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Final dissertation:

The impact of prematurity on visual attention: how Gestational Age influences disengagement in toddlerhood.

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ABSTRACT

Preterm birth, an early birth before the pregnancy is completed, is a very common condition that affect almost the 10 % of all live births. Together with the burden that this condition brings to families and health systems, it significantly impacts the neurodevelopment, leading to an increased risk for long-term difficulties in cognition and behavior. Prematurity represents a biological vulnerability for the development of neural and cognitive system and research should focus on finding early markers that could predict some of the adverse consequences associated with prematurity. That is why in the present work we investigated attentional capacities, which represent a good early marker of atypical neurodevelopment. With my final dissertation I intend to empirically support that *gestational age* at birth is an early key predictor of differences in attentional performance observed later along development. To pursue this aim, the study that we conducted and that I will here report explored the impact of gestational age on visual attention, in particular on orienting capacities, in a sample of late preterm and full-term toddlers. We administered a Gap-overlap task to a group of 35 toddlers at 16 months born between the 34 and 41 weeks of gestation. Their performance was measured in terms of rapidity to orient attention to the target and number of failures to disengage from the center of the screen; then we analyzed how gestational age, taken as a continuous variable, could impact on attentional task performance. What we found was that orienting capacities varied depending on gestational age; specifically, the results associated lower gestational ages with less rapidity to orient visual attention and worst endogenous control of attention. Our findings supported the need to further investigate early attentional development also in the population of late prematurity, because these early difficulties could have a detrimental impact on later cognitive and behavioral development.

1

PRETERM BIRTH: WHEN GESTATION ENDS TOO SOON

1.1 Preterm Birth: an overview

As the World Health Organization (WHO) defines it, preterm birth is a condition that comprehends all the live births that happen before 37 completed weeks of gestation (WHO, 2012). According to the global report of WHO, "*Born too soon*", preterm birth constitutes roughly the 10% of all live births worldwide, even if this percentage varies depending on the geographic area, as it can be seen in Figure 1 (WHO, 2012). In Europe, the incidence of preterm births is about 5 to 9 %, while in some regions of Africa and Asia it can be over the 15% (Blencowe, Cousens, Oestergaard, Chou, Moller, Narwal, ... & Lawn, 2012; WHO, 2012); anyway, it surely represents a global spread and impacting phenomenon.

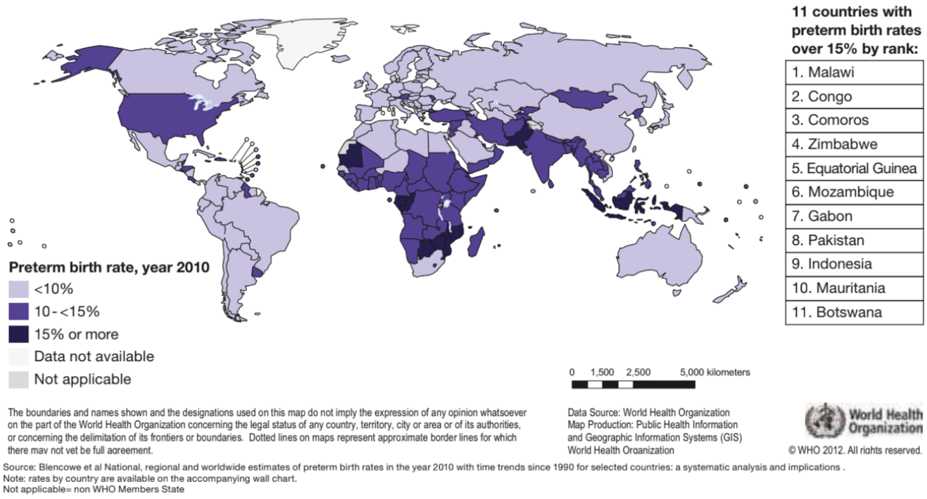

Figure 1. Geographic distribution of preterm births

(WHO, 2012, p. 3)

Delivering birth too soon results in giving life to premature infants, namely, neonates that begin their life outside the uterus in a moment in which their physical and neural maturation is not completed; the typical fetal growth is interrupted, and the newborn are suddenly forced to adapt to environmental stimulations that they are not ready to receive. The environment that the infant finds outside the uterus is over-stimulating, because of, for example, the greater amount of light and noises to which the baby is exposed, but also for the invasive medical procedure that could be implemented. At the same time, the external world is under-stimulating for the baby, since it is missing the heat of mother's body, the constant contact with mother's voice and the freeness to move provided in the uterus by the amniotic liquid (Guarini & Sansavini, 2019). The early interruption of gestation and the atypical environmental stimulation that the newborn have to face in such a sensitive period of their lives, produce a distinctive developmental trajectory of the neural system and of the whole organism (Guarini & Sansavini, 2019), suggesting that prematurity represents a risk for atypical developmental outcomes. For these reasons, preterm birth is considered an issue of public interest and it has been as well addressed in the research field to understand its consequences, its etiology and the possible interventions aimed to prevent and reduce its impact.
There are several reasons for which prematurity must be considered a public health issue; first, preterm birth is associated with increased risk of mortality (see Fig. 2), indeed it is the major direct cause of neonatal mortality and the second cause of deaths before 5 years of age (WHO, 2012). In addition, preterm birth can lead to death in an indirect way, putting the infant at a bigger risk for mortal diseases, such as infections.

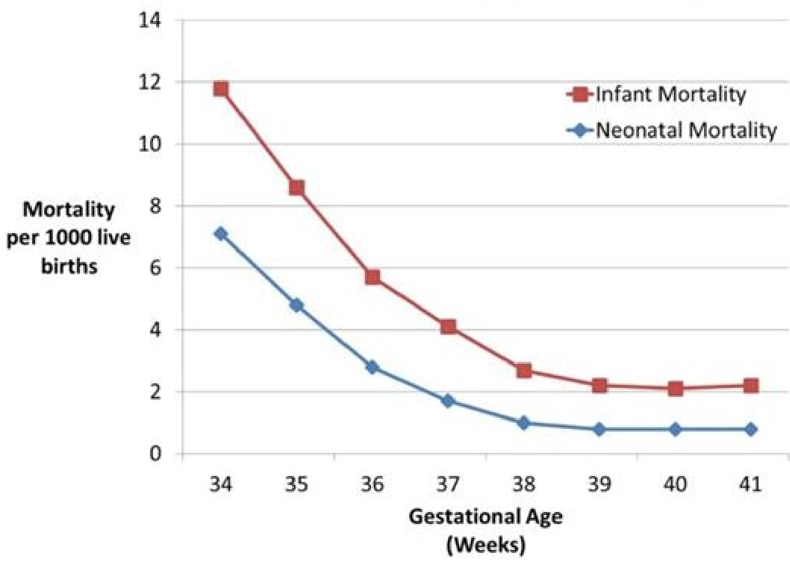

Figure 2. Neonatal and infant mortality by Gestational Age

(Steward et al., 2019, p. 2)

Secondly, preterm birth increases the risk for neonatal morbidity; depending on how soon the delivery happens, that is, depending on the *Gestational Age* of the baby, the premature newborn could suffer short-term complications, such as respiratory and cardio-vascular problems, which could require a period of hospitalization and/or intervention in the Neonatal Intensive Care Units (Guarini & Sansavini, 2019).

With the progress of technology and neonatal care techniques, nowadays it is always more common that premature babies can survive (Chung, Chou, & Brown, 2020). That said, preterm birth remains a major problem because its effects can impact physical, cognitive, and mental health during the whole lifespan. Long-term consequences of preterm birth, especially, make it an issue of public interest since they are not only impacting the child, but they are also likely to stress and burden families, society, and the healthcare system (WHO, 2012).

Given that preterm birth represents a major health issue, it is important to investigate which are the risk factors that increase the possibilities of an early interruption of gestation. The preterm delivery can happen in a spontaneous way, with something causing the uterus to start active contractions before the due time (WHO, 2012); there is not a unique cause for spontaneous preterm delivery but, generally, it is an interplay of genetic predisposition, epigenetic processes, and environmental factors (WHO, 2012). Anyway, the cause of spontaneous preterm births remains uncertain in more than half of the cases.

A first set of threats for spontaneous preterm delivery stands in the health of mothers, like the presence of pre-existent maternal medical conditions, such as diabetes, hypertension, or thyroid diseases. The age of the mother represents another factor that can determine anticipate delivery, in fact the pregnancies for adolescent and advanced-aged mothers are more likely to end up with spontaneous anticipate delivery; the same can be said for multiple pregnancies (i.e., twins or triplets) and short inter-pregnancies interval. Even issues related to maternal lifestyle can increase the risk for preterm birth: the presence of stress and mental health problems, smoking, using drugs, the excessive physical activity and alcohol consumption.

An anticipate delivery can also be provider-induced, namely with a cesarean birth; this especially happens in developed countries, where cesarean section is a common procedure. When the mother's health is at risk or when there are fetal conditions that requires it, doctors can decide for an anticipated risk. There are still many provider-induced preterm birth that happens even without a medical need, for examples due to errors in Gestational Age assessment (WHO, 2012). WHO recommends not to plan cesarean birth before the 39 weeks of gestation, unless medically indicated, because, as it will be later argued, even births between 37 and 39 weeks can show suboptimal outcomes. So far prematurity has been addressed as categorical (i.e., term vs preterm), unitarian and homogenic condition, but it is fundamental to state that all the risks, consequences and wellbeing of preterm children should be described differentiating for the severity of prematurity. In the past it was common procedure to use the weight of the baby at birth (birthweight) to classify for gravity; in the last decades, the practice has shifted to the measurement of *Gestational Age* (GA), which has been proven to be a better predictor of mortality and long-term consequences (WHO, 2012). GA is generally indicated in weeks, and it represents the time between the moment of conception and the birth of the baby. There are different methods used to assess GA: one is based on the date of the last menstrual period (LMP), and it calculates the days of gestation starting from the expected ovulation. This method has low accuracy because it is not sure if the conception happened in the day of ovulation and even if that was true, the length of menstrual cycle varies a lot between women. The most precise method is early ultrasound assessment (Steward, Barfield, Cummings, Adams-Chapman, Aucott, Goldsmith, ..., & Puopolo, 2019), which is taken in the first trimester of pregnancy and enables accurate fetal measurement. Nowadays a very used method is the "best obstetric estimate", which combine the ultrasonography and the LMP to estimate GA. The accurate assessment of GA is crucial in the definition of term birth, and errors in the calculation of GA can have a substantial impact leading to a misprediction of the expected date for delivery.

In the clinical practice and in the research field, GA has been used to classify preterm births into different subcategories, in order to have shared terminology and criteria. The report "*Born too soon*" (WHO,2012) talks about three subgroups of prematurity, which are the following: Extremely Preterm (EPT - less than 28 weeks of gestation); Very Preterm (VPT - between 28 and 31 weeks of gestation); Moderate-Late Preterm (MLPT - between 32 and 37 weeks of gestation). However, there is still disagree in literature about criteria and terminology, and it seems necessaire to update classifications based on new findings. More recent categorizations, as the one embraced by Steward et al. (2019) and by Karnati, Kollikonda and Abu-Shaweesh (2019), give more detailed definition of subcategories, as it can be seen in Table 1.

The first intention of this recent categorization is to provide updated and shared criteria, since in literature it is easy to find disagreement between one study and another. Secondly, these definitions differentiate also within the group of term birth, in order to implement new findings that maternal and neonatal outcomes can vary across the 5 weeks commonly defined as term (37-41 weeks). (Steward et al., 2019)

Preterm	Extreme preterm (EPT)	<28 weeks
	Very Preterm (VPT)	$28^{0/7}$- $31^{6/7}$
	Moderate Preterm (MPT)	$32^{0/7}$ - $33^{6/7}$
	Late Preterm (LPT)	$34^{0/7}$- $36^{6/7}$
Term	Early Term (ET)	$37^{0/7}$ - $38^{6/7}$
	Full Term (FT)	$39^{0/7}$ - $40^{6/7}$
	Late Term	$40^{6/7}$ - $41^{6/7}$
Post Term		> $42^{0/7}$ weeks

Table 1. Classification of preterm birth based on Gestational Age
(Karnati et al., 2019, p. 39)

It has been found a U-shaped relationship between GA and adverse outcomes, with the lowest risk positioned between 39 and 41 weeks of gestation (Steward et al., 2019), supporting the idea that birth between the 37^{th} and the 39^{th} weeks are also associated with suboptimal outcomes. In this period falls the group defined Early Term (ET), that indeed has been also associated with heightened risks for mortality and for development; as it can be seen in Figure 3, ET represents the 26% of all live births, so neuropsychologists and doctors should be aware of the possible adverse outcomes that this wide slice of population could face, such as higher risk for developmental delay and negative academic outcomes at school age (Steward et al., 2019).

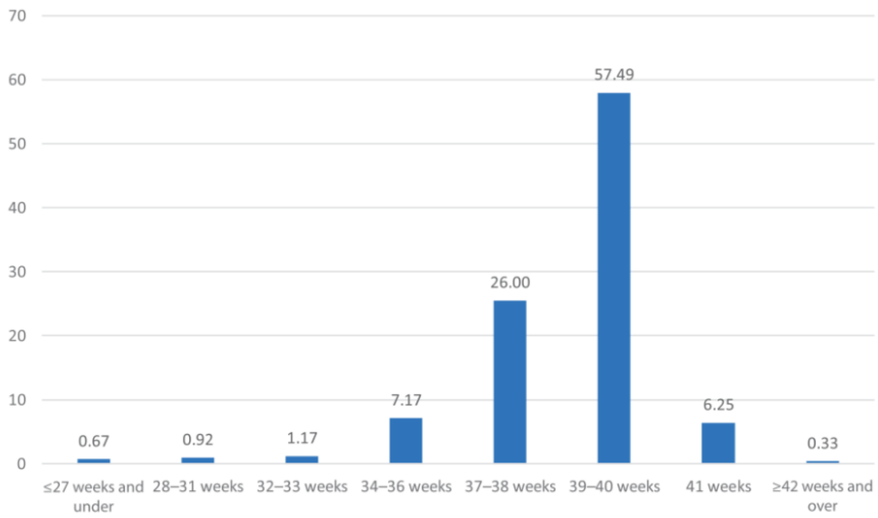

Figure 3. Prevalence of births by Gestational Age

(Steward et al., 2019, p. 3)

Considering the characteristics of ET group, it is hard to differentiate them from Late Preterm (LPT) group; an always vaster literature is analyzing the outcomes associated with LPT and ET birth, which makes sense given that these slices of population represent more than 30% of the total live births. In the most recent categorizations, LPT is defined as an independent category, since this subgroup alone represents the 7% of all the live births and the 70% of the preterm births (Steward et al., 2019); many studies started to show the clinical relevance of this subgroup pointing to all the risks and outcomes associated with it. Even if, as it is expectable, the groups of EPT and VPT are associated with the worst consequences, the group of LPT is also associated with medical conditions and adverse neurodevelopmental outcomes. Some of the most common short-term health problems associated with LPT are respiratory problems, feeding difficulties, hypoglycemia, and hypothermia; LPT group also gets the attention of neurodevelopmental psychology since, for instance, those children seem to be at risk for cognitive delay, school difficulties, special education needs and diagnosis of Attention Deficit-Hyperactivity Disorder (Karnati et al., 2019). All the risks and consequences linked to the condition of late prematurity will be analyzed in detail later, since it is relevant for the theoretical background of the present work. Anyway, it is clear that LPT group deserves attention since they represent the vast majority of preterm births. Furthermore, after a period of decline in preterm birth rate, in the years between 2014 and 2018 it has been reported a new increasing trend in the percentage of preterm births in the United States, that seems to be attributable to the increase in the rate of LPT births

(Steward et al., 2019, Karnati et al., 2019), other reason to support the research and clinical interest toward this population.

