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UNIVERSITÉ PARIS DESCARTES

ÉCOLE DOCTORALE « COGNITION, COMPORTEMENTS, CONDUITES HUMAINES »

DOCTORAL THESIS

Visual-manual development in low risk preterm born infants

Maja Petkovic

Paris, june 2016.

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Supervisor: Jacqueline Fagard, PhD

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Acknowledgments

To my family....for not questioning my reasons.

To my friends...for listening me when it was hard.

To my mentor...for her patience and guidance.

To my colleagues...for time to come back to work.

To my families and children...for waiting for me.

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Chapter 1

Preterm birth

1.1. Definition of preterm birth

The World Health Organization (WHO) defines preterm infants as those born before 37 weeks of completed pregnancy (WHO, 1977). Every year an estimated 15 million infants are born preterm (from range of 5% - 18% in different countries). Based on the gestational age, preterm birth is divided into several sub-categories:

- extremely preterm (<28 weeks)
- very preterm (28 to <32 weeks)
- moderate to late preterm (32 to <37 weeks).

80% of preterm births occurs between the 32-37 weeks of gestation. About 10% preterm births are from 28 to 32 weeks and 10% under 28 weeks. Preterm birth can be seen as a syndrome with variety of causes which can be classified into two general subtypes: spontaneous preterm birth and induced delivery (Goldenberg et al., 2012). Risk factors for both of the categories are presented in Table 1.

Subtype	Risk factors	Examples
Spontaneous preterm birth	age at pregnancy	adolescent pregnancy advanced maternal age
	multiple pregnancy	
	infection	urinary infections, hiv
	maternal chronic medical conditions	diabetes, hypertension, anemia
	nutritional	obesity, micronutrient deficiencies
	lifestyle work related	smoking, alcohol consumption
	maternal psychological health	depression
	genetic and other	family history, genetic risk
Induced delivery	medical induction or caesarean birth for obstetric indication and fetal condition	pre-eclampsia, placental abruption, uterine rupture, fetal growth restriction,
	other – not medically indicated	

Table 1: Types of preterm birth and risk factors

In almost all high- and middle-income countries of the world, preterm birth is the leading cause of child death under the age of 5 years (Liu et al., 2012). The complications of preterm birth arise from immature organ systems that are not yet prepared to support life in the extrauterine environment. Some of the complications following premature birth affect: **respiratory system** (respiratory distress syndrome (RDS) – seen in 80% of infants born before 27 weeks of gestation), **cardiovascular system** (patent ductus arteriosus – seen in 5% of low birth weight infants), **visual system** (retinopathy of prematurity (ROP) – seen in 16 – 84% of infants born with gestational ages of less than 28 weeks); **central nervous system (CNS)** (CNS injury –interventricular haemorrhage (IVH) – bleeding in the germinal matrix system under lateral ventricles and periventricular leucomalacia (PVL) – seen in 74% of children with cerebral palsy). CNS injuries are today considered to be one of the important factors in development of neurodevelopmental disorders in preterm children, and are often related to degree of prematurity (Volpe, 2009).

In the past decades, great improvements have been made in the quality of services in neonatal intensive care units, resulting in increasing rates of survival of infants born preterm (De Weijer-Bergsma, Wijnroks & Jongman, 2008). According to Moster and colleagues (Moster, Lie & Markestad, 2008), the risks of disabilities in adulthood increase with decreasing gestational age at birth.

Extremely and very preterm born infants are under greater risk for development of neurodevelopmental disorder than moderate and late preterm born infants. One of the possible reasons for this is the immaturity of the central nervous system which is very sensitive to disturbances in blood circulation during labor, causing hypoxia and often intraventricular haemorrhage (IVH) (Pitchford, Hagger & Marlow, 2002). One of the most common **motor disorders** in extreme (80 per 1,000 live births) and very preterm birth (54 per 1,000) is cerebral palsy. It was also found that extremely preterm born school age children, with no neurological abnormalities, had developmental coordination disorder with significantly lower results on visual processing and praxis tests in 30-50% of cases (Goyen, Lui & Humell, 2011). Similar results were found in some other studies (Goyen, Lui & Woods, 1998). Along with motor functioning, it has been found that extremely preterm and very preterm birth has an effect on **cognitive abilities**. Marlow and colleagues (2005) found that 21% of children born extremely preterm had intellectual disabilities at the age of 6 years. It was also found that gestational age and birth weight were directly proportional to the mean cognitive test scores (Salt & Redshaw, 2006). **Executive function** (EF) skills underlying cognitive and adaptive functioning assessed at 8 to 9 years of age in extremely and very preterm born children,

showed a significant global deficit with significantly lower results on visual-spatial reasoning attention and working memory and processing speed compared with their matched, normal birth weight peers (Anderson, Doyle & Victorian Infant Collaborative Study Group, 2004). In **speech and language development** results of the follow-up studies showed that vocabulary and receptive language functions were within the normal range, but mean length of utterance and more complex language skills such as verbal reasoning and understanding of syntax were deficient (Briscoe, Gathercole & Marlow, 1998). Unfortunately, based on the results of follow-up studies, the prevalence of developmental disabilities in extremely and very preterm born children is high although they constitute only 10% of preterm population.

