107	0.889 ± 0.094	ns
Pallidum	R	0.882 ± 0.095	0.899 ± 0.093	ns

Data are given as mean ± SD
Note: p-values adjusted for FDR (Benjamini & Hochberg, 1995); bold p-values are adjusted with Bonferroni correction

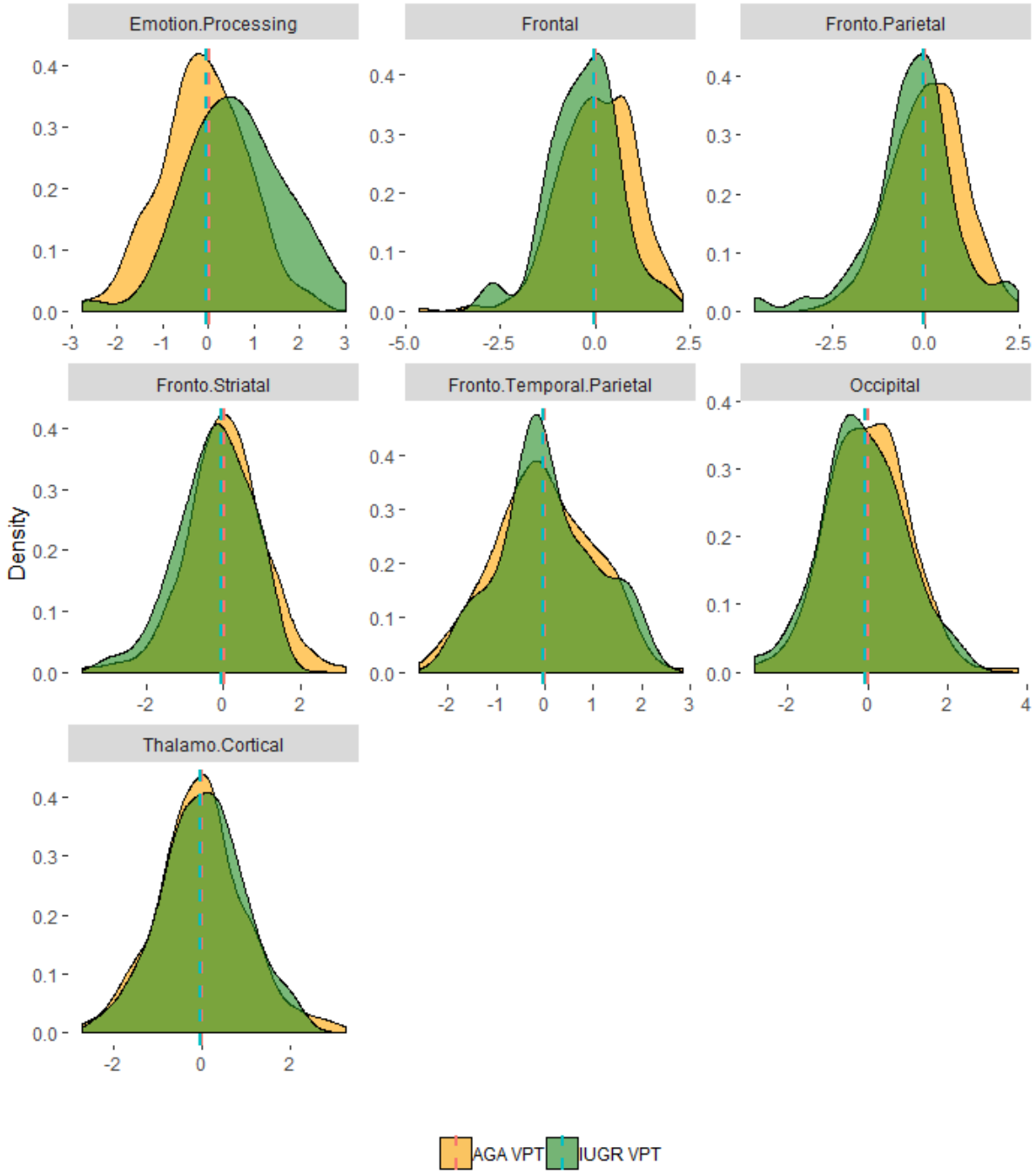

Figure 1S. PCA factor scores mean and distribution in the IUGR and AGA VTP new-borns

A3.