To close the topic of subcategorization, a graphical representation provided by Steward and colleagues can be seen in Figure 4; in this figure it is possible to note how little and arbitrary is the difference between what is considered "preterm" and what is instead "term", an issue that leads us to consider the limitation of the categorical definition of preterm birth.

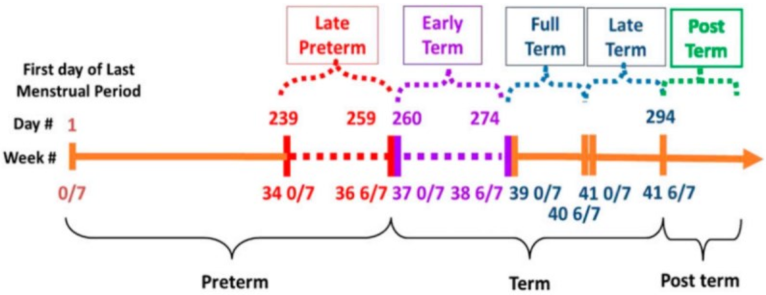

Figure 4. The continuum of Gestational Age

(Steward et al., 2019, p. 2)

The main problem of cutting-off Preterm and Term births is that we are not considering the nature of gestation and fetal growth, which is continuous. The decision to put a cut-off at the 37th week of gestation is arbitrary (Fleischman Oinuma, & Clark, 2010), and as the recent findings show, we cannot state that the births that happens after that moment are free from any risk or negative outcome. It is not possible to find a critical threshold for morbidity rate, on the contrary, the morbidity risk gradually decreases with the increasing of GA, reaching a minimum in the 39th -40th week (Fleischman et al, 2010). Most of the literature about preterm birth is aimed at comparing preterm with full-term individuals and they often take in account early prematurity, since it is easier to find the biggest difference with the full-term counterpart. As above mentioned, the LPT group and the ET group should be further investigated since their clinical relevance, however in literature there is disagreement on how to define those subcategories, mostly regarding the inclusion of the 37th week in the preterm or in the term group, and this does not help the progress of knowledge (Favrais & Saliba, 2019). A possible and useful way to overcome these limitations, could be considering GA as a continuum and studying the risks, outcomes, and consequences in relation to this continuous variable. Searching for associations between GA and possible adverse developmental outcome it is not only a way to overcome limitations about the disagreement in terminology and subgroup definition in the condition of prematurity, it is also an advantage because it allows to be more accurate; indeed with this method there will not be the risk to "lose" results about those borderline GAs, and the goal will not be to find a difference between groups but to see what is the impact of GA on development. Eventually, knowing the probability of adverse outcomes associated with any GAs allows to personalize intervention programs and to provide better care and prevention service.

The aim of this introductive part was to provide a general description of the prematurity issue, to create reference for terminology and to give the basis for supporting the theoretical flow of this work. In the present study GA will be considered as a continuum and the condition of prematurity will be accounted in a dimensional way, i.e., considering it as low GA at birth. In the following paragraph it will be described the continuous process of fetal growth and it will be addressed in more detail which are the outcomes associated with low GA, to have a deeper understanding of what does premature birth entails.

1.2 Risks associated with low Gestational Age

In the previous pages it was anticipated that premature children are subject to an atypical path of development, which starts with the unexpected interruption of pregnancy and implies the forced exposure to the ex-uterus environment. To understand which are the implications for the development of the neural system of the premature baby, it is useful to talk briefly about which are the dynamics and times of brain development during gestation.

At the beginning of gestation, the embryo if formed by totipotent cells, which are stem cells capable of anything. The processes that guide evolution of those cells are specialization and differentiation, through which the fetus becomes a complex organism with all the organs and structures necessaires to survive in the outside world. In this early prenatal development, the specie-specific genetic programs play a fundamental role, but also environmental and epigenetic factors concur in influencing and directing the entire process (Mandolesi & Petrosini, 2017). After a week of gestation, the embryo is divided into three layers of cells, one of which, the *ectoderm*, will give rise to the Neural System. During the third week of pregnancy the ectoderm layer starts to fold on itself creating a tube, the *neural tube*, which will originate the Central Nervous System. Subsequently the neural tube starts differentiating in distinct parts, generating different brain parts and hemispheres. At the same time, starting even before the differentiation of ectoderm, a process of cell *proliferation* is going on, allowing the neural system to expand; the peak of neurons and glial cells proliferation happens between the 2nd and 5th month of gestation (Mandolesi & Petrosini, 2017). Another key process is the *migration* of these new cells towards the areas of brain where they will specialize, a process which starts from the 6th week of gestation and goes on till the 6th month after birth. Once the cell gets to its expected destination, the process of *synaptogenesis* starts, allowing cells to create networks and transmitting information. All these complex dynamics that characterize the first five/six months of pregnancy are crucial for the development and functioning of the human brain and they are advancement does not end during intrauterine life; indeed babies are born with a brain just partially developed and the brain maturation goes on with different timings in different areas till early adulthood, leaving a lot of space to environmental stimulations to play a key role in directing this development (Mandolesi & Petrosini, 2017, Valenza & Turati, 2019).

Thinking about premature birth, let's focus on what happens during the last trimester of gestation, which is when the majority of preterm births happen; even if, as we have stated, the process of neural maturation starts very early during pregnancy, also the last three months of intrauterine life are crucial for the typical brain development. During this period, it starts the neuronal selection, through the process of apoptosis; the aim of this procedure is to eliminate those cells that are not useful or that migrated in wrong areas in order to reduce the surplus of cells and connections (Mandolesi & Petrosini, 2017). Furthermore, between the 34th and the 40th weeks of gestation the brain gains approximately one-third of its weight at term, facing a very rapid expansion, especially in the volume of gray matter and myelinated white matter (Woythaler, 2019 & Favrais & Saliba, 2019). These last six weeks of gestation are also characterized by intense synaptogenesis and dendritic arborization (Favrais & Saliba, 2019). In conclusion, the early interruption of gestation, even if it happens in the last weeks of pregnancy, determines an alteration of the typical development of the neural system resulting in an immature brain at birth (Woythaler, 2019).

Many studies to present have addressed the issue of neurodevelopmental outcomes associated with preterm birth, focusing on different severity of prematurity, on different ages of assessment and on different domains. Before going deeply into this topic, it is important to say that for the neuropsychological evaluation of preterm in comparison to full term it is common, both in clinical and research practice, to correct the age of the premature infants. Correcting for prematurity starts from distinguishing between *chronological* and *corrected age*; *chronological age* represents the age of the infant counted from the actual date of birth, while *corrected age* is calculated by subtracting the weeks that the baby was born preterm (considering 40 the definition of full-term gestation in weeks) from his/her *chronological age* (Harel-Gadassi, Friedlander, Yaari, Bar-Oz, Eventov-Friedman, Mankuta, & Yirmiya, 2018).

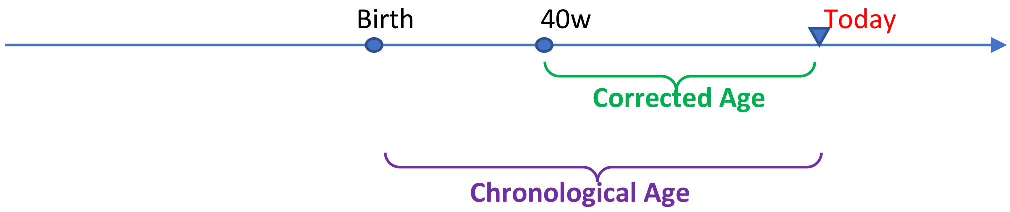

Figure 5. Representation of the difference between Corrected and Chronological Age

The theoretical idea that supports this practice is the B*iological and maturational perspective* (Harel-Gadassi, 2018); according to this view, babies born preterm are not comparable to their full-term counterpart, because they do not have the same level of maturation. Indeed, no one would compare the weight of an extremely premature baby at birth with the weight of a full-term baby because it is obvious that the EPT baby would be in disadvantage (Doyle & Anderson, 2016). For what concern neuropsychological development, the use of *chronological age* in the evaluations would underestimate the capacities of preterm; for this reason, the practice of correcting the age allows to compare premature babies with full term at the same level of maturation. Correcting age also carries some risks because, on the other hand, using *corrected age* could overestimate the abilities of preterm since they would be compared with babies that have less time of experience in the outside world. It is important to adopt shared guidelines for the practice of correcting for prematurity; in the literature there is not complete agreement on when to stop, during development, the practice of age correction, in particular, there are contrasting opinion between the age of 2 and 3 years old (Harel-Gadassi, 2018). The more children grow up, the more effects of maturational disadvantage will be compensated by the environmental stimulations, so it is plausible that it will not be necessaire to correct for prematurity anymore; however, there is some evidence that even at 8 years the use of *corrected age* could comport a significant difference in cognitive evaluation for children born extremely preterm, while for late preterm the same pattern of results have been found at 2 years old (Harel-Gadassi et al., 2018, Parekh, Boyle, Guy, Blaggan, Manktelow, Wolke, & Johnson, 2016). A study conducted by Harel-Gadassi et al. in 2018 was aimed to proof the effects of correcting for prematurity at different ages and different GA at birth. In this study the authors evaluated preterm infants with the Mullen Scale of Early Learning (MSEL), which is an instrument for testing motor abilities, visual perception, language, and global neurodevelopment from birth to 68 months (Harel-Gadassi et al., 2018). The evaluation was conducted longitudinally at 1, 4, 8, 12, 18, 24 and 36 months of *corrected age* and for each time point they were calculated two scores, comparing with norm tables at *corrected* and *chronological age*; the sample of premature babies was formed by preterm born between the 24 and 34 weeks of GA (EPT, VPT and MPT). The authors found a significant difference between the use of *corrected* and *chronological age* in the composite score of the MSEL and in all the subscales; especially, when *chronological age* was used, preterm had lower scores in the MSEL compared to when *corrected age* was used. This was found at all ages and for all the three groups of GAs, even if lower GA were associated with greater differences between *corrected* and *chronological age* scores from 1 to 24 months of age. Furthermore, it has been found that the effect of age correction was bigger at the initial stages of development, and this is probably due to the rapid changes that the brain undergoes in the first months. In conclusion, this study reported evidence that the practice of correcting age allows a "fairer" evaluation of premature infants and children, that does not underestimate their abilities; according to the findings reported by Harel-Gadassi and colleagues, age correction should be applied at least until the age of 36 months, because it still seems to have a significant impact.

Another work, conducted by Parekh and colleagues (2016), studied the impact of correcting for prematurity in a sample of moderate-late preterm (32-36 weeks of gestation). The purposes of this study were to compensate the lack of research about how correcting age affects cognitive evaluation and developmental delay attribution in late prematurity, and to clarify if this practice is necessaire also for GAs that are closer to term. They used Bayley Scales of Infant and Toddler Development 3rd Edition (Bayley-III) to assess cognitive, language and motor development at 2 years *corrected age*. They found that mean composite *corrected age* scores were significantly higher than scores for *chronological age*; in addition, using *chronological ages* led to a significantly higher prevalence of developmental delay, defined by the authors as a cognitive or language composite score inferior to 80. The authors concluded that, also for the group of moderate-late preterm, correcting for prematurity leads to smaller but significant differences.

In conclusion, the practice of correcting age in preterm births is recommended in the research field, at least till 3 years of age, because it seems to impact the evaluation of early neurodevelopmental outcomes; in addition, correcting for prematurity has been found to be also affecting higher GAs prematurity. In the clinical field, the difference between *corrected age* and *chronological age* use can influence the access to diagnosis and treatments and consequently can influence family burden. For these reasons, in the clinical practice, it should be considered both corrected and chronological scores (Harel-Gadassi et al., 2018), in order to have a better understanding of the cognitive development of the child and to take in account both maturation and experience contributions.

It is now time to go deeply into the topic of what kind of outcomes are associated with anticipated births, focusing on the possible adverse consequences for neural, cognitive, and behavioral development. In the first paragraph it has been said that being born prematurely has some short-term consequences for the baby, that mostly depend on the forced exposure to a new environment and on the immaturity of organs and neural system. Furthermore, we said that prematurity entails the interruption of the typical neural development, driving to a forced re-adaptation of brain functions and structures; the atypical development of neural system represents a risk for long-term adverse outcomes in cognition, motor capacities and behaviors. Allotey and colleagues. (2017) conducted a big meta-analytic study that included 74 studies involving 64.061 children born prematurely with different degrees of severity. The aim of the work was to include studies assessing general intelligence, motor skills, academic performance and behaviors of children born preterm and to compare them with full-term cohort, starting from the 2 years of age till early adulthood. The objective was to find robust evidence of which are the long-term neurodevelopmental outcomes associated with low GAs. First, it was found that GA correlated with general intelligence, explaining between 38 and 48% of IQ variance; moreover, IQs indexes were consistently lower in preterm groups, for VPT, MPT and LPT, at all ages. Secondly, preterm had worst motor skills in pre-school years and the pattern persisted in school years. Thirdly, prematurity was associated with worst academic performance, with difficulties persisting till secondary school. Finally, GA was negatively correlated with behavioral problems, such as ADHD; preterm were more likely to receive ADHD diagnosis, and these association was found for all subcategories of prematurity. Other works, focusing on long-term outcomes associated with prematurity, reported in addition a higher probability in preterm to develop Autism Spectrum Disorder (ASD), anxiety and depression (Chung et al., 2019).

In general, we can say that there is a moderate effect of prematurity on neurodevelopment, with the worst outcomes found for lower GAs and lower birth weights (Chung et al., 2019); however, also for Late Preterm, it was found increasing risk of lower scores in IQ *full scale* and *performance index*, in addition to higher probability to be diagnosed with ADHD (Allotey et al., 2017). Indeed, not only early preterm, but also late preterm should be involved in program of neonatal care, long-term monitoring, and parents' psychoeducation, in order to explain the risks associated with low GA at birth and to warn about possible long-term consequences.

The findings regarding adverse outcomes of late prematurity and near term GAs are contradicting and it is not easy to have clear guidelines on how to intervene in case of late prematurity; as it was argued at the beginning, late prematurity is a condition that should be addressed since, even if the risks are lower, they are still present; in addition, the prevalence of late preterm births is high, so even small differences may have broad consequences (Woythaler, 2019). In the clinical practice there should be awareness of what to expect and what to do to promote the best developmental outcomes. Furthermore, we said that gestation is a continuum and even an interruption of gestation that happens in the last six weeks of pregnancy still represent a challenging event for the developing brain. We will now analyze more deeply the evidence about neurodevelopmental outcomes in late prematurity, with the aim of providing a better characterization of this specific population, which is of interest in the present study.