Late and moderate preterm born infants, on the other hand, comprise of 80% of all preterm births and their number has been increasing at a greater rate than all other preterm birth subgroups over the last two decades (Morag et al., 2013). In one study, a cohort born at 32-34 weeks achieved lower scores on **tests of intelligence, visuoperception, visuomotor integration, receptive language, working memory, and sustained attention** (Caravale et al., 2005) at age 3. By age 5, language delays resolved but visuomotor and visuoperceptual competence remained poor (Caravale et al., 2011). Late preterm born infants showed more *subtle* differences than moderate preterm infants when compared to full-term infants in terms of lower scores, not reaching significance in executive function (Baron et al., 2009), attention (Linnet et al., 2006), language (Nepomnyaschy et al., 2011), visuomotor and visuospatial functions (Baron et al., 2009). Some studies stress the need for the distinction between late and moderate preterm infants based on the results from school outcomes (van Baar et al., 2009). Comparison of academic performances between late and moderate preterm children and term groups at kindergarten through fifth grade found differences between moderate and late preterm group. Late preterm group had lower scores in reading only in first grade, while moderate preterm group had lower results in reading and math across all grades comparing to their full-term peers. In addition, moderate preterm group had, across all grades, higher percentage of requirement for individualized educational plan (IEP) and special educational services than late preterm group (Chyi et al., 2008). Taken together, this growing literature suggests that late and moderate preterm children experience **specific cognitive deficits** and exhibit behavioral problems when they are in preschool and school period. These specific cognitive deficits have been detected in area of *visual-motor integration, explicit and auditory memory and attention*, contrary to moderate to severe neuropsychological impairments seen in very or extremely preterm birth (Baron et al., 2012). But what raises a concern is the presence of these subtle weaknesses evident in children from these two sub-groups (late and

moderate) with no history of perinatal complications, and no high risk factors such as brain abnormalities.

The possibility of detecting a specific cognitive deficit, even in these preterm infants free of brain abnormalities, may add information on the effect of the “prematurity” per se on their neuropsychological performance and the need for long-term follow-up. In the following section, we will review the studies concerning specifically those preterm infants who seemed free of brain abnormalities at birth, also referred to as “low risk” preterm infants. Even though these infants are more often found among the late and moderate preterms than among the very and extremely preterm infants, the definition does not refer to a specific degree of prematurity.

1.2. Low risk preterm born infants

Low risk preterm born infants are classified as infants with no indication of visual or hearing impairment, normal neuropediatric examination suggesting a lack of major cerebral damage (e.g. periventricular leukomalacia, intraventricular haemorrhage level III and level IV, hydrocephalus, retinopathy of prematurity) and no congenital malformations established by MRI and/or by cranial ultrasound (Gonzalez-Gomez & Nazzi, 2012). In different studies on preterm infants, low risk preterm infants can be found in late (Mouradian, Als & Coste, 2000) and moderate subgroups (Gonzalez-Gomez & Nazzi, 2012) and in some cases in very preterm group (Scher et al., 1997; Ricci et al., 2008; Mercuri et al., 2012). Some authors use the term “healthy” to refer to low risk preterm born infants (Gonzalez-Gomez & Nazzi, 2012; Nan et al., 2013). These “healthy” preterm infants, due to absence of neurological abnormalities, are in lower risk for developing developmental disorder than preterms with evident brain damage. Still, these infants have an increased risk of altered developmental trajectories than full-terms. Therefore, in the following text, the term low risk preterm infant is used as being more appropriate than “healthy”.

Although classified as low risk preterm, there is a growing body of cross-sectional and longitudinal research showing that even they have poorer intellectual and neuropsychological performance than full-term children (Sansavini, Rizzardi, Alessandroni & Giovanelli, 1996; Vicari, Caravale, Carlesimo, Casadei & Allemand, 2004; Linnet et al., 2006; Baron, Ahronovich, Erickson, Gidley & Litman, 2009; Sansavini et al., 2010; Sansavini et al., 2011; Caravale, Mirante, Vagnoni & Vicari, 2012; Gonzalez-Gomez & Nazzi, 2012;

Nepomnyaschy, Hegyi, Ostfeld & Reichman, 2012; Sansavini et al., 2014). A mildly negative impact of low risk preterm birth has been reported in intelligence (Baron, Erickson et al. 2011), executive function (Baron et al. 2009; Baron, Kerns et al. 2011), attention (Huddy, et al. 2001; Linnet et al., 2012; Talge et al. 2010), language (Caravale et al., 2005; Nepomnyaschy et al., 2011), visuomotor and visuospatial function (Baron et al., 2009; Caravale et al., 2011) and overall academic achievement (Morse et al., 2009; Nepomnyaschy, et al., 2011).

Visual-manual coordination has been well studied in low risk preterm infants, both in preschool and in school-age period (Luoma, Herrgard, Martikainen & Ahonen, 1998; Baron et al., 2009; Crowe, Deitz, Bennett & TeKolste, 1988; Herrgard, Luoma, Tuppurainen, Karjalainen & Martikainen, 1993; Foreman & Fielder, 1997; Goyen, Lui & Woods, 1998; Caravale, Tozzi, Albino & Vicari, 2005; Goyen et al., 2008; Schneider et al., 2008; Geldof, van Wassenaeer, de Kieviet, Kok & Oosterlaan, 2012). For instance, Baron and colleagues (2011) observed deficits in 3-year-old preterm infants on visual-spatial manual tasks (block construction, puzzle assembly) and executive functions, but not on pure dexterity. In addition, it was found that there are more non-right-handers (NRH) and more non-lateralized children among children born preterm compared to their full-term peers (Fox, 1985; Rose & Feldman, 1987; Marlow, Roberts & Cooke, 1989; Schafer, Lacadie & Vohr, 2009; Soria-Pastor et al., 2009; Domellöf, Johansson & Rönnqvist, 2011).). Even at the age of 8, preterm born children were still more often mixed-handed than same-age full-term born children (Ross, Auld, Tesman & Nass, 1992). Low risk preterm infants have also been found to have significantly lower performance on paper-and-pencil components of the Visual-Motor Integration Test (Beery & Buktenica, 1997), component used extensively in school entry process. *How the visual-manual coordination deficits observed in low risk preterm children during preschool time arise remains conjectural.* One aspect of coordination never investigated in preterm infants, to our knowledge, is bimanual coordination. Contrary to unimanual grasping of objects, manipulation is often bimanual. Bimanual coordination of complementary movements requires a fully functioning corpus callosum (Preilowski, 1972; Fagard & Corroyer, 2003), and white matter structure seems to be affected by preterm birth (Braddick & Atkinson, 2013; Marlow, Hennessy, Bracewell, Wolke & EPICure Study Group, 2007).