CHAPTER 3: Socio-emotional and cognitive development in Intrauterine Growth Restricted and typical development infants: early interactive patterns and underlying neural correlates

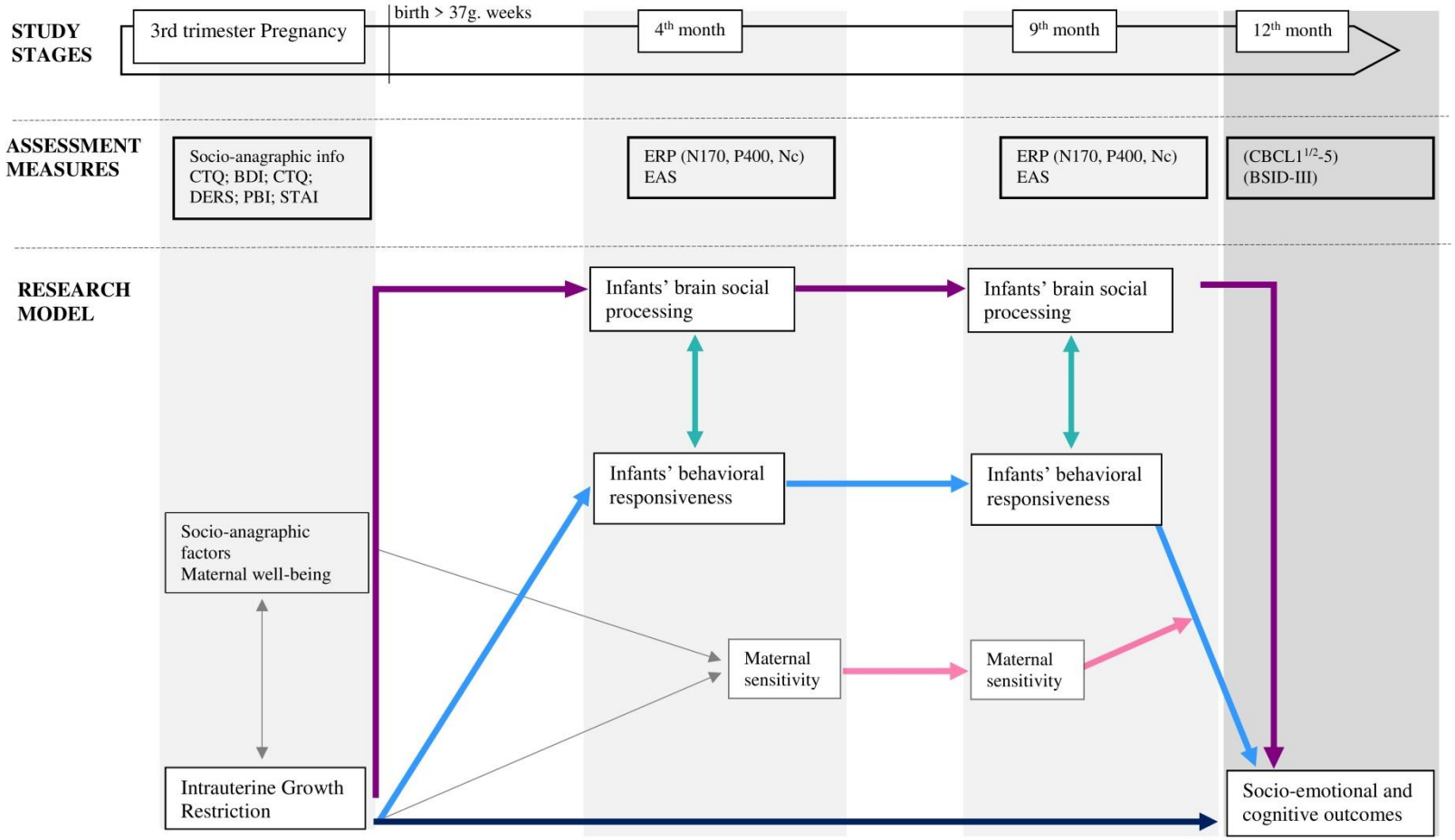

Figure 1. Research design and methods

Note: PBI = Parental Bonding Instrument (Parker, 1989); CTQ = Childhood Trauma Questionnaire (Bernstein et al., 2003); BDI = Beck Depression Inventory-II (Beck et al., 1996); STAI = State Trait Anxiety Inventory (Spielberger, 1983); DERS = Difficulties in Emotion Regulation (Gratz and Roemer, 2004); ERP = Event-related potentials, EAS = Emotional Availability Scales (Biringen, 2008); CBCL1 1/2-5 = Child Behavior Checklist ½ - 5 (Achenbach and Rescorla, 2000); BSID-III = Bayley Scales for Infant and Toddler Development – Third Version (Bayley, 2005).

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"Mi affascina il desiderio di consegnare tutto,
insieme alla sua fragranza,
a *poche necessarie* parole"

[Borges J.L., (2012)
Il linguaggio dell'intimità]

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