First of all, the impact of late prematurity can be seen at a neural level: the brain of late preterm babies is immature at birth, and this makes it more vulnerable. It is more likely for late premature brains to be injured, given the possibility of concurring medical conditions, such as respiratory difficulties, which can damage neural tissue; if injuries occur during such a sensitive period, they can change the course of brain development, resulting in distinct neurologic outcomes (Woythaler, 2019). In fact, evidence coming from Magnetic Resonance Imaging (MRI) studies revealed a maturational delay at term-equivalent age for babies born late preterm; especially, they seem to have smaller gray matter and cerebellum volume if compared to full-term infants (Favrais & Saliba, 2019). Differences on brain volume are visible also in children aged 6 to 12 years: a study found a reduction in the size of right temporal and parietal gray matter in LPT children if compared to full-term (Woythaler, 2019). Volumetric measurement of gray matter, white matter, whole brain, and cerebellum, together with cortical folding delay at term-equivalent age was found to be associated with later neurodevelopment and difficulties at 2 years of age (Favrais & Saliba, 2019); similarly, gray matter reduction in right temporal area was associated with greater anxiety at school age (Woythaler, 2019). In conclusion, there is initial evidence that late prematurity can consistently impact brain development and that these neural differences can account for neurodevelopmental problems.

Talking about cognitive and behavioral outcomes that have been found to be associated with late prematurity, it is useful to consider the evolvement of difficulties and problems during development. Some literature has focused on early outcomes in preschool years, from 2 to 5 years old, comparing late preterm with full-term; it has been found that late preterm show significantly worst performance at 2 years in cognitive, motor and language assessment (Woythaler, 2019), in addition to poorer executive functions development (Hodel, Senich, Jokinen, Sasson, Morris, & Thomas, 2017). Late-preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. Pediatrics, 126(6), 1124-1131.. However other findings show that this significant difference is found only when *chronological age* score is used, and not with *corrected age*; this raises the issue of whether to correct for prematurity, if that could lead to losing information about likely future difficulties (Woythaler, 2019). In addition, during preschool years, LPT seem more likely to show speech and language delay, communication impairment, together with a higher rate of access to early intervention care, a proxy of developmental delay (Woythaler, 2019).

Probably, the most impacting and important outcomes to look to are in the school age period; in this time of development any difficulty manifested can have a big impact on academic performance, on social and emotional development, on family and social burden. Furthermore, looking at academic performance and school success is a good predictor for later success in many spheres of adult life, such as socio-economic status, employment, and adult health (Woythaler, 2019). During first school years, there is some evidence that LPT children have difficulties in reading, writing, math, and expressive language; in a study conducted in the UK it was found that, in the first year of elementary school, lower GA was associated with a higher risk of not reaching a good level of overall achievements, and this was true also at 7 years old (Woythaler, 2019). In addition, these difficulties result in a higher probability to be part of special education programs for late preterm children if compared to full-term (van Baar, Vermaas, Knots, de Kleine, & Soons, 2009). Functioning at school age of moderately preterm children born at 32 to 36 weeks' gestational age. Pediatrics, 124(1), 251-257.. For what concern behavioral and cognitive outcomes during school age, LPT children seem to manifest more attentional problems (Talge, Holzman, Wang, Lucia, Gardiner, & Breslau, 2010) and be addressed as more "problematic" on a behavioral level by teacher and parent evaluations. Specifically, they manifest higher rates of inattention and internalizing behaviors (Woythaler, 2019), which is coherent with the findings associating late prematurity with higher risk for ADHD diagnosis, especially the inattentive subtype (Ginnell, Boardman, Reynolds, & Fletcher-Watson, 2021).

Few studies followed the outcomes of late preterm till adolescence and adulthood, but it is hard to drive conclusions because the samples taken are old cohorts and many things in neonatal care have changed since then. However, the available findings seem to point to few adverse outcomes in this age period, regarding mainly higher risk for disability, health problems, mental retardation, (Woythaler, 2019), lower IQ, higher mortality (Karnati et al., 2020), and alteration in brain anatomy and cortical organization (Nosarti et al, 2014; Olsen et al., 2018); on the other hand, no impact was found in many other areas such are psychiatric disorders, unemployment, criminality, and level of education (Woythaler et al., 2019). Furthermore, some other factors seem to intervene to exacerbate the adverse outcomes like socio-economic status and the condition of being small for GA added to being LPT.

As it was seen, there is evidence supporting the impact of late prematurity, but there are also contradicting results that found no significant difference comparing LPT with FT and no increased risks associated with late prematurity; in order to clarify the issue, more research is needed. Future research should conduct longitudinal studies in order to understand if the difficulties showed during early development determine life-long consequences or if they possibly resolve with time (Woythaler, 2019). In addition, future research should investigate if there is opportunity to intervene for the prevention of adverse outcomes in late prematurity.

1.2.1 Investigating preterm birth with a probabilistic approach

This far, the possible outcomes associated with being born prematurely have been analyzed and described, considering the domains of neural development, cognition, language, health, and behaviors. Those seen above are probable outcomes, which could be observed starting approximately from the 2 years of age throughout childhood, adolescence, and adulthood. It is important to specify that they are not sure consequences of prematurity, indeed what can be said is that preterm babies are at increased risk to develop those kinds of outcomes and to experience those possible consequences. The concept of risk introduces the idea that the process of development is not predetermined, fixed and immutable; this vision is supported by the *Neuroconstructivist approach* (Karmiloff-Smith, 1992), which gives a definition of development as a dynamic and interactive process. As previously argued, at birth our neural system is just partially developed and the same can be said for our mind and cognitive system. The mind and brain of a baby are not just the smaller version of adult's ones, they are qualitatively different; the process of development is not just maturation and growth, but it is a complex mechanism that involves genetic predispositions, environmental stimulation, and active interactions with environment (Valenza & Turati, 2019). This bidirectional interaction between the individual and the environment is supported by the presence of basic cognitive processes, which allow the cognitive system to work and develop thanks to its own functioning (Valenza & Turati, 2019). The process of development can be described with a metaphor provided by Waddington, "*The epigenetic landscape*" (see Fig. 6), that compares the course of development to a ball running down a hilly landscape; during this path, a small deviation that happens near the top of the hill will drive the ball to totally different destination. The same can happen for the neuropsychological development: a small early neurodiversity, with a cascade effect, can turn into a big phenotypical difference which will be visible only later in time. In this perspective, the deterministic vision must be abandoned, preferring instead a probabilistic conception of development; the probabilistic approach has the advantage to leave space for intervention in order to compensate early deviations from the typical trajectory of development.

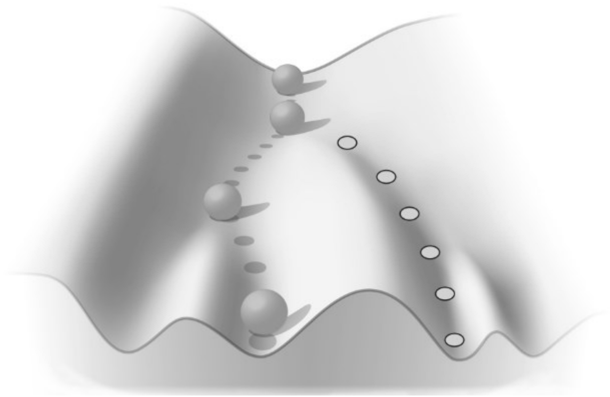

Figure 6. Waddington Epigenetic Landscape
(In Valenza & Turati, 2019, p. 21)

With all this in mind, it results clear that it is important to monitor the trajectories of development since the very beginning of life, and not just to look for outcomes. For this purpose, it is useful to search for early markers, i.e., indicators of dysfunctionality that are visible since the early phases of development (Valenza, 2019). The early marker can be an early neurodiversity or deviation from the typical expected development, but it is not certain that it will determine adverse outcomes. In order to find early markers, it is important to look at the first 1000 days of life of a child, which are the days between conception and the 2nd birthday; in this period children are really sensitive to the environmental effects, many changes are happening in the development of the brain and mind, and, at the same time, they are also more vulnerable. Early markers can be found in those basic cognitive processes that are present very early during development, and that will be the basis for the development of more complex cognitive processes emerging later in development; the cognitive processes where to look for early markers are perception, attention, memory, and motor system. For what concerns preterm birth, it represents a biological vulnerability for the development of neural and cognitive system. For this reason, it is fundamental to apply this approach also to prematurity and to look for early markers that could predict some of the adverse long-term consequences that this condition can imply. My final dissertation has empirically investigated a specific early behavioral marker, efficiency in attentional disengagement, in infants with different GA. In the next chapter we will focus on the attention system, describing this basic cognitive process and providing a general view of the typical development of attention in the first years of life. Building on this knowledge, I will explain why attentional disengagement is a good early behavioral marker for delineating the developmental trajectory of preterm infants.

2

ATTENTION AS AN EARLY BEHAVIOURAL MARKER

2.1 The attention system of the human brain

Attention can be defined as a multidimensional cognitive system that allows us to select the information that will access our consciousness (Rueda & Conejero, 2020). The environment is full of stimulations, details, events, and our cognitive system is not able to consciously process them all; through the function of attention, it is possible to direct the limited resources of human mind to salient information, for their enhanced detection. Attentional capacities are based on a proper state of activation, which allows to select inputs from the world and to control behavioral responses. The allocation of attentional resources can be triggered by characteristics of environmental stimuli and events, or it can be driven by a conscious intent; these two forms of attention are called, respectively, exogenous (bottom-up) and endogenous (top-down) form of attention. The abilities to orient, control and sustain attention for a certain amount of time are fundamental skills in everyday life, and are the basis of many complex activity that we carry out as adults; furthermore, attention plays a key role during the development of cognitive system, supporting the progress of higher cognitive processes, such as social cognition, goal setting, and cognitive flexibility (Ginnell et al., 2021).

There is agreement in literature on the definition of attention as a complex, multidimensional construct, comprising aspects of activation, selectiveness, and control (Rueda & Conejero, 2020; Conte, 2020; Ginnell et al., 2021; Petersen & Posner, 2012), as it is represented in Figure 7. A classical model of attention was proposed by Posner and Petersen in 1990, who provided evidence that it is possible to differentiate between distinct brain networks involved in attention, as many behavioral and lesion studies showed. This classical work had a huge impact on the study of attention, with nearly 11.000 citations at present, and it supported the growth of literature in this field. The original review of 1990 stated the following basic concept about attention system: attention is anatomically separated by other cognitive processing systems, it involves a specific network of anatomical areas in the brain, each of which carries out specific cognitive functions (Petersen & Posner, 2012). The main contribution of Posner & Petersen was to define three networks that takes part in the attention system, which are anatomically and functionally distinct, but interrelated (Ginnell, 2021); these networks are Alerting, Orienting and Executive Control. The classical model of attention was revised and complemented by Petersen and Posner in 2012, who updated the original vision in the light of new evidence coming from neuroimaging studies; in the following pages the three sub-networks of attention will be described in detail, in their definitions, features, measurements and neuroanatomical basis.

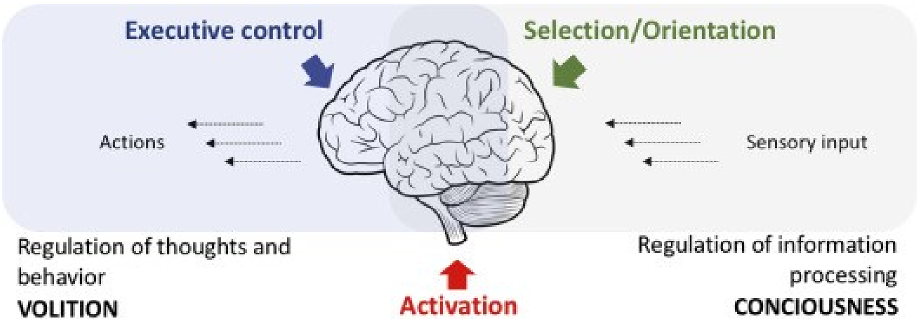

Figure 7. The different facets of attention

(Rueda & Conejero, 2020, p. 506)

2.1.1 The Alerting network

The Alerting network supports the ability to be alert, i.e., achieving and maintaining a state of high sensitivity to incoming stimuli (Conte, 2021). In the conception of Posner & Petersen (2012), alertness is the proper arousal level that allows reaching optimal vigilance and task performance. Alerting can be defined also as the ability to successfully allocate attention in time, as complementary to the allocation of attention in space carried out by the Orienting system (Valenza, 2019). It is possible to distinguish between two components of alertness; the *phasic* component is the transient response of activation that is characterized by dismissing the resting state to prepare for the detection of expected salient stimuli (Petersen & Posner, 2012). This component of Alerting system is generally studied with tasks that provide a warning cue before the presentation of a target stimulus; it has been demonstrated that the presence of a warning signal improves the reaction time to the target and determines changing at a brain level (Petersen & Posner, 2012), supporting the idea that an optimal level of alertness enhances target detection. The second component of Alerting is the *tonic* alertness, i.e., a general state of activation which allows to maintain attention during a large task in an exploratory mode (Valenza, 2019; Rueda & Conejero, 2020). The level of tonic activation is subject to changes during the day due to circadian rhythms (Petersen & Posner, 2012), and it is usually measured in laboratories with large and boring tasks, in order to stress vigilance and sustained attention. An example of a spread-used task to assess vigilance is the *odd-ball paradigm*, which consists in the presentation of a sequence of regular stimuli, in which there is a rare and unpredictable appearance of infrequent stimuli that requires a response of the participant (Valenza, 2019). The same paradigm can be applied also with early infancy, without asking any response, just measuring brain activity at the appearance of the odd stimulus (Valenza, 2019). Generally, it has to be said that the phasic component of Alerting is an automatic reaction, while the maintenance of a tonic vigilance requires motivation and volition (Rueda, 2018). For what concerns the neural substrates, Alerting system is supported by the activity of the Locus Coeruleus (LC), a nucleus of gray matter localized in the brain stem, which is the main node of the Norepinephrine (NE) pathway. The more recent evidence on the neural basis of attentional networks, reported in the work of Petersen and Posner (2012), comes from neuroimaging studies on the human brain and from studies on animal models; as it can be seen in Figure 8, LC has projections toward many cortical and subcortical areas of the brain.

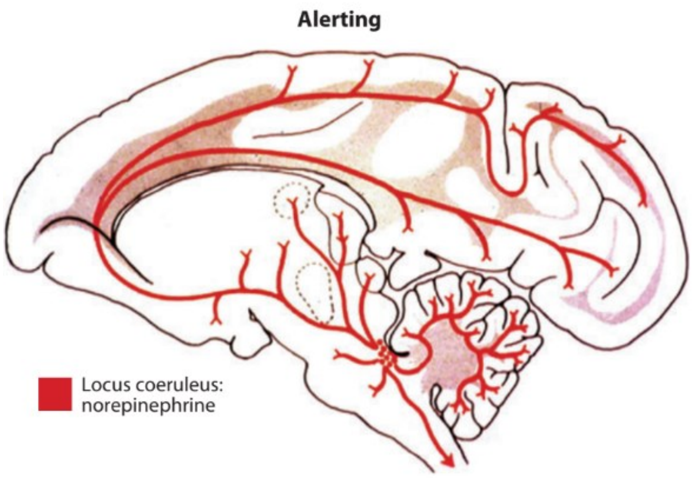

Figure 8. Locus Coeruleus projections in a macaque brain.