Although substantial number of studies on low risk preterm children has been performed in preschool and school years, the same cannot be said for early infant period. Current anatomical knowledge suggests that even though neuronal proliferation and migration to cortex are complete by 24 weeks, brain growth and networking complete only during the

last 6 weeks of gestation. Brain volume increases considerably over the final weeks of gestation. Late preterm brain weight at birth is about 60–65 % of term brain weight (Adams-Chapman 2006; Kinney 2006). Gray and white matter volume reductions and alterations in cortex and deep nuclear structures have been related to the degree of immaturity at birth and to abnormal neurodevelopmental outcome (Inder et al., 2005; Kinney, 2006; Scher et al., 2011). As such, there is an extended maturational timetable to consider due to which corrected age (age of the infant based on his due date) is used in different neuropsychological assessment of preterm infants up to the second year of life. *One important question is whether it could be possible to detect early indicators of later visual-manual coordination deficits.*

Studies on visuo-motor development of low risk preterm infants in the first two years of life are few in number. Some studies have followed preterm infants until the second year of life and showed that by correcting their age for prematurity, low risk preterm have a similar mental developmental index (MDI) as full-term infants at 12 and 18 months (O'Sullivan, 2003; Romeo et al., 2012). In contrast, some studies, focused on the motor development of low risk preterm infants, showed weaker motor skills in preterm infants with a nonlinear pattern of motor acquisitions of skills. According to one study, the greatest number of motor skill acquisitions is accomplished between 6 and 8 months, while at 8 and 10 months of age, the motor development seems to slow down (Formiga & Linhares, 2011). Some studies tried to explain this early developmental lag in motor acquisition of skills as a result of imbalance between flexor and extensor muscle strength, seen as oscillations in muscle tone, low gestational age and low birth weight group (Pineda et al., 2013; Plantinga, Perdock & de Groot, 1997; Pin, Eldridge & Galea, 2010; Lundqvist-Persson, Lau, Nordin, Bona & Sabel, 2012; Formiga & Linhares, 2011)

Contrary to this, other studies showed that when correction for prematurity is used, low risk preterm infants have similar motor development index from 8 to 12 months of age to full-term infants (O'Callaghan et al., 1993; Saigal et al., 1992; Mancini et al., 2002). As can be seen from the studies presented above, there is still controversy in the literature whether the early neurodevelopment of low risk preterm infants is delayed or equivalent to those of full-term infants. These studies were mainly interested in performance differences between preterm and full-term infants. Studies focused on the underlying mechanisms leading to these differences yielded also contradictory results.

For instance, some studies aimed at disentangling the influence of visual versus motor deficits that bear on visual-motor impairment in preterm children found that preterms' visual-manual deficits are due more to a fine motor deficit than to low visual perception (Teplin et

al, 1991; Goyen et al, 2008) However, a number of studies on preterm infants, including low risk group, in their first year of life have shown visual functions to be affected (Rose, 1983; Rose, Feldman, Wallace & McCarton, 1989; Ricci et al., 2011; Romeo et al., 2012). In addition to obvious cerebral visual impairments (CVI), including deficits in central oculomotor control as well as in visual and spatial cognition (Dutton, 2014; Philip & Dutton, 2014) in the first year of life, visual attention as assessed through fixation shifts was less mature in preterm than in full-term infants (Ricci et al., 2010). In the same vein, preterm infants had a lesser proportion of smooth pursuit eye movements (Grönqvist, Brodd & Rosander, 2011) and required more exposure time to recognize a visual stimulus after familiarization (Rose, 1983), showing less visual recognition memory (Rose, Feldman & Jankowski, 2001). On the other hand, in some studies (Ricci et al., 2008) it was found that extrauterine experience accelerates visual function development (better vertical and arc tracking, stripe discrimination) in preterm group, making them more successful than their full-term peers.

Based on the results from presented studies, the question of underlying mechanisms of differences in visual-manual coordination development in low risk preterm group remains open. Another open question concerning the developmental lag observed in preterm infants is that of the importance of motor control versus more cognitive factors involved in the interaction with objects.

Generally speaking, understanding visual versus motor performance as a separate set of milestones is one way to approach the question of underlying mechanisms of visual-motor deficits in preterm infants. The other way of approach is from an action perspective. An action approach to motor development gives central importance to the planning and prediction of movements, motivational factors in motor development and finally stresses more perceptual guidance of movements rather than the acquisition of motor programs (von Hofsten, 2004). Action systems do not appear ready-made, neither primarily determined by experience. They are the result of a process of central nervous system and subject's dynamic interactions with the environment (von Hofsten, 2004). Thus, acquisition of reaching and grasping in early sensorimotor period may be considered as an important step in child's understanding of the environment (Corbetta, 1998). Motor skills have been described to emerge from the combination of intrinsic and extrinsic factors (Kamm, Thelen & Jensen, 1990). For reaching and grasping skills, intrinsic factors include: infant's age (Rocha, Silva & Tudella, 2006); experience in performing the task (Carvalho et al., 2008); level of postural control (Fallang, Saugstad, & Hadders-Algra, 2000); exposure to risk conditions, such as prematurity,

congenital alterations and CNS lesions (Zoia, Pelamatti & Rumiati, 2004). Extrinsic factors are: body position (Carvalho, Tudella & Savelsbergh, 2007); object physical properties (Rochat, 1987; Fagard & Jacquet, 1996; Rocha et al., 2006; Fagard & Lockman, 2005); spatial orientation of the object (Lee, Liu & Newell, 2006) and object speed (Van Hof et al., 2005).