(Petersen & Posner, 2012, p. 75)

Other nodes of the Alerting network are the thalamus, the Anterior Cingulate Cortex (ACC), Orbitofrontal (OFC) regions, dorsolateral Prefrontal Cortex (dlPFC) and parietal cortex (Rueda & Conejero, 2020; Petersen & Posner, 2012; Ginnell et al., 2021). Furthermore, it has been found a dissociation between left hemisphere, more involved in the phasic alertness response, and the right hemisphere, who activates majorly for the tonic component (Petersen & Posner, 2012). Finally, evidence from Electroencephalography (EEG), show that an event related potential, called Contingent Negative Variation (CNV), is consistently observed in response to a warning signal and may remain present until the target presentation; the CNV source seems to be at ACC level, and it is detectable at contralateral parietal level (Petersen & Posner, 2012).

2.1.2 The Orienting network

The second network of attention conceptualized by Posner and Petersen is Orienting; this network allows to select specific sensory inputs based on their spatial position or sensory modality (Petersen & Posner, 2012). Spatial attention can happen in an *overt* way, namely involving eye and/or head movements, or in a *covert* way, without eyes or head movements. Visual orienting of attention can be compared, in a metaphoric way, to a spotlight moving in the visual field and shedding light to target of particular interest or salience, making their elaboration more efficient; in addition, the size of the spotlight can be modulated, meaning that attention focus can be enlarged or restricted (Valenza, 2019). The process of orienting attention can be decomposed in three sub-components: *disengagement* occurs when attention is released from an attentional object; *shifting* occurs when attention is moved towards other objects, finally *engagement* occurs when attention is allocated to the new object (Posner et al., 1984). Many paradigms have been proposed for the study of Orienting, even if it is hard to provide a task measuring purely this mechanism (Ginnell et al., 2021); an example is the *Posner paradigm*, a very known task consisting in responding rapidly to a target that can appear in the left or right side of a screen; in each trial the target is anticipated by a cue and the trials can be valid, i.e., the cue and the target appear in the same side , or invalid, i.e., the target appears in the opposite side of the cue (Posner et al., 1984). The effect of the cue in valid trials is to facilitate the elaboration of the incoming target through a mechanism of covert orienting that precedes the target occurrence; it has to be said that the facilitation is observed only if the interval between stimulus and target is brief (maximum of 150 ms in adults and 450 ms in infants – Hendry, Johnson, & Holmboe, 2019), otherwise an effect of Inhibition of Return is observed (Hendry et al., 2019). The *Posner paradigm* can be adapted to distinguish between exogenous form of orienting, if the cues appear directly in one of the sides, or endogenous orienting, if the cues appear centrally on the screen, conveying meaning that suggests where the target will appear (for example with an arrow). To note that the *Posner paradigm* can also be used with infants, employing simple stimuli and cues that babies can understand (for example gaze direction – see Figure 9).

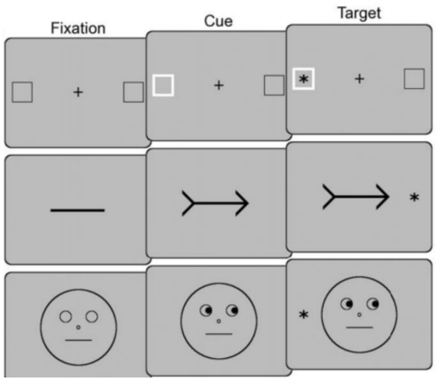

Figure 9. Posner paradigm examples

(Keehn et al. 2013, p. 167)

Another common paradigm used to study Orienting mostly in babies, is the *Gap-Overlap paradigm.* This task measures the latency to orient toward a peripheral target in two conditions: the gap condition (the central stimulus disappears before the peripheral target appears) and the overlap condition (the peripheral target appears while the central stimulus remains on display). The main effect of this task shows that latencies are lower in gap than overlap condition; these results are visible in adults, but the effect is bigger in infancy (Hendry et al, 2019).

Talking about neural substrate, while NE seemed to play a key role for the Alerting network , the Cholinergic (Ach) system, arising in the basal forebrain, seems to be the primary neuromodulation involved for Orienting network. The main cortical areas implicated in the mechanism of Orienting are parietal and frontal areas. In particular, it is possible to distinguish between two networks responsible of different aspects of orientation (see Figure 10). A first network, the bilateral dorsolateral parieto-frontal network, comprises the Intraparietal sulcus (IPS), the Superior Parietal Lobule (SPL), and the Frontal Eye Fields (FEF); activity in these areas has been associated with rapid and strategic control over attention (Petersen & Posner, 2012), meaning an endogenous form of orienting (Rueda & Conejero, 2020). The second network comprises the Temporoparietal Junction (TPJ) and the inferior frontal cortex; this network is associated with detection of infrequent or miscued targets, and gives rise to more automatic, bottom-up, response (Rueda & Conejero, 2020).

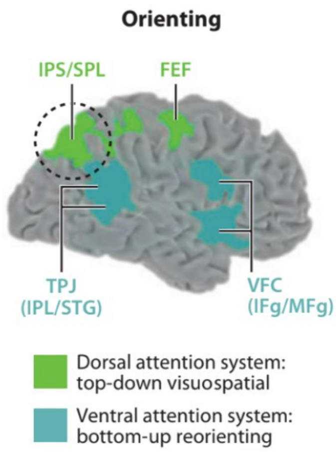

Figure 10. Neural substrate of the Orienting system

(Petersen & Posner, 2012, p. 76)

2.1.3 The Executive control network

The third network is the Executive Control (Posner & Petersen, 1990), defined as the component of attentional system that allows to monitor and resolve conflict, to inhibit distraction, to divide attention between two or more tasks, and to select information for further processing (Ginnell et al., 2021; Conte, 2021). To sum up, this attentional component is the one that provide control over our behaviors, thoughts, feeling and goals, and at the same time requires effort; the Executive Control system support the high-level processes, such goal-directed and voluntarily regulated behavior, and it facilitates focused attention even in the presence of distractors (Ginnell et al., 2021). In order to test Executive Attention in laboratory, conflict-inducing tasks are generally used; a first example is the famous *Stroop Task*, in which names of colors are presented and the subject has to name the color of the word, that, at times, doesn't correspond with the meaning of the word itself. A second conflict-inducing task is the *Flanker Task*, which can be used also with children; it consists in responding to a target stimulus which is surrounded by competing distractors. Another very known task is the *Go/No-Go task*, in which participants must respond to a set of frequent stimuli but retain the response when some target, infrequent, stimuli appear. A report of the just mentioned tasks can be seen in Figure 11 below, taken from Rueda and Conejero (2020).

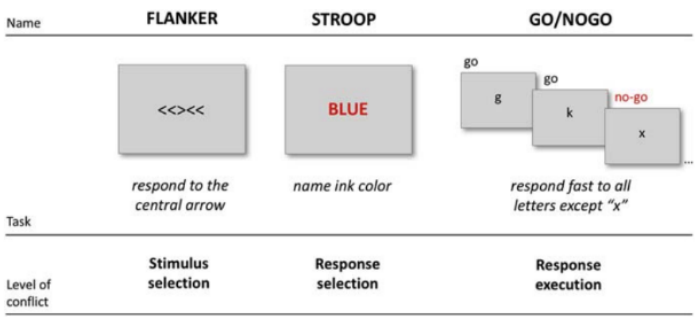

Figure 11. Conflict-inducing tasks for testing Executive Attention.
(Rueda & Conejero, 2020, p. 508)

The neural areas that have been associated with the Executive Control system are the medial areas of the frontal cortex, lateral prefrontal areas, parietal regions, and cerebellum (Conte, 2021; Ginnell et al., 2021). Connectivity and lesion studies have pointed out the existence of two dissociated networks of Executive Control, which appear clearly separated in adults, while they seem to have common activation during early development (Petersen & Posner, 2012): the Frontoparietal and the Cinguloopercular networks. The first network, positioned more laterally, includes dorsolateral prefrontal cortex (dlPFC), inferior parietal lobe (IPL), dorsal frontal cortex (dFC), intraparietal sulcus (IPS), precuneus, and middle cingulate cortex (mCC) (Rueda & Conejero, 2020); this network is distinct from the Orienting network, and lesions in those areas are associated with perseverative behavior and lack of cognitive flexibility (Petersen & Posner, 2012). The cinguloopercular network is made of more medial regions, such as the anterior prefrontal cortex (aPFC), anterior insula/frontal operculum (AI/FO), dorsal anterior cingulate cortex/medial superior frontal cortex (dACC/ msFC), and the thalamus (Rueda & Conejero, 2020); this network, is related to control of goal directed behaviors and lesion in these areas can lead to incapability to initiate behaviors intentionally (Petersen & Posner, 2012). To conclude, evidence from the study of Event-Related Potentials (ERPs) has shown that two components are consistently observed in response to target detection: the N2 and P3 components, localized at frontoparietal medial level; these components increase their amplitude when there is a conflict trial, meaning that they are good measures of the effort required for Executive Control of attention (Rueda & Conejero, 2020).

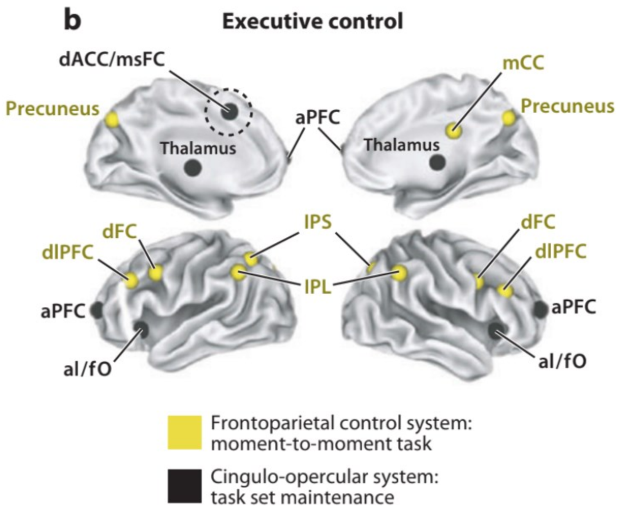

Figure 12. Neural areas involved in the Executive Control system.

(Petersen & Posner, 2012)

In the review of 2012, Petersen and Posner talk about another cognitive process that was found to be strictly interconnected with attention, which is Self-regulation. This term is used in developmental cognition to indicate the ability to control emotions and cognition, together with the faculty to inhibit dominant responses and produce less dominant ones (Petersen & Posner, ,2012); the same set of ability has been called with different names, especially, in adults it is common to talk about self-control instead of self-regulation. The main reason why this construct has been implemented in the conceptualization of attentional facets is that it involves a common neural substrate with attentional networks, especially with Executive Attention: the ACC and the Anterior Insula (Petersen & Posner, 2012). This communality between the ability of self-regulate and control of attention appear logic, since attention regulation is fundamental to select the information that reach consciousness, ignoring irrelevant information, managing cognitive resources and maintain the focus on specific tasks (Rueda & Conejero, 2020). During childhood the crucial role of attention in contributing to the emergence of self-regulation is a further motivation for the need to monitor attentional abilities and to support their typical development.

The following paragraph will discuss how attentional abilities develop in the first years of life in the typical population.

2.2 Development of attention in typical population

In the previous section, it was provided a conceptualization of the attention system in adults, namely when the process of development has already concluded. For the study of typical development of attention, it should be kept in mind that the developing brain and cognitive system are qualitatively different from the adult's ones. Attention is a component of cognitive system which emerges early and evolves fast during development; some attentional capacities are present even at birth, see Figure 13, and they develop rapidly, while other emerge later and continue evolving till adolescence (Valenza, 2019; Rueda & Conejero, 2020).

The three attentional networks described in the previous chapter, Alerting, Orienting and Executive Control, emerge and develop with different timings; in the following pages I will describe in detail the typical developmental course of each attentional network.

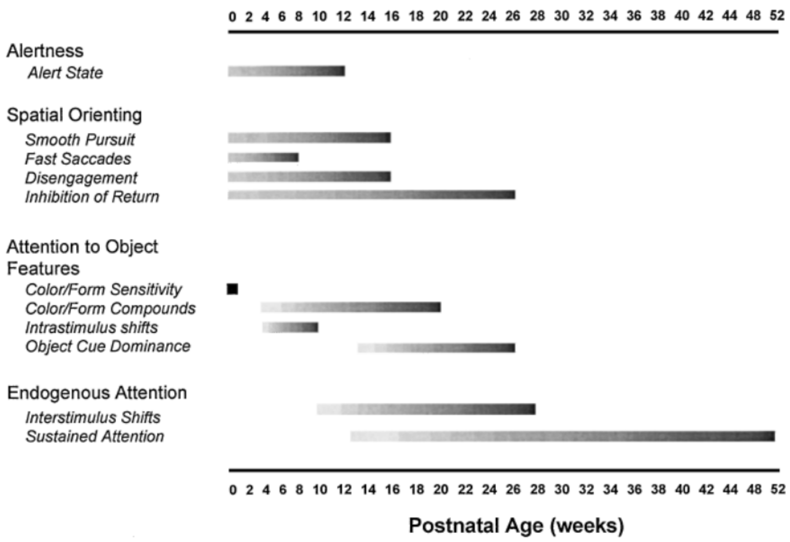

Figure 13. The early emergence of attentional capacities
(Colombo, 2001, p. 356)

2.2.1 The Alerting network

Alertness is the simplest and earliest form of attention (Conte, 2020), and both the phasic and tonic components develop soon during the first months of life (Valenza, 2019). Let's start by describing alerting during infancy, namely the period of time that precedes the first birthday of a baby. Newborn show already a functional capability of alertness, which allows them to be responsive to physical changes in the environment (Rueda & Conejero, 2020). In the first months alertness is rudimental, controlled by subcortical pathways of the NE network, and based on external regulations provided by the caregivers. After the third month of life babies increase their awake time and acquire more regularity in sleeping-awake patterns, meaning that their arousal system is evolving (Rueda & Conejero, 2020). The ability to sustain attention, strictly related with alerting, is already present in infants and it depends on the complexity of stimuli to which the baby is exposed; the more the babies grow, the more the simplest stimuli loose of interest and they prefer maintaining their attention at dynamic and complex stimuli (Rueda & Conejero, 2020). In addition, it seems that during the first months of life the Alerting system provides basis for a primitive form of attentional focus modulation, which cannot be controlled by the Executive Control system since it is yet not mature enough (Rueda & Conejero, 2020). Studies have shown that regulation of arousal level can influence looking time at an object, with higher arousal levels associated with lower looking time and vice versa; this means that, depending on the level of alert, the infant can have enhanced responsiveness leading to quicker processing of stimuli, or, on the other hand, lower responsiveness to distractors leading to longer periods of focused attention (Rueda & Conejero, 2020).

Following, during the second and third years of life, which are referred to as toddlerhood, a massive maturation at neural level is observed, involving especially white matter. The process of myelinization of axons see a huge increment during toddlerhood, with the peak happening around 2 years old (Rueda & Conejero, 2020); this process enhances the specialization of neural connection and leads to emergence of modular networks and observable behavioral changes (Rueda & Conejero, 2020). There is evidence that, during toddlerhood, attentional system is already divided in the three sub-components that characterize adults' system; a study carried out by De Jong, Verhoeven, de and van Baar (2016) used a set of four ET tasks to test attentional capacities in toddlers of 18 months of age. For each task they measured different dependent variables and conducted a factorial analysis to see if the attentional performance could fit a three-factorial model, as the one proposed by Posner and Petersen (1990). Results confirmed this hypothesis , giving proof of a differentiation of attentional system at the age of 18 months. In toddlers, the main changes in the Alerting system are observed in the capacity to sustain attention. The duration of sustained attention increases between 17 and 24 months of age (Rueda & Conejero, 2020), an improvement which is observable while letting the child play freely with toys; if toddlers are left alone to play with a toy they will engage in the play and keep their interest on it for a longer period of time, while during infancy they get easily bored. It has to be noted that sustained attention still has many limitations at this age; in fact, only a 40% of correct target detection has been found during vigilance tasks at 2 years of age (Rueda & Conejero, 2020). With preschool years, children show a consistent improvement in vigilance: at 3 years old they are capable to re-focus attention on the task after a period of inattention, and one year after they can stay vigilant during the whole duration of the task. The development of sustained attention goes on till adolescence years and finally at 13 years old the performance of a teenager is comparable to the adults' one (Rueda & Conejero, 2020).

2.2.2 The orienting network

Like alertness, also orienting emerges during infancy, with infants showing a predisposition to orient their attention towards faces and moving stimuli, even before the third month of life; however, in this initial phase, the act of orienting relies completely on the characteristics of external stimulation (exogenous attention), and infants seem to struggle at disengaging attention from a central stimulus. In this initial period orienting is regulated by Superior Colliculus, a subcortical structure located in the midbrain, because the cortical pathway is still not mature (Rueda & Conejero, 2020). Some studies have shown that, during a Gap-Overlap task, infants of 1-2 months of age are really slow to disengage from the central stimulus in the overlap condition and many times they are not disengaging at all (Hendry et al., 2019). From the fourth month infants start to improve their disengagement abilities, being able to disengage easily in the overlap condition of a *Gap-Overlap task* (Hendry et al., 2019). By that time, it is possible to observe changes also at a neural level, with an initial increase in the involvement of FEF and parietal cortex during orienting tasks (Hendry et al., 2019); these modifications correspond with the development of a more endogenous control of Orienting and adults-like effects of orienting cues during *Posner spatial paradigm* (Rueda & Conejero, 2020). In the second half of the first year infants already exhibit a well-developed Orienting system, capable of voluntary orient attention towards interesting stimuli, disengage attention and re-fixate it, track a moving object, and covertly orient attention (Conte, 2020). Even if Orienting network emerges and develop rapidly during infancy, further improvements in performance are observable during preschool years, when children become faster, more accurate, and more efficient in redirecting attention. At this age they are also able to control orienting endogenously, indeed they start to be subject to the effect of central cues in the Posner paradigm (Rueda & Conejero, 2020).

2.2.3 The Executive control network

For what concerns Executive Attention, its development happens later if compared to the other subcomponents of attention; only after the 9th month it is possible to observe the ability to inhibit distractors and to flexibly adapt the behavioral response in the *A-not-B task*, which is a task that evaluates the capacity to inhibit prepotent response. However, these early executive abilities show up at a rudimental level and will better develop during toddlerhood; at this age it has been observed a better performance in more complex version of the A-not B task or in self-restrain tasks (i.e., not touching a toy they have been told not to touch) (Rueda & Conejero, 2020). In addition, toddlers are quicker and more accurate at tasks that induce spatial conflict between appearance of distractors and targeted position (Rueda & Conejero, 2020). The improvement in Executive Attention allows the emergence of self-regulation abilities, which, at this developmental stage, still need support from adults; the more toddlers grow up the more control behaviors will become self-initiated (Rueda & Conejero, 2020).

At a neural level, the Executive Control network continues to evolve significantly during childhood and following to adolescence; neuroimaging studies have found an increase in connectivity between ACC and AI, areas involved in the cinguloopercular network of Executive Attention, during childhood years. Children show a development of executive abilities also at a behavioral level: between 6 and 7 years old the conflict effect given by distractors in a *flanker task* diminishes and reaches adult performance levels (Rueda & Conejero, 2020). Finally, Executive Attention continue to improve in terms of efficiency till adolescence and up to early adulthood (Rueda & Conejero, 2020).

To sum up, attentional capacities emerge, at a basic level, very early during development; this allows the babies to have the proper instruments for the interaction with external environment and learning. While Alerting and Orienting develop faster during infancy, Executive Control emerges later, showing a great development during toddlerhood and continuing to evolve till adolescence and early adulthood.

2.2.4 Individual differences

The present paragraph addressed the topic of typical developmental trajectories of attentional capacity; to conclude this subject, the meaning of “typical” has to be explained. The concept of typicality in neurodevelopmental psychology is based on the idea that, even if there is variability, in the end, the process of the so-called typical development will lead to a functional and adaptive cognitive system. Typicality is strictly linked to the concept of normality, indeed the typical trajectories of attentional development presented above were studied on general population. It must be kept in mind, though, that individual differences exist even inside the range of what is defined as typical; every single baby will face a unique process of development (Rueda & Conejero, 2020) with unique patterns and timings. In the evaluation of attentional capacities in infants, toddlers, or children, it should be always considered that the level of maturation of attentional networks is not the same for every child at the same exact age. The sources of such individual differences can lay on internal factors, like genetic predispositions, child’s temperament, or on external factors meaning the environment in which a child grows, for example the Socio-Economic Status of the family or the quality of parenting (Rueda & Conejero, 2020). That said, having data about typical development allows to compare the attentional performance of a child with what would be expected for his/her age. In the clinical field it is fundamental to have the possibility to find out abnormalities in developmental trajectories in order to recognize and prevent a possible future adverse outcome; for this aim it is important to study developmental trajectories, to monitor development from early stages and to detect possible early markers of atypical development.

2.3 Why is attention a good early behavioral marker?

In chapter 1 it was underlined the importance of early markers as anticipatory signs of possible atypical neurodevelopment; it was said that it is important to monitor developmental trajectories from early infancy, in order to observe those basic cognitive processes that support the development of the cognitive system itself and to have the possibility to intervene with prevention programs directed at promoting typical development. Early markers can be found in those processes that underpin cognitive functioning, occur very early in development, and are associated with later, more complex, cognitive abilities. Attention is one of those processes, and it represents an especially good domain for the search of early markers.

There are three main reasons for which attention, and in particular visual attention abilities, results to be an efficient early behavioral marker (Valenza, 2019); first, as it was previously reported, attention emerges very early in development. Neonates show basic attentional capacities like alertness, selective attention for simple features (shape and colors), as well as the ability to orient attention (Valenza et al.1994; Farroni et al. 2002). Attention is one of the first means that neonate have to interact with the environment, collect useful information and learn from them (Valenza, 2019); for this reason, early vulnerabilities in the attention system, will have a huge impact on the development of many high-level cognitive and social abilities.

Second, the improvements in technology, allowed researchers to plan suitable methods to detect and measure of attentional behaviors even in the first months of life (Valenza, 2019). Eye Tracking (ET) is the most spread-used instrument in the study of early attention: it estimates the direction of gaze and track the eye movements over time comparing the position of the corneal reflection with the center of each eye's pupil (Conte, 2021). The assumption of using eye tracking for investigating visual attention in infancy, is that the baby will direct his/her look towards the image on a computer monitor which capture his/her attention with this instrument it is possible to measure looking behaviors, saccadic latencies, gaze durations, pupil dilatation and exploration strategies. A strength of this instrument is that it only requires the baby to be sitting in front of a computer, it is not an invasive technique, and it overcomes all the limitations associated with parents' questionnaires, (a more subjective measure) and cognitive tests (requires to give verbal instructions to the child). Furthermore, ET provides fine and precise measurement of abilities, allowing the detection of small individual differences in infants' performance;

this is particularly relevant in the study of early markers, because atypicality are not easily detectable during the first phases of development. However, there are also some weaknesses associated with ET, since to have accurate measures the sample size should be large , but data loss is quite common in developmental research (Ginnell et al., 2021). Finally, another reason that motivates the monitoring of attention capacities as early marker is that a large body of literature support the presence of dysfunctions in visual attention processes in many neurodevelopmental disorders (Valenza, 2019; Conte, 2021). For example, Autism Spectrum Disorders (ASD) has been found to be predicted by performance in early attention (Valenza, 2019; Hendry et al., 2019). Similarly reading difficulties at school have also been associated with early dysfunctionality in visuo-spatial attention (Franceschini et al., 2012).

For what concern the condition of prematurity, studies have reported that impaired attention may anticipate the more widespread cognitive delays reported in preterm population, predicting later academic attainment and later diagnosis of ADHD (Ginnell et al., 2021). Since many neurodevelopmental disorders are characterized by early attention impairments, attention should be targeted in prevention programs aimed at promoting typical neurodevelopment and at producing generalized benefits for the cognitive system (Conte, 2021).

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2.4 The impact of prematurity on attentional mechanisms

2.4.1 Attention in relation to Gestational Age

The above mentioned long-term cognitive and behavioral consequences associated with prematurity could have, as a common basis, an early disfunction in the attentional system (Ginnell et al., 2021); indeed, it has been found a body of evidence supporting the idea of a less optimal maturation of visual attention in children born preterm (De Schuymer, Groote, Desoete, & Roeyers, 2012). This sub-optimal attentional development could comport *cascade effects,* affecting cognitive functioning in later years. For this reason, some studies have investigated the early attentional development in preterm population; in the following pages I will report the existent knowledge about prematurity and visual attention development, focusing on those studies that involved attention orienting tasks, since this literature guided the hypothesis for the present study.

A recent review conducted by Ginnell and colleagues (2021) offers a complete overview of the findings about attentional development in preterm population; they framed the work on the network theory of attention proposed by Posner and Petersen (1990), and they included studies that measured alerting, orienting or executive attention abilities. The overall sample collected in the review comprised preterm groups and term-control groups, with wide range of ages from infancy to adulthood. Starting from alerting abilities, the review on eye tracking studies provides evidence of early impairments associated with prematurity, namely, poorer focused attention at 12 months for VPT and poorer alertness at 18 months in MLPT group; however, many studies fail to find significant differences between groups. For what concerns Executive Control, the majority of studies fail to find differences between preterm and full-term before the 2nd year of age, but this is probably due to the fact that before that age executive attention is still rudimental and all the groups, preterm and control, struggle in executive tasks. With childhood and adolescence, instead, it is common to observe difficulties in executive control associated with prematurity.

Talking about the Orienting network, different studies with eye tracking and observational measures found early disadvantages associated with prematurity; in general, those findings hint that preterm groups have a less mature orienting behavior and are slower in orienting attention (De Schuymer et al., 2012) . A metanalytic study conducted by Burstein, Zevin and Geva (2021) seems to confirm this view, finding a main effect that favors control in the variable *latency to fixate,* meaning that control groups tend to be more rapid in fixating a salient stimulus that appears on a screen. It is useful to remind that it is hard to find tasks that measure pure orienting capacities and there is disagreement in literature about terminology and interpretation of the same attentional subcomponent; keeping this in mind, I will now report in detail the studies that investigated visual orienting in infants and toddlers born preterm, which provided the theoretical basis for our experimental hypothesis.

2.4.2 Prematurity and early orienting of visual attention

a. Early and late infancy

The study by De Schuymer and colleagues (2012) was aimed at investigating if the orienting abilities in non-social context of infants born preterm were related with the early difficulties that they manifest in dyadic social interaction. The attentional performances of 20 preterm infants (GA between 28 and 34 weeks) were compared with those of 42 full-term infants (GA between 38 and 42 weeks); disengagement and shifting abilities were collected at 4 and 6 months of corrected age through a computerized task based on a *noncompetition/competition* paradigm (Frick, Colombo, & Saxon, 1999). This task consists in presenting a stimulus in the center of a screen accompanied by a sound to attract the infant attention, then presenting a peripheral stimulus either in the left or right side of the screen. The variable of interest was the latency to fixate the peripheral stimulus, which could appear in two conditions: in the *noncompetition* trials the central stimulus disappeared right before the peripheral stimulus appeared, while in the *competition* trials the central stimulus remained present. This paradigm is based on the same mechanism of the Gap-Overlap task, described in the previous chapter. The results they found showed a main effect of condition at 4 months, meaning that the 4-month-old infants were slower in the competition trials than in the noncompetition trials. Moreover, the statistical significance of the main effect of group revealed that preterm infants were significantly slower than the full-term controls in both conditions. From 4 to 6 months, it was observed a decrease in latencies, especially in the condition of competition, reflecting the maturation of orienting system that happens at that age. To note that, at 6 months Authors did not find any significant effect of condition nor of group, meaning that infants showed same latencies for noncompetition and competition trials and there was no difference between preterm and full-term groups. These results are interesting because they show how early in development it is already possible to observe effects on orienting of attention due to GA at birth. However, it is hard to draw general conclusion by this study since the small sample size , the inclusion of only very and moderate preterm and the absence of significant effect at 6 months.

Another study that investigated orienting of attention in infants born preterm was conducted by Ross-Sheehy, Perone, Macek and Eschman (2017) who ran a spatial cue task, called *Infants Orienting With Attention* (IOWA), to a sample of preterm and full-term infants. The sample was divided in two age groups, one at 5 months (corrected for preterm, who had mean GA of 33 weeks) and the other at 10 months (corrected for preterm, who had mean GA of 31 weeks). The task started with the presentation of a stimulus in the center of the screen, then a cue was presented and subsequently, the target stimulus appeared on the left or right side of the screen; to respect to the cue position trials could be valid or invalid, similarly to *Posner paradigm*. The results showed that preterm infants were significantly slower than controls at 5 months of age in all the task conditions, but no difference was found at 10 months. This result seems coherent with the one reported by De Schuymer and colleagues (2012). For what concerns accuracy, they found interestingly that preterm were more accurate then controls at 5 months but not at 10 months. Even if this finding might seem a contradicting result, it is important to consider that a certain amount of error in the invalid trials is indicative of an optimal sensitiveness to the cues. Considering that preterm showed to be slower in orienting attention, a lack of errors could be due to an incapacity to pre-orient attention rapidly to the cued side. The work of Ross-Sheehy and colleagues is useful to support the existence of early vulnerabilities in the development of the attentional orienting system associated with prematurity. However also this study shows some weaknesses as the wide age range of the sample forced in two age groups and the absence of a longitudinal design which makes difficult to draw general conclusions. Secondly, the authors do not consider the variety of gestational ages included in the preterm sample, so it is hard to say if the effect is only driven by subjects with very low GA. Finally, the method used to collect data does not benefit of fine measure recorded by eye tracking technology.

Altogether this evidence supports the presence of early impairments of orienting of attention associated with prematurity, but they do not say anything on what happens during late infancy and toddlerhood.