Although the influence of intrinsic and extrinsic factors on the development of reaching and grasping skills in full-term infants has been extensively described in the literature, the effect of such factors on preterm infants is still poorly understood (de Campos et al., 2009). Studies have shown that low risk preterm infants demonstrate poor reaching skill development that differs from full-term infants (Guimaraes et al., 2013). Specifically, low-risk preterm infants performed poorly when regulating muscle strength of the upper limbs during hand function (Plantinga, Perdock & de Groot, 1997) and performed reaches with less velocity and more corrections compared with full-term infants over the first year of life (de Toledo & Tudella, 2008; Grönqvist, Strand Brodd & von Hofsten, 2011). In addition, when reaching for a moving object, preterm infants showed delay in onset of reaching and anticipation of object reappearance (van der Meer et al., 1995).

As infants reach and grasp objects, they adjust their action to what the objects afford (Gibson, 1988; von Hofsten, 2009). Another question that arises is how reaching and grasping strategies are related to the perceptual knowledge of object properties. Studies on full-term infants showed discrepancy between perceptual knowledge of object properties and use of this knowledge in action planning. For instance, visual habituation studies show that infants at three months seem to understand the principle of solidity (an object cannot move through a solid barrier) (Spelke, Breinlinger, Macomber & Jacobson, 1992) but two-year-olds still open the door beyond an obstructing panel to reach for a rolling ball that disappeared behind an occluder, as if not expecting that the high panel visible above the occluder will prevent the ball from rolling (Berthier et al., 2000). In ecological point of view defined by Gibson (1988) and, more recently, Lockman (2000) infants discover objects' affordances by acting on objects. There are no similar studies in preterm infants and one can wonder to what extent a delay in reaching could reflect a delay in perceiving the objects' affordances. One example of affordances studied in full-term infants and not, to our knowledge, in preterm infants is that of a tool. Tool use is one of the hallmarks of sensorimotor period (Piaget, 1936; Rat-Fischer, O'Regan & Fagard, 2012). While it has been shown to develop during the second year in full-term infants (Rat-Fischer, O'Regan & Fagard, 2012), so far there have been no studies carried out on preterm infants. As such, investigating the development of this skill could bring us

closer to understanding the relation of visual-manual coordination and cognitive deficits seen in preterm children.

In summary, the occurrence and underlying mechanism of visual-manual coordination deficits in low risk preterm infants remain open question. Answering this question might help identify possible markers of later subtle neuropsychological deficits, as well as other learning disabilities reported in these children at school age and improve future early assessment and intervention services.

1.3. Goal of the thesis

The main goal of the thesis presented here was to investigate the development of visual-manual coordination in low risk preterm infants born after 33-36 weeks of gestation and examined from 5 to 23 months of chronological age.

During the course of the thesis we conducted series of studies with specific goals. We observed the development of visual-manual coordination, motor control and handedness in low risk preterm born infants from 6 to 12 months of chronological age and its relation to visual perception at 5 months. We also investigated how infant's action on object is related to understanding of object affordance when grasping a composite object at 6 to 10 months. Finally, we observed performance difference in preterm and full-term infants in the development of tool-use between 15 and 23 months.

Before giving more details about specific goals of the conducted studies and presenting in depth the results, following is chapter about early sensorimotor development in typical full-term born infants.

Chapter 11

Sensorimotor development

2.1. Development of visual-manual coordination

Sensorimotor period has been defined by Piaget as the period starting from the child's birth until the 2nd year of life. According to Piaget, during this period infant moves from reflex level to relatively coherent organization of sensorimotor actions (Piaget & Cook, 1952). However, more recent observations have shown intentionality in action to originate earlier than Piaget thought. The foundation of anticipation and control of the sensory effects of self-motion are to be searched early in development, being evident in some actions of the fetus well before birth (Delafield-Butt & Gangopadhyay, 2013).

The first movements of a new human organism occur toward the end of embryogenesis, in the 7th gestational week. These first movements are spontaneous and self-generated (Einspieler, Prayer & Prechtel, 2012). Soon after the earliest onset of movement, at 8 to 10 weeks of gestation, fetal arm movements are directed to parts of the body, especially to the face and head (Piontelli, 2010). Between 10-14 weeks of gestation these movements quickly become differentiated into individual, isolate actions with increasing goal-direction to parts of the body (Piontelli, 2010). The development of fetal movements in the second trimester shows an increase in prospective control and sensorimotor anticipation. For example, from 19 weeks of gestation, 4D ultrasound data show anticipatory mouth opening during hand movements directed there, suggesting intersensorimotor anticipatory coupling (Myowa-Yamakoshi & Takeshita, 2006).