Two studies measured attentional capacities during late infancy, with preterm infants of 9 and 12 months. A first study by Hodel, Senich, Jokinen, Sasson, Morris, and Thomas (2017) was aimed at investigating early executive markers in a sample of MLPT. Using a battery of eye tracking and behavioral tasks it was assessed the executive control abilities at 9 months of age (corrected for preterm). One of these tasks consisted in the presentation of a peripheral target, without distractors or cues, and measuring the latency to fixate it, providing a measure of processing speed which influences orienting abilities and later executive function development. Authors found no significant difference between the preterm group and the controls; in addition, GA as a continuous variable was not associated with processing speed. In contrast, a work by Downes, Kelly, Day, Marlow, and de Haan (2018) found that preterm were significantly slower than full-term in fixating a target at 12 months of corrected age. It has to be said that neither of these two studies was aimed at measuring orienting of attention, but they provided a measure of disengagement which could be interpreted as the rapidness of the infants to orient their attention. To note that the study by Downes and colleagues had a small sample size of VPT and EPT and a large gap between groups in terms of GA, while in the study by Hodel et al. the preterm group comprised only MLPTs. Thus, it could be that early difficulties in orienting of attention are visible only for severe prematurity; however, data are still too scarce to draw conclusions.

b. Toddlerhood

The study by De Jong, Verhoeven, Hooge, and Van Baar (2015) is particularly relevant for the present dissertation, since provides data on visual orienting of attention in a group of MLPT (32 to 36 weeks of GA) toddlers at 18 months; to my knowledge, this is the only study on visual orienting of attention in toddlers, which includes Late Preterm in the sample. The study had a longitudinal design, with attention development monitored at 12, 18 and 24 months through parent reports, but only at 18 months the families went to the laboratory and eye tracking task was administered. The battery of *Utrecht Tasks of Attention in Toddlers using Eye tracking* (UTATE – De Jong, Verhoeven, Hooge, & Van Baar, 2016b) was used to assess the three attention networks of the Classical Model of Attention (Posner & Petersen, 1990). This battery comprised four tasks, from which they computed three general scores: Alerting, Orienting and Executive Attention. One of the tasks was specifically aimed to measure disengagement and it consisted in the presentation of a central stimulus and after 2 seconds a peripheral target appeared, while the central stimulus remained present; this task was basically the same as the *competition* condition used by De Schuymer and colleagues (2012) and the *overlap* condition in the Gap-Overlap paradigm. The variables of interest in the disengagement task, such as the latency to fixate the target and the proportion of correct disengagement, contributed to the Orienting score, a proxy of the well-functioning of Orienting system of attention. The results showed a significant difference, between preterm and controls, in Orienting scores, empirically supporting that even during toddlerhood and even with a group of MLPT it is possible to observe difference in the efficiency of Orienting system. Even if the development of orienting of attention happens early during the first half of the first year of life, during toddlerhood and childhood there are further developments in rapidity, accuracy, and efficiency of orienting; in addition, toddlerhood is a critical age for the development of endogenous control of attention (De Jong et al., 2015), and this can have consequences on the performance at a disengagement task.

To sum up, the literature that investigated early orienting of attention in preterm population shows that there is replicated evidence of impairments during early infancy, while for late infancy the evidence is contradicting. In addition, there is evidence of orienting deficits of attention during toddlerhood, but these results should be replicated before drawing conclusions. It must be kept in mind that the literature so far presented considered prematurity in a categorical way, trying to find difference between preterm and full-term; as it was discussed in the first chapter, this approach is based on the arbitrary cut-off within a measure that has a continuous nature (Fleischman et al, 2010). A study by De Jong, Verhoeven, Hooge, Maingay-Visser, Spanjerberg, and van Baar (2018) considered GA as a continuum (in a range between 32 and 41 weeks), analyzing its relationship with attentional abilities at 18 months and cognitive functioning at 24 months. They found that GA had a significant positive correlation with Orienting score at 18 months (same procedure of De Jong et al., 2015). In addition, attentional capacities at 18 months mediated the relationship between GA and cognitive functioning at 24 months, showing the power of GA of explaining attention development and later cognitive function, and supporting its use as a predictive factor.

The main aim of the present chapter was to support the choice of focusing on attention as an early marker of atypical development; in addition, it was provided evidence that prematurity and GA have an impact on early orienting abilities The next chapter will put together the topics faced so far, since the present work, which I will describe here, focus on the impact of GA on early attentional capacities.

3

THE EFFECT OF GESTATIONAL AGE ON VISUAL ATTENTION: AN EYE TRACKING STUDY

As it was extensively discussed in the previous pages, preterm birth is a condition that can have a substantial impact on neurodevelopment; the early interruption of pregnancy leads to an atypical neural development, and this increases the risk for long-term adverse outcomes in cognition and behavior. *Gestational Age* is a measure that allows to classify preterm birth for severity and is a good predictor of the short and long-term consequences that this condition can entail; very low GAs are generally associated with greater risks for development, but data show how even near-term GAs comport risks. In the present study we analyzed attentional capacities that, as it was argued in the previous chapter, represent a good early marker of atypical neurodevelopment, since differences in attention development may anticipate cognitive delays, learning difficulties and later diagnosis of ADHD (Ginnell et al., 2021). The main aim of my final dissertation was to provide empirical proof that it is possible to observe early differences in attentional performance depending on Gestational Age at birth; indeed, the study I will here report investigated the impact of GA on visual attention, in particular on orienting capacities, in a sample of late preterm and full-term toddlers.

3.1 The present study

3.1.1 Aims and hypothesis

The aim of this study was to analyze the efficiency of the visual orienting network through a Gap-Overlap task in a sample of toddlers born at different GAs. The present work will bring novelty to the existent literature for two reasons: first, in this study we overcame the limit of a categorical subdivision between preterm and full-term by considering GA as a continuous independent variable, as De Jong and colleagues (2018). Second, while previous studies included wider ranges of GA within the preterm group making it difficult to control the severity of prematurity, our study will focus especially on LPT population, a group for which the early development of attention has been scarcely studied.

The main objective of the present study was to investigate the impact of GA on the Gap-Overlap performance in a sample of toddlers; as we saw previously, toddlers begin to develop endogenous control over their attention, and this can have an impact on the execution of orienting tasks. We had two main hypotheses: first, we expected to replicate the so-called *gap effect*, namely we expected delayed attentional orientation in the overlap condition compared to the gap condition (Hood & Atkinson, 1993; Elsabbagh, Volein, Holmboe, Tucker, Csibra, Baron-Cohen, ... & Johnson, 2009; Cousijn, Hessels, Van der Stigchel, & Kemner, 2017; Hendry et al. 2019). Our second hypothesis, based on the literature discussed in the previous paragraph, was that GA would significantly influence the performance in the Gap-Overlap task; in particular, we expected that babies with lower GAs would show poorer performance in visual orienting of attention, in terms of rapidity and accuracy in target fixation.

3.1.2 Participants

The sample analyzed in the present study was part of a larger sample taken from the BEXAT study, a running project by the Developmental Cognitive Neuroscience Lab of the University of Granada; the BEXAT is a longitudinal study aimed at following the typical behavioral, cognitive, and neural development of attentional control capacities. Infants included in the BEXAT sample have been recruited through advertisement in health centers and maternity hospital of Granada, and they underwent laboratory session of data collection at 6, 9, 16 and 36 months of age. For my thesis, the sample was taken from the subjects who completed and had valid data in the Gap-Overlap task at 16 months; the sample of the present study is made of 35 Spanish toddlers (18 females and 17 males), with an average age at session of 16.77 months (SD= 1,71; range= 15,19 – 19,07 months, age corrected for prematurity). The mean GA of the sample was 38,78 weeks (SD= 2,02; range= 34,00 – 41,56 weeks), with 11 toddlers born at GA ≤ 37 complete weeks, 18 born between 38 and 40 weeks and 6 with GA> 40 weeks.

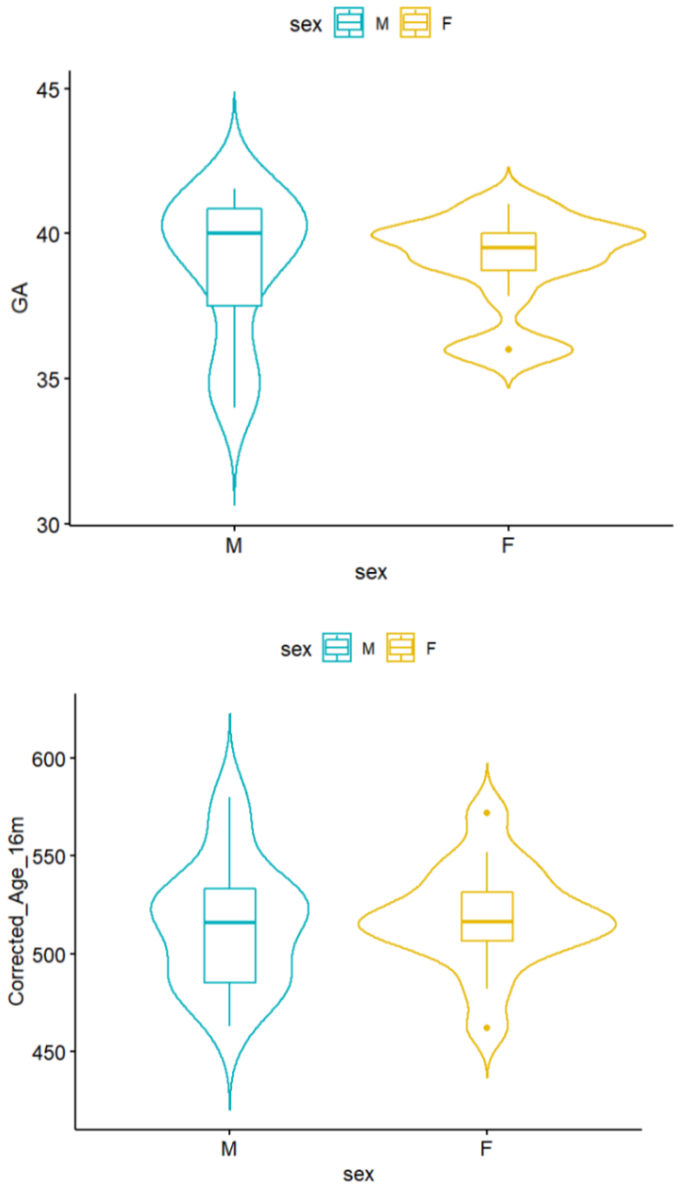


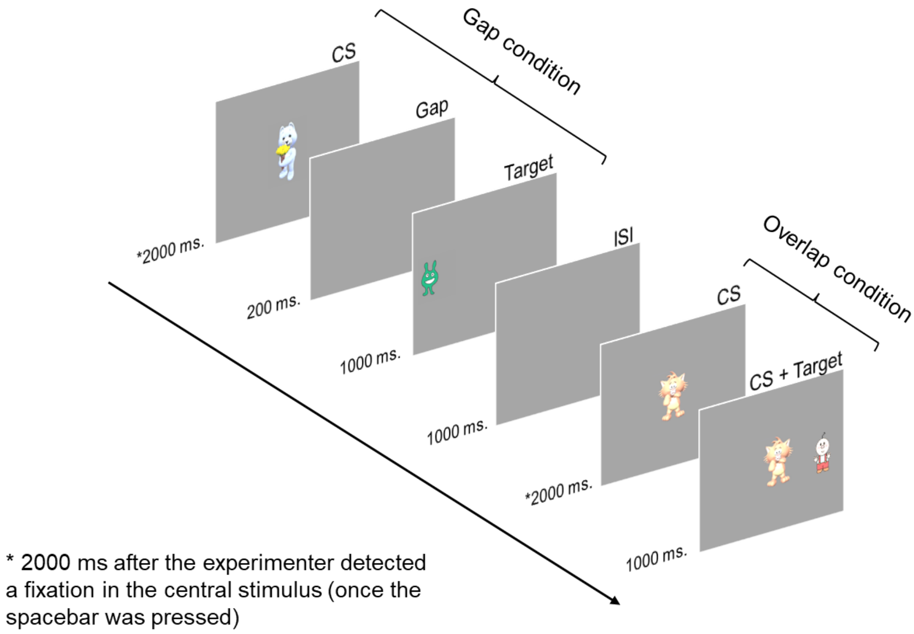
Figure 15. Violin and Boxplots of the corrected-age-at-session distribution split for sex. Lower and upper box boundaries 25th and 75th percentiles, respectively, line inside box median, lower and upper error lines 10th and 90th percentiles.

3.1.3 Task and procedure

The Gap–Overlap task was used to assess the visual orienting network. It is a disengagement task suitable for studying attention from infancy to adulthood (Cousijn et al., 2017). The Gap–Overlap paradigm, briefly described in the previous chapter, is aimed at measuring orienting abilities and its three mechanisms: the disengagement of attention from a central stimulus, the shifting of attention towards a peripheral target and the engagement of attention to the target stimulus (Hood & Atkinson, 1993). The paradigm generally includes a *gap condition*, where there is a temporal gap, typically of 200 ms, between the disappearance of the central stimulus and the appearance of the peripheral stimulus, and an *overlap condition*, in which the central stimulus remain present on the screen during the presentation of the peripheral stimulus (i.e. target; Hood & Atkinson, 1993; Elsabbagh et al., 2009; Cousijn et al., 2017). The gap condition implies an automatic disengagement (Hood & Atkinson, 1993), while in the overlap condition the disengagement is more difficult since there is competition between the two stimuli contemporary present on the screen. This results in a difference between the two conditions in terms of saccade latency, the *gap effect* (Cousijn et al., 2017), for which latencies are generally shorter in the gap condition. The gap effect is considered a measure of disengagement, because the cost associated with overlap condition is attributable to the time needed to disengage attention from the central stimulus (Hood & Atkinson, 1993; Cousijn et al., 2017). The gap effect decreases with age during infancy (Cousijn et al., 2017), since from the 4th month infants start to improve their disengagement abilities (Hendry et al., 2019; Rueda & Conejero, 2020), however the effect of condition in the Gap-overlap task remains present until adulthood (Hood & Atkinson, 1993).

The version of the Gap-overlap paradigm used in the present study was similar of those previously developed by Holmboe, Bonneville-Roussy, Csibra, and Johnson (2018). Families were received at the Developmental Cognitive Neuroscience Lab of the University of Granada; while parents filled out consent forms, the experimenters spent some time playing with toddlers in order to make them feel comfortable in the setting. Subsequently, one parent and the child entered in the eye-tracking room to start the task; the parent was asked to seat in front of a monitor keeping the child on their lap, and to avoid interaction with the child during the whole procedure. Experimenters controlled the task from an adjacent room, monitoring the child position and engagement on the task through a webcam. The administration of the Gap-overlap task was part of a session of data collection that comprised other two eye tracking tasks, two behavioral tasks and EEG recording. At the end of the session families received a 10 € voucher to spend at a toy store, as a reward for their participation at the session.

The Gap-Overlap task was composed of forty-eight trials, presented in a pseudo-randomized order, namely avoiding more than two consecutive trials of the same condition. Trials started with the presentation of an animated stimulus on the center of the screen (10.31º x 10.31º). Once the experimenter observed a fixation on the stimulus, a key was pressed to continue with the trial. Two experimental conditions were manipulated: in overlap conditions, the central stimulus remained on screen during the presentation of an animated peripheral target (6.76º x 6.76º); in the gap conditions the central stimulus disappeared from screen, and a 200 ms gap interval was introduced before the onset of the peripheral target. Peripheral targets were presented on the left or right side (13.11° of eccentricity to the nearest edge of the stimulus) of the screen for 1000 ms.



(CS = Central stimulus. ISI = Interstimulus interval.)

Figure 16. Illustration of the Gap-Overlap procedure

In order to validate the trial, it was required that the participant looked at the central stimulus during the last 200 ms before the peripheral target presentation, otherwise the trial was considered invalid and removed from further analyses. The participants included in the analyses had achieved a minimum of four valid trials in each experimental condition and did not experienced family interference during task administration.

3.1.4 Stimuli

Central and peripheral stimuli were randomly chosen from a pool of 74 and 6 stimuli for central and peripheral stimulus, respectively. Both central and peripheral stimuli were dynamic: central stimuli were representing three-dimensional animated animals' cartoons, while peripheral stimuli were bi-dimensional drawings moving sideways. Two

16.34º x 20.47º areas of interest (AOIs) were created for the peripheral targets, while a 15.4º x 20.47º AOI was generated for the central stimulus.

3.1.5 Apparatus

Gaze was recorded using the remote mode of an EyeLink 1000 Plus (SR Research, Ontario, CA) corneal-reflection eye-tracker with a sampling rate of 500Hz and 0.01º of spatial resolution. A 16mm lens attachment and an 890 nm illuminator were used for this purpose. Stimuli were presented with Experiment Builder software (SR Research) in a LG 24M37H-B 24-inch LED monitor with a native resolution of 1920 x 1080 pixels (52 x 30 cm). A five-calibration points child-friendly procedure was initiated previously to stimulus presentation, using animated colorful shapes (1.97º x 1.97º of visual angle) accompanied with melodic sounds. Calibration points were manually presented in the corners and center of the screen and were repeated until a satisfactory calibration result was determined by the experimenter. Raw gaze data through sample report for each participant was extracted using Data Viewer (SR Research).

3.1.6 Statistical Analysis

a. Dependent variables

To evaluate attentional performance in the Gap-Overlap task we used two dependent variables:
Saccade latency. Defined, as the duration of the temporal gap between the occurrence of the peripheral target and the first saccade which reached the area of interest of the target.
Disengagement failure. Defined as the number of trials in which the participant never disengages from the center of the screen for the whole duration of the trial (*remaining fixed response* – Nakagawa & Sukigara, 2013).

b. Data analysis

The entire process of raw data filtering, cleaning and processing has been conducted with the software R (R Core Team, 2020) using generalized additive mixed-effects models (GAMMs) with the mgcv package (version 1.8-38, Wood , 2015). Specifically, to test the interaction between GA and Gap-Overlap performance it was used an extension of typical regression methods, the Generalized Additive Mixed effects Model (GAMM – Lin &

Zangh, 1999; van Rij, Hendriks, van Rijn, Baayen, & Wood, 2019). This method is an extension of linear regression techniques, which models the relation between dependent variable and factors as a smooth function, not necessarily a linear function (van Rij et al., 2019). The output of the model has to be explored visually, interpreting the effect of independent variables over dependent variable reading the estimated regression line (van Rij et al., 2019). Our choice for the analysis was driven first by the willingness to consider GA as a continuous variable and overcome the limitations of a group difference analysis (typically performed with ANOVA). Second, we decided to use GAMM because literature brought some evidence of a non-linear relation between attentional capacities and GA (Eryigit-Madzwamuse & Wolke, 2015), so we did not want to force our data a priori as a linear regression model would have asked. Finally, using GAMM, we could process data for each single trial, increasing the statistical power of our results, considering inter- and intra-individual variability, and controlling for random effects.

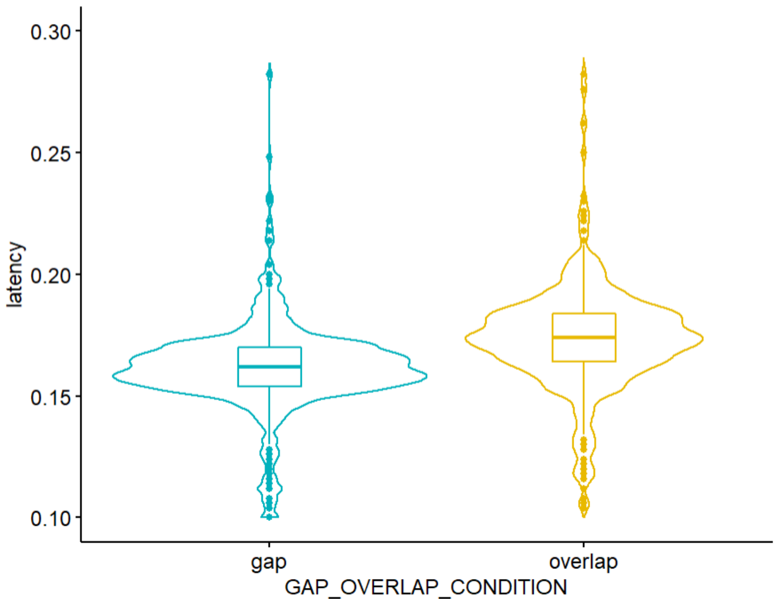
Two analyses were run, respectively for saccade latency and disengagement failure, to investigate if the interaction between GA and Gap-Overlap manipulation would result to be the best predictor of data. In both cases, to evaluate the goodness of the output model, it has been compared with a null-model which did not include as factor the Gap-Overlap manipulation. For *model selection* (Wagenmakers & Farrell, 2004), namely the choice of the model that approximate reality at best, we looked at *residual deviance* and at two transformations of the *Aikake Information Criterion* (AIC - Aikake, 1998), the *delta AIC* and the *AIC weight*. What we search for is the model which can be the most accurate in representing reality, while using the minimum number of factors to explain it (Wagenmakers & Farrell, 2004); for this aim, the best model should have the lower residual deviance, the lower AIC (pointed out by a null dAIC) and the higher AIC weight.

3.1.7 Results

A descriptive report of sample characteristics and task performance is shown in Table 2. For a visual representation of how the Gap-Overlap manipulation affected outcomes of saccade latency and disengagement failure see Figure 16 and 17. From both means and visual distribution, it is possible to observe a difference in attentional performance depending on the condition of the task.

Demographic	
Sample dimension	35
Gender (% female)	51,4
Age at session (months)	16,77 (1,71)
Birthweight (g)	3.095,80 (559)
GA (weeks)	38,78 (2,02)
Gap-overlap performance	
Gap saccade latency (ms)	221
Gap disengagement failure (%)	2
Overlap saccade latency (ms)	455
Overlap disengagement failure (%)	15

Table 2. Demographic characteristics of the sample and descriptive report of the Gap-overlap performance (Means and Standard Deviations)



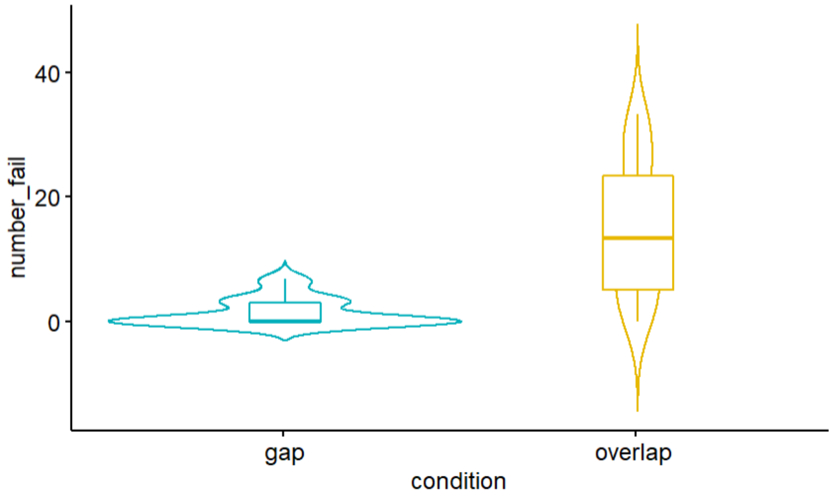


Figure 16. Violin and Boxplots of saccade latency (in seconds) and disengagement failure distribution, split for condition (Gap vs Overlap). Lower and upper box boundaries 25th and 75th percentiles, respectively, line inside box median, lower and upper error lines 10th and 90th percentiles.

a. Saccade Latency

Table 3 illustrate a report of the two models that were ran and compared for the dependent variable *saccade latency.* It is possible to observe that the experimental-model (1) results to be the best fitting for our data, since it has the lower residual deviance, the lower AIC (pointed by the null dAIC) and the higher AIC weight. This means that data are explained at best by the interaction between GA and the Gap-Overlap manipulation.

	Model	**Residual Dev.**	**dAIC**	**AIC weight**
0	Saccade latency – +(GA, BW, Age, subject ID)	17.469,78	355,1	0
1	Saccade latency – gap/overlap condition +(GA, BW, Age, subject ID)	17.468,68	0	1

Table 3. Models' comparison for saccade latency

The selected model, analyzing our data trial by trial (923 trials included, 507 gap and 416 overlap), estimated the following effects:

- A significant mean effect of condition (b = 0.08, SE= 0.016, t= 5.05, p<0.0001), with the Overlap condition predicting longer saccade latencies compared to the Gap condition (Figure 18).

- A significant interaction between GA and Gap-Overlap manipulation, which is visible in the two non-linear trends reported in Figure 19. The GAs < 37 weeks show overall higher latencies and no clear effect of condition, with an overlapping of the gap and overlap trends. In contrast, GAs between 37 and 40 weeks show a clear difference between gap and overlap latencies, an effect that seems to be driven especially by the higher rapidity in the gap condition. For what concerns GAs > 40 weeks, the overlap-gap distance is less marked, and the trend show a slight increase in latencies for both conditions.

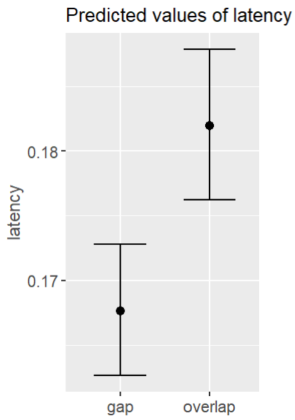


Figure 18. Estimated mean effect of condition for saccade latency

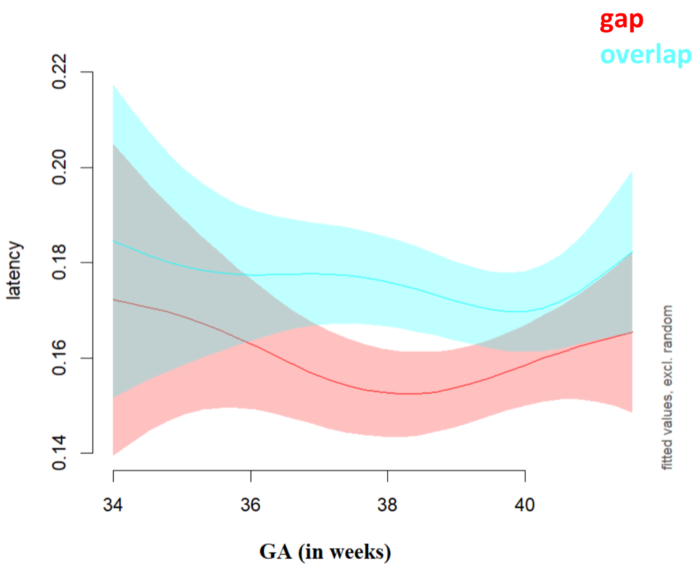


Figure 19. Interaction between GA and Gap-Overlap condition predicting saccade latency.

b. Disengagement Failure

.We conducted first the procedure of model selection. In Table 4 is reported a synthesis of the two models ran. As for saccade latency, the experimental-model (1) results to be the best fitting for our data. This means that variability in disengagement failure is explained at best by the interaction between GA and the Gap-Overlap manipulation.

	Model	Residual Dev.	dAIC	AIC weight
0	Dis. Failure – +(GA, BW, Age, subject ID)	40,1	8,4	0,01
1	Dis. failure – gap/overlap condition +(GA, BW, Age, subject ID)	40,9	0	0,99

Table 4. Models' comparison for disengagement failure

The selected model estimated two different trends based on task condition: during the gap condition we observed that higher GAs predict lower disengagement failure following a linear decreasing trend. In contrast, during the overlap condition the estimated effect shows that higher GAs are associated with higher disengagement failure, in a linear increasing trend.

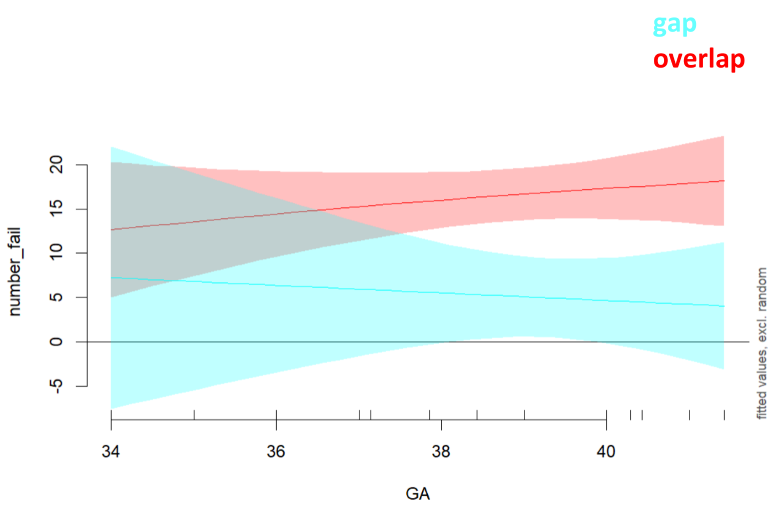


Figure 19. Interaction between GA and Gap-Overlap condition predicting disengagement failure

3.1.8 Discussion

We expected to replicate the *gap effect, a* widely reproduced effect which shows how latencies are lower in the gap condition if compared with overlap condition (Hood & Atkinson, 1993; Elsabbagh, Volein, Holmboe, Tucker, Csibra, Baron-Cohen, ... & Johnson, 2009; Holmboe et al., 2018). The analysis of saccade latency confirmed a significant effect of condition supporting our expectations. Thus, our results are in line with the existent literature of gap-overlap studies, validating our experimental paradigm and giving support to the interpretation of our data in terms of visual orienting of attention and disengagement. For what concerns the variable disengagement failure, overall, the number of failures was quite low, a result that we expected since toddlers should be capable to disengage attention properly (Hendry et al., 2019; Rueda & Conejero, 2020). Despite that, we observed that for the overlap condition the mean number of failures was higher than for the gap condition, suggesting that this variable is also sensitive to task condition.

The main aim of this study was to investigate the impact of GA on Gap-Overlap performance; the results pointed out, for both the variables examined (i.e. saccade latencies and disengagement failures) that the interaction between GA and task condition was the best predictor of data, confirming our prevision that GA has an impact on the efficiency of the visual orienting of attention even in toddlers. Indeed, we found that in toddlers with a GAs between 34 and 37 there was no significant difference between the gap and the overlap condition, while the gap-effect became wider and significant for GAs between 37 and 40 weeks. If we consider only the variation of the gap effect, we could interpret this finding assuming that lower GAs are associated with better disengagement abilities, since a decrease in the gap effect is associated with maturation of the orienting system of attention (Hood & Atkinson, 1993; Cousijn et al., 2017; Hendry et al., 2019). However, it is interesting to notice that the variability in the magnitude of gap between the overlap and the gap condition is mainly derived by the performance in gap condition. Indeed, while the latencies in the overlap condition remained quite stable through the whole spectrum of GAs, latencies in gap were clearly higher for GAs below 37 weeks and over 40. The higher saccade latencies observed for both the condition (gap and overlap) suggest that toddlers with lower GAs do not benefit of the automatic disengagement induced by the gap condition. This pattern of data suggests that that the optimal performance, in terms of saccade latency in a Gap-overlap task, was associated with the range of GAs between the 37 and 40 weeks. The results here presented confirmed our hypothesis that being born at lower GAs increases the probability of suboptimal abilities in terms of rapidity to orient visual attention, in line with the findings of previous studies (De Jong et al., 2015; De Jong et al., 2018; Downes et al., 2018); in addition our data suggests that different rate of disengagement efficiency can be observed even for late preterm toddlers, a population that was scarcely investigated in the existent literature about early orienting capacities (Ginnell et al., 2021).