Newborn period (1st month)

At birth, more detailed kinematic measurements become possible. In the neonatal period, neonatal movements are traditionally described as reflexes. Sherrington (1906) defines reflex as a hardwired sensorimotor loop organized at a spinal or para-spinal level. Reflexes are considered as stereotyped, elicited, automatic responses, not goal-directed or driven by motivation (von Hofsten, 2009). However, studies show that most neonatal behaviors are prospective and flexible goal-directed actions. *Rooting*, for instance, is traditionally described as a typical neonatal reflex. It refers to the infant's search for the nipple of the breast (von Hofsten, 2009). However, rooting is more than a simple reflex. Wherever the face is touched, the newborn turns his head in that precise direction indicating that the response is flexible and goal-directed rather than stereotyped. *Sucking*, for instance, relies on a complex interaction of muscle contractions that are prospective in nature. Within days after birth, newborn is able to suck with an amazing control (Craig & Lee, 1999). Such ability relies on adjusting the change

in sucking pressure to the flow of milk that is different from suck to suck. Newborns are also able to use sucking to access their mother's voice. For instance, DeCasper and Fifer found that newborns alter their sucking rate (suction rhythms) in order to select mother's voice over specific sounds emitted through headphones (DeCasper & Fifer, 1980). Furthermore, newborns can control their gaze and direct it to significant sources of information like faces and eyes (Farroni et al., 2002), they show preference for speech over filtered (Spence & DeCasper, 1987) and reversed speech (Pen a et al., 2003), they can imitate facial gestures just minutes after birth (Pilling, Orvos & Molnar, 2013). When it comes to *reaching*, although successful reaching does not appear until around 4 months of life (Corbetta & Spencer, 1996; von Hofsten, 1979), the sensorimotor link between eye and hand can already be seen in newborn infants. Von Hofsten (1984) observed that newborn infants aimed their extended arm movements towards an object when fixating it. This "pre-reaching" needs particular conditions of postural support and quiet environment to be elicited (Grenier, 1981). Similar results were found in study of Van der Meer (1997) who made a horizontal beam of light pass in front of newborn infant in a way that the light was not visible unless the child happened to put their hand into the beam. After the first event of this kind, the infant put his hand repeatedly into the beam and rapidly altered the position of hand as the beam moved. However, in this neonatal period, the newborn cannot grasp yet, due to low level of postural control over arm and hand movements (Fagard & Corbetta, 2014). These studies stress important developmental function of newborn's spontaneous hand movements – establishment of early link between perception and movement control (von Hofsten, 2009).

Development of reaching and grasping

In the first few months of life, sensorimotor coupling is shaped by maturation of the central nervous system and by infant's opportunity to be active in his environment (von Hofsten, 2009). This link between brain, body and the outside world can be seen in the development of functional reaching and grasping. In order for infant to successfully reach, he needs to have: differentiated control of the arm and hand, postural control, precise perception of depth through binocular disparity, perception of motion, control of smooth eye tracking, enough strength of muscles to control reaching movements and a motivation to reach (von Hofsten, 2009).

Studies have shown that first functional reach emerges at around 3/4 months of age in typical full-term infants (von Hofsten, 1979; Corbetta & Spencer, 1996). In order to reach accurately, infants first need to encode object's location. Direction and distance are the first

parameters of the object that infants take into account (von Hofsten & Rönqvist, 1988). An infant reaching in this age is composed of several units, more than the adult's two phases. During the first unit called ballistic (without path correction), infants approach their hand close to the object. During the last phase, which is shorter, infants adjust the movement according to the object's physical characteristics, but their hand is often not well adapted to the object, as we will see below. In between these two phases, there are often several phases of adjustment and correction (Fagard & Corbetta, 2014). At the age of four months, in approaching phase, infant's movements are characterized by abrupt arm movements and low level of skill control (von Hofsten, 1991). Between 5 and 6 months there is an increase in linearity (e.g. straightness index), movement velocity and reaching frequency (Rocha, Silva & Tudella, 2006).

Unimanual versus bimanual reach

In a supine or otherwise supported position, 5-month-olds increase their chances of making contact with an object using a bimanual reach where they approach the object with both hands from either side, regardless of the object size (Rochat, 1992; Fagard, 2000). With supplementary postural support to the pelvic girdle and upper legs or trunk, nonsitters can be induced to carry out more mature reaches, moving just one hand to the object (Hopkins & Rönqvist, 2002; Marschik et al., 2008). In line with this, unimanual reaching increases around 5 to 6 months of age (Fagard, 1998; Fagard, 2000; Fagard & Lockman, 2005). Between 6 and 7 months, infants demonstrate two aspects of bimanual role differentiation (Fagard, Spelke & von Hofsten, 2009). One aspect is related to the characteristics of the target of the reach (e.g. large vs small objects) and the second is related to the functional roles of the two hands (e.g. supporting an object with one hand while manipulating it with the other) (Fagard, 1998; Bojczyk & Corbetta, 2004). At 7 months infants start to show signs of modifying their reaching according to the context, which is interconnected with development of distal aspect of reach (Clearfield & Thelen, 2001). At the end of the first year, the reach and grasp movements become often bimanual, even for small objects, as the infant starts walking independently (Corbetta & Mounoud, 1990). At 13 months, infant's grasp of large objects follows a bilateral approach, indicating that bimanual grasping results from anticipation and not merely from the haptic feedback which bring us to following phase - distal adjustment and its role in infants grasp (Fagard & Jacquet, 1996).