Regarding the impact of the GA and the task condition on disengagement failures, the result is challenging to interpret; we observed that higher GAs are associated with a better performance (i.e., lower number of failures to disengage) in the gap condition, supporting the results found for the saccade latency. However, in the overlap condition higher GAs are associated with a worst performance (i.e., a higher number of failures), an unexpected result. So, putting together the two conditions, we found that higher GAs are associated with lower disengagement failure in the gap and higher disengagement failure in the overlap, as well as with a wider overlap-gap difference in performance. This pattern of results is in line with an interesting work by Nakagawa and Sukigara (2013) who found that a worst performance (in terms of higher latencies to disengage) in the overlap condition at 18 and 24 months was associated with higher *Effortful Control*; this temperamental trait indicates the ability to inhibit a dominant response, detect errors, perform planned behaviors, basically showing a good executive control (Rothbart, Ellis, Rueda, & Posner, 2003). The result they found was specific for this range of ages, suggesting that the developmental change in executive control abilities, which takes place during toddlerhood, might have an influence on how the Gap-Overlap task is performed; since toddlers become more able to endogenously control their attention, it could be plausible that they decide to keep the focus on the central stimulus and inhibit the peripheral target. If this is the case, our results may be interpretated as higher GAs showing better executive abilities and endogenous control of attention, because they tend to remain more focused on the central stimulus. This could mean that lower GAs, which shows higher failures in the gap condition and lower failures in the overlap, are less able to control their attention endogenously, maybe as a result of a maturational delay in attention development, but this interpretation should be verified with a longitudinal analysis.

To sum up, the findings of the present work support the idea that gestational age at birth is a good predictor of attentional visual orienting during toddlerhood, with lower GAs showing the worst performance in terms of rapidity in orienting and endogenous control of attention.

CONCLUSION

With the present work, I intended to explore the issue of early markers of the cognitive outcomes associated with prematurity. The study that we conducted pursued this aim by analyzing the impact of gestational age on attentional visual orienting during toddlerhood; the results we found supported our hypothesis that gestational age, or in other words the length of pregnancy, can be a key factor in determining early attentional development. It is important to address some limitations of the present study, which should be reminded before generalizing the results. First, the size of the sample we included in the analysis was limited, making it hard to generalize to the entire population; to compensate this limitation and to give more statistical power to our findings we decided to conduct a trial-by-trial analysis making the outcome effects more trustable. A second limitation concerning the sample is that the distribution across GAs was not homogeneous, with most subjects belonging to the range between 38 and 40 weeks of GA; this different distribution of the sample could have in part influenced the trends of our results. Talking about the stimuli used in the Gap-Overlap task, a possible limitation could be that the central and the peripheral stimuli had different levels of attractiveness, with the central ones being catchier since they were bigger and moving. This bias could have influenced the performance during the task, making it even harder to disengage attention from the center in the overlap condition.

The literature that studied outcomes associated with prematurity provide strong and replicated evidence that an early interruption of prenatal growth is associated with long-term and long-lasting consequences for the cognitive system. Despite this established knowledge, research on early markers of atypical neurodevelopment is still too scarce, especially for the population of late preterm which represents the vast majority of preterm births. Future works addressing the topic of prematurity should focus on early attentional development, since attentional capacities built the basis for the development of more complex cognitive functions. Furthermore, future studies should use a longitudinal design in order to provide a better understanding of developmental trajectories in the early life of preterm; in addition, longitudinal studies should also focus on finding trustable methods to promote the development of a well-functioning cognitive system, thus supporting better life quality for preterm population and their families.

APPENDIX

Central stimuli

Peripheral targets

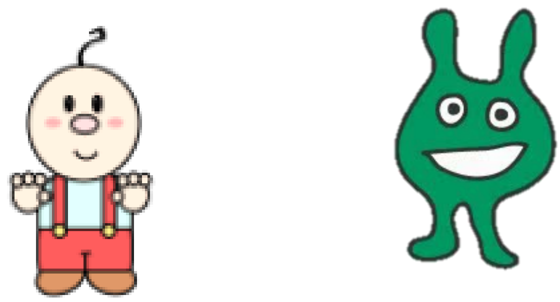


Figure A.1 – Examples of the stimuli used in the Gap-Overlap task

MODEL ESTIMATES

```
Family: gaussian
Link function: identity

Formula:
latency ~ GAP_OVERLAP_CONDITION + s(GA, by = GAP_OVERLAP_CONDITION,
    k = 13) + s(GA, by = BW, k = 13) + s(GA, by = SIDE_CONDITION,
    k = 13) + s(GA, id, bs = "fs", m = 1)

Parametric coefficients:
                             Estimate Std. Error t value
(Intercept)                  0.192345   0.014665  13.116
GAP_OVERLAP_CONDITIONoverlap 0.014392   0.003047   4.724
                                          Pr(>|t|)
(Intercept)                  < 0.0000000000000002 ***
GAP_OVERLAP_CONDITIONoverlap           0.00000271 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Approximate significance of smooth terms:
                                       edf      Ref.df     F
s(GA):GAP_OVERLAP_CONDITIONgap     1.00001818  1.00003454 1.293
s(GA):GAP_OVERLAP_CONDITIONoverlap 1.00002897  1.00005581 0.865
s(GA):BW                           2.82341910  3.13925034 1.420
s(GA):SIDE_CONDITIONleft           0.00001685  0.00003248 0.046
s(GA):SIDE_CONDITIONright          1.00000748  1.00001434 0.338
s(GA,id)                           7.70564014 27.00000000 0.515
                                   p-value
s(GA):GAP_OVERLAP_CONDITIONgap       0.256
s(GA):GAP_OVERLAP_CONDITIONoverlap   0.353
s(GA):BW                             0.206
s(GA):SIDE_CONDITIONleft             0.999
s(GA):SIDE_CONDITIONright            0.561
s(GA,id)                             0.011 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Rank: 332/333
R-sq.(adj) =  0.0458   Deviance explained = 6.18%
fREML = -1436.5  Scale est. = 0.0019549  n = 868
```

Figure A.2 Additional details about the selected model for Saccade latency

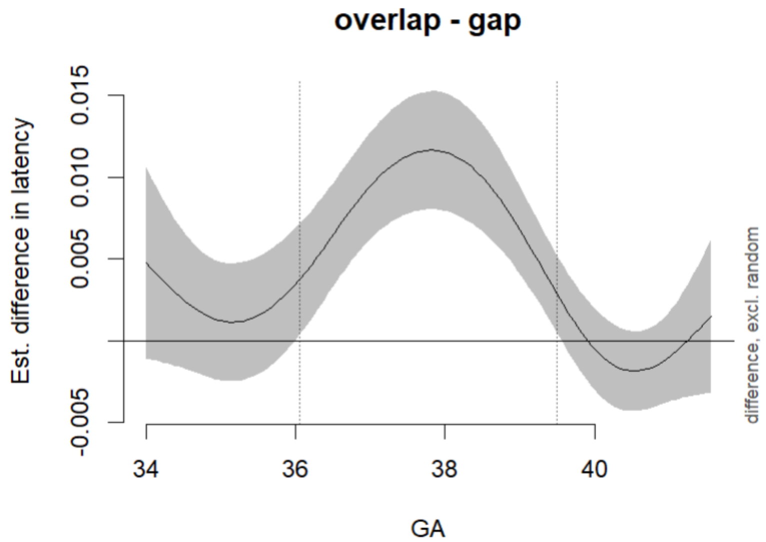


Figure A.3 – The estimated Gap effect changing through the spectrum of GAs

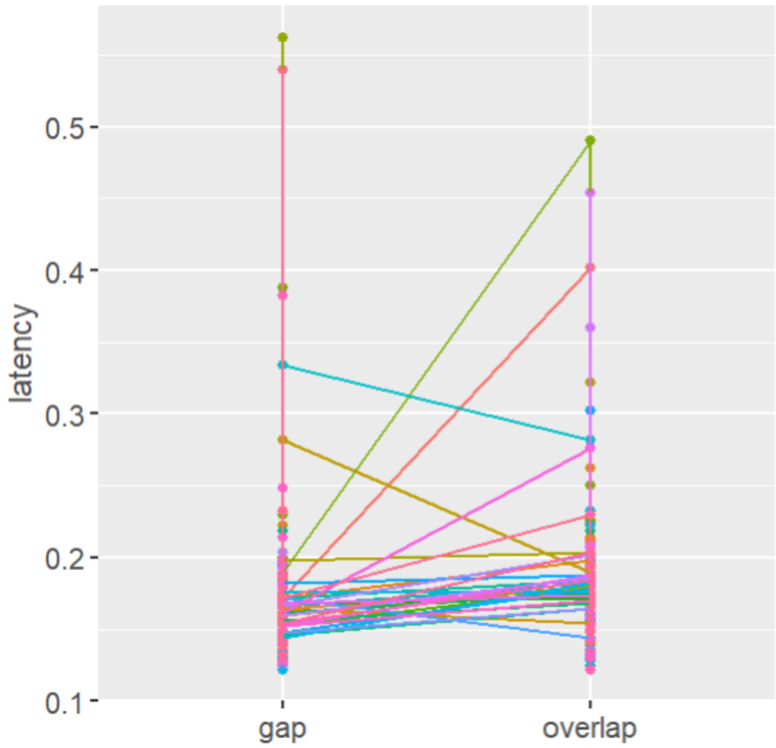


Figure A.4 – Saccade latencies represented for each subject (dots stand for each trial and colored lines connect the same subject across conditions)

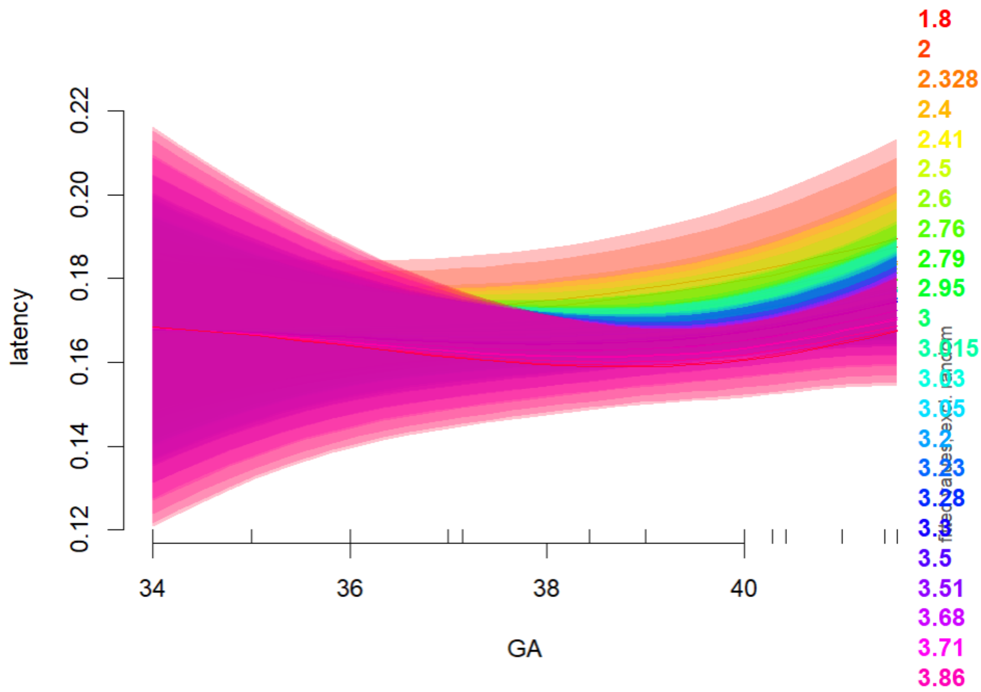


Figure A.5 – Estimated trend of saccade latencies through GAs' spectrum, smoothed for birthweight.

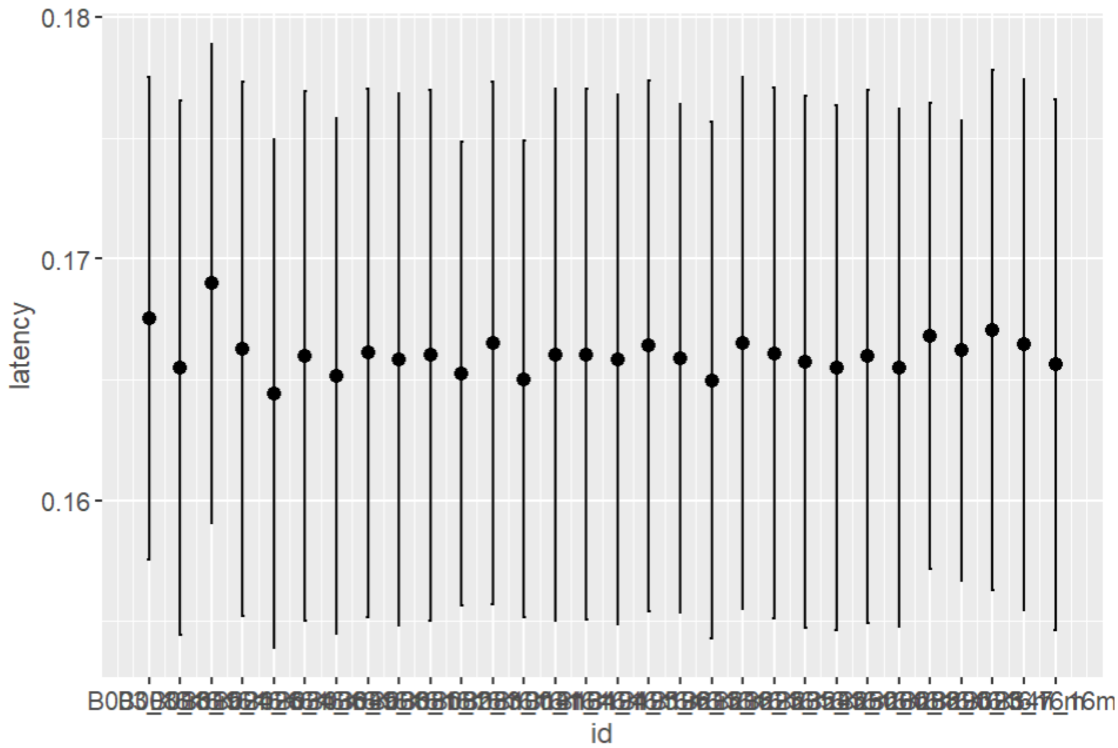


Figure A.6 – Predicted values of saccade latencies estimated for each subject

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