Distal adjustment (grasping phase)

Reaching studies consistently found that infants begin orienting and pre-shaping their motor response (bimanual or unimanual reach) as a function of the visually perceived properties of objects (object size) at around 7–8 months of age (Corbetta et al., 2000; Fagard, 2000). It was also found that object properties (e.g. size) have an effect on distal adjustment of movement (e.g. hand opening). Grasping an object requires coding of the intrinsic features of an object, such as its size, shape and orientation (Arbib, 1985; Jeannerod, 1988). Between 5 and 9 months, infants start to open their hand during reaching (von Hofsten & Rönqvist, 1988) and adjust it to fit the object size (von Hofsten & Rönqvist, 1988; Siddiqui, 1995; Fagard & Jacquett, 1996), shape (Pieraut-Le Bonniec, 1990) and orientation (von Hofsten & Fazel-Zandy, 1984). Studies by Fagard (2000) found that at around 7/8 months of age the frequency of thumb-index finger angle opening during reaching and the adaptation of angle size to object diameter increased, with a significant age-related change between 5 to 6 months. This research indicates that major developments occur between 5 and 7 months of age in the timing of infants' manual anticipations. Typically, infants older than 7 months of age align their hands to the object while a reach is in progress, and 5-month-old infants align their hands only after making contact with the object (McCarty, Clifton, Ashmead, Lee & Goubet, 2001; Witherington, 2005). These studies suggested something of a developmental lag between when infants reach for objects and when they can incorporate visually available information about the object into their actions on the object. At 10 months there is a significant shift in infant's capacity to change hand orientation in relation to object orientation and at 11 to 12 months to object's diameter (Fagard, 2000). As infant's reach becomes more functional, he can now explore the environment and actively discover "laws" of the physical world.

Perception and visual habituation studies – infants comprehension of objects

Before being capable of active exploration, infants look at objects and at other people interacting with objects. Many studies focused on the competence of infants before they can actively explore their environment. These studies are based on the habituation-novelty technique or variation of it. They revealed that, as long as no active manual response is required, infants demonstrate early perceptual and cognitive comprehension of objects properties. For instance, 3 month-old infants seem to understand the principle of solidity (an object cannot move through a solid barrier) (Spelke, Breinlinger, Macomber & Jacobson, 1992) or show surprise when all parts of an object do not move together (Spelke & Van de

Walle, 1993). They are also able to detect discrepancies between shapes. Geometrical shapes (curvilinear or rectilinear topological relations; full shapes or shapes pierced with a hole) are well differentiated from the age of 2 months (Streri, 1987; Streri & Milhet, 1988). At this age, infant is also capable of discriminating a volumetric object (a cotton reel) from a flat object (a cross) (Streri & Molina, 1993). Studies show that infants aged 2.5 and 3.5 months are aware that objects continue to exist although masked by other objects, that objects cannot remain stable without support (e.g. box falls if it loses contact with platform), they show understanding of collision phenomena (e.g. object remains stationary if not hit) and that objects move along spatial continuous path (Baillargeon, 1994). Some of these competencies cannot be observed before a certain age. For instance, studies assessing infant perception, which commonly use habituation or preference looking methods, found no sign that infants younger than 2 months of age perceive velocity (e.g., Dannemiller & Freedland, 1989; Wattam-Bell, 1990), that infants only at 6.5 months expect the box to fall unless certain proportion of its surface lies on platform (Baillargeon, 1994), or that infants at 6.5 can realize that size of a moving object can be used to predict how far stationary object will be displaced (Baillargeon, 1994). However, it seems that this knowledge of objects' properties is not integrated in preparation of reaching movements well before few months, as we will see below.

Perception-action developmental lag

Some authors stress the importance of distinguishing between the age when a child shows perceptual knowledge like in visual habituation studies, and the age at which it can use that knowledge for action planning (Fagard & Corbetta, 2014). For instance, visual habituation studies showed that infants seem to understand principle of solidity at 3 months (Spelke, Breinlinger, Macomber & Jacobson, 1992), but another study showed that two-year-olds open the door beyond an obstructing panel to reach for a rolling ball that disappeared behind an occluder, giving the impression that they do not expect that the high panel visible above the occluder will prevent the ball from rolling (Berthier, DeBlois, Poirier, Novak & Clifton, 2000). Despite findings from habituation-novelty studies, this technique is limited by the simplicity of the response variable (e.g. infant looks longer at one event than another), leaving the observer with question of understanding of infant's differential looking. For example, when infants are presented with an object which follows a path behind a screen, the measure is how long infants look at the event as a whole, not whether they visually track the object, visually anticipate its emergence, or manually search for it when it is out of sight

(Bremner, 2000). However, other measures could yield more convincing evidence of knowledge, for example, in tasks in which infant needs to use the knowledge in his reaching attempt towards the object. There is a need for new insights on the ongoing debate whether understanding of physical causality is present in infancy well before infants act consistently in goal-directed action or whether such understanding is progressively built up from infants' sensorimotor experience with the physical world (Rat-Fischer, O'Regan & Fagard, 2014).

One way of tackling this question could be in classic means-end studies involving cloth-pulling, string pulling, cane pulling, etc., first explored by Richardson (1932), Piaget (1936), Uzgiris and Hunt (1975), Bates, Carlsonluden, and Bretherton (1980) or Willatts (1984). The notion of "connectedness" (contact between objects) has been explored in infants from 6-9 months, using two paradigms: pulling a support to retrieve an out-of-reach object placed on top of it, and pulling a string attached to the out-of-reach object (Rat-Fischer, O'Regan & Fagard, 2014). We know from visual habituation studies that at 6 months infants understand some dynamic aspects of objects, such as cohesion of two objects moving together in the same direction (Spelke et al., 1992) and the principle of contact (Leslie & Keeble, 1987) in which one object is affected by another only if there is contact between them. According to researchers using the violation of expectancy (VOE) paradigm, infants understand the notion of object support at around 3 months, but it is not until around 9–10 months that they have sufficient understanding to be able to pull a string (e.g. simple means end task) in order to retrieve an out-of-reach toy (Bates, Carlsonluden & Bretherton, 1980; Baillargeon, 1994). Still, it is not until 14 months that they are able to solve multiple string tasks, after several repeated trials (Brown, 1990). However, Sommerville and Woodward (2005) observed that 10-month-olds could identify the goal of string-pulling when they watched an actor doing it only if they could themselves "planfully solve a similar sequence". In same vein, Rat-Fischer and colleagues (2014) found that in multiple string task only infants who successfully performed the action task could visually anticipate which string the adult would pull in the visual task, as opposed to those who failed at the action task. Thus, even if the notion of connectedness is present earlier in infants' development, they may need time and experience to integrate this notion and use it in more complex tasks. These results are in line with direct matching hypothesis formulated by Rizzolatti et al. (2005) in which observers understand actions on the basis of motor knowledge. This means that understanding of actions observed is based on mapping this action onto motor representations of the same action.

During all these manual acquisitions in the first months of life, one important characteristic of manual control emerges, namely hand preference. We already saw that by 11 months, infants use one or two hands to grasp objects depending on object size, and that they also shift between periods of predominant one-handed reaching to periods of predominant bimanual reaching, depending on postural development. Bimanual coordination of complementary actions with the two hands, both active, emerges toward the end of the first year (Fagard, 1998; Michel et al., 1985; Kimmerle, Mick & Michel, 1995). Hand preference can be observed quite early in unimanual simple reaches, but also in the hand chosen for the active part of a bimanual task, as we will see below.

2.2. Development of handedness

For some period of time, it was believed that handedness could not be determined before the age of three years that is when child begins to draw (McManus et al., 1988). Contrary to this, new studies on development of handedness show different story, its onset early in fetal period.

Fetal period and postural manual asymmetries

At the onset of 9-10 weeks first unilateral movements of the arm can be observed (right over left arm) (McCartney & Hepper, 1999). Thumb sucking is the first directed behavior observed for a manual preference and it was shown that fetuses tend to suck their right arm more than left. This early asymmetry is observable in 80% of fetuses (Hepper, Shahidullah & White, 1991). It was also found that infants' sucking of the preferred thumb was connected to their head orientation. And more interestingly, almost 60 infants out of 60 who suck their right thumb in utero were right-handed at 12 years (10 of the 15 having sucked their thumb left were left-handed) (Hepper, Wells & Lynch, 2005). From these studies, early signs of handedness can already be detected in fetal period. Studies also show that last period of pregnancy is important for reinforcing the fetus' right-hand preference, as sometimes suggested (Fagard, 2013).

Pre-reaching period

After birth, majority of infants, same as fetuses, orient their head to right, either spontaneously (Michel & Goodwin, 1979), or after being gently forced medially

(Rönqvist & Hopkins, 1998). Some studies observed that orientation of the head is related to handedness observed several months later, stressing the role of vision in handedness strengthening (Michel, 1981). Upon birth infants are more alert when an object is present and in these first pre-reaches they tend to use significantly more their right hand over the left in the presence of the object (von Hofsten, 1982). Contrary to this, some studies observed little difference between both hands and sometimes a difference in favor of the left hand (DiFranco, Muir & Dodwell, 1978; Morange & Bloch, 1996).

Kinematic studies, on the other hand, observed the difference in performance between two hands, in favor of preferred hand (Fagard, 2012). Corbetta and Thelen (1999) did not observe significant differences in speed motion of hands in pre-reaching phases. Some other studies found more opening of the right than the left hand during the approach phase (Morange & Bloch, 1996). From the results of these studies, in pre-reaching period, manual asymmetries can already be observed.

Functional reach and grasping phase

Follow-up studies on development of handedness in first months showed the instable growth curve (Corbetta & Thelen, 1999; Fagard & Peze, 1997). Cross-sectional studies, on the other hand, have shown in this first phase of functional reaching period little manual preference with a rapid increase in the preference for the right hand between 5 and 7 months (Ramsay, 1980), between 6 and 8 months (Fagard, Spelke & von Hofsten, 2009) and between 9 and 13 months (Cornwell, Harris & Fitzgerald, 1991). In fact, during the first year, there are huge fluctuations in the hand chosen, both within and between sessions (Carlson & Harris, 1985; Corbetta & Thelen, 1999; Fagard, 1998; McCormick & Maurer, 1988). Also, some authors stress that these observations of fluctuations in handedness might depend on methodological approach used in different studies (Michel et al., 1985; Fagard, 2012). The differences in methodological approach are numerous, ranging from: number of items, statistical formulas used in extraction of laterality index, presentation of object (in the middle and/or medial or lateral position), type of object used (requiring normal grasp or precision grasp, bimanual manipulation or not) and variables observed (behavioral or kinematic). Some authors stress the need to standardize means to assess infant handedness.

Results from behavioral observation studies (e.g. type of objects used) show that handedness is stronger for tasks requiring precision. For instance, Fagard and Lockman (2005) described differences in the choice of one particular hand or of a one-handed versus two-handed strategy during object grasping and exploration (e.g. tube/container task) in

children from 6 to 48 months of age. According to the authors, task constraints influenced the expression of handedness. For reaching tasks that required precision grasping, the variability of hand-use decreased with the right hand clearly being preferred by a majority of the infants in each of three different age groups (6–12, 18–24, and 30–36 months). In addition, when grasping involved bimanual manipulation, hand-use preference emerged more clearly for 18- to 36-month-old infants. Similar results in favor of right-handedness (as measured by the manipulating hand) were also found in other studies that used bimanual tasks (Fagard & Marks, 2000; Potier, Meguerditchian & Fagard, 2012). For instance, it was found that as early as 12 months, infants used right hand more often than the left, not only to grasp the base object, but also to remove the pieces (e.g. active part of task) after transferring the base object from the right to the left hand. These results are in agreement with the notion that handedness is related to the precision required from the active hand. Some other studies observed the relation of handedness and position of the object in space. Infants, to a greater extent than older children and adults, tend to use their ipsilateral hand to reach for a laterally-presented object and this tendency is weaker for the left than the right side (Fagard, 1998; Sacco, Moutard & Fagard, 2006).

Studies that used kinematic measures observed that infant's right and left reach-to-grasp movements showed early signs of side differences (Corbetta & Thelen, 1999; Hopkins & Rönnqvist, 2002). Rönnqvist and Dömellof (2006) found that right-left side differences in kinematic parameters (e.g. less segmented and straighter right-arm reaching movements in comparison to the left arm) are consistent at 6, 9, and 12 months of age in the majority of the infants investigated. In addition, these right-left differences were related to hand preference at 36 months of age.

As can be seen from the result of the follow-up studies, handedness fluctuates during the first months of prehension, and infants may alternately use their left hand, right hand, or both hands depending on the session and methods used, although the overall percentage shows always a clear tendency towards using the right hand in the majority of infants (Fagard, 2012). Early observation of handedness supports a view of handedness as partly genetically originated. Although Annett's (1973) and McManus's (1985) theory of one gene or two alleles of one gene being responsible for right-handedness has never been supported by molecular genetic studies and is clearly out-of-date, it seems clear that some genetic factors are involved in the emergence of handedness (Fagard, 2013). According to Fagard's theory, these genetic factors are likely to be indirect and to have a limited impact on hand preference. The majority of children become right-handed as their slight hand preference is reinforced during early

development; position in the womb during the last weeks of pregnancy, asymmetric ATNR toward the right at birth and imitation of care-taker's hand preference are examples of reinforcing factors. However, because the tendency to choose preferentially one hand is not very strong, hand preference is likely to fluctuate until writing, a repeated and automatized behavior, fixates the choice of hand.

Some authors consider these fluctuations to arise from interaction of biological, environmental and experiential factors that change and evolve as infants and children grow using dynamic system approach (Thelen, 1995; Thelen & Smith, 1998). For instance, Corbetta & Thelen (2002) discovered an interesting relationship between the locomotor patterns that infants were developing at different points in time during their first year of life and the pattern of hand use that infants were adopting at those particular developmental times. Early in development, prior to the emergence of crawling, infants tended to display a preferred right bias for reaching (Corbetta & Thelen, 1999). As they began to crawl, those preferred right biases in reaching and steady division of hand role in object retrieval dissipated (Corbetta & Thelen, 2002). Also, Corbetta & Bojczyk (2002) observed another change in hand use a few months later, when infants began to walk independently in terms of return to more one-handed lateralized reaches (instead of previous two-handed) and began again to show a steadier division of hand roles in the object retrieval task. The same authors also observed that infants who learned to walk quickly and gained balance control within a few weeks also demonstrated a short period of two-handedness in reaching, while infants who displayed a slower progression in walking over a longer period of time also displayed a longer period of two-handed reaching (Corbetta & Bojczyk, 2002). These observations see fluctuations in hand as being associated with the emergence of novel sensory-motor experiences. In line with this, some author found that language development reinforces handedness strength until second year of life (Ramsay, 1984; Bates, O'Connell, Vaid, Sledge, & Oakes, 1986) or at least that there is a link between the emergence of right-handedness and the development of language (Esseily, Jacquet & Fagard, 2011; Nelson, Campbell & Michel, 2013).

In conclusion, despite these fluctuations, handedness in the first sessions predicts handedness in later sessions rather well (Corbetta & Thelen, 1999; Coryell & Michel, 1978; Ferre, Babik & Michel, 2010; Flament, 1975; Gesell & Ames, 1947; Ramsay, 1985). Also, studies show that the preference observed at 7-8 months is correlated with most stable preference at the end of the second year (Jacquet, Esseily, Rider & Fagard, 2012) and finally,

that handedness increases gradually over first 2 years of life (Cochet, Jover & Vauclair, 2011; Jacquet, Esseily, Rider & Fagard, 2012).

In summary, during the first year of life, the majority of infants tend to use their right hand over the left, especially if the task requires precision. Also, handedness is sensitive to changes in other areas of development, but none the less, there is a certain continuous path of handedness development starting from fetal period up until the 1st year of life.

2.3. Tool use development

The ability to use a tool is an important skill, observed in many animal species including humans (Creem & Proffitt, 2001), chimpanzees (McGrew & Collins, 1985), capuchins (Visalberghi & Trinca, 1989), Californian crows (Chappell & Kacelnik, 2002) and non primates such as dolphins (Krutzen et al., 2005), among others. Despite some pioneering studies such as Piaget (1936), only very recently has the emergence of this skill, during the first years of life, been the focus of studies. Following is a short review of existing studies on tool use development during the early sensorimotor period. A generally accepted definition of tool use is the ability to use one object to extend the limit of our physical body in order to act upon another spatially independent object (Beck, 1980).

Trajectory of tool use development

Tool use in human infants develops from 8 to 24 months of age (McCarty, Clifton & Collard, 2001). In the period from 8 to 12 months infants start to sequentially plan steps to attain a goal, such as to retrieve an out of reach object when no spatial gap disrupts the link between the tool and the toy (e.g. toy on a cloth, at the end of a string and inside or against the tool) (Bates, Carlsonluden & Bretherton, 1980; Brown, 1990; Willatts, 1999; Van Leeuwen, Smitsman & van Leeuwen, 1994). Although these conditions have been extensively studied in infants, they are not considered real tool use behavior, more means-end behaviors in which infants plan a sequence of actions to reach a goal in a situation where an obstacle prevents the direct attainment of a goal, as we shall see below. Willatts (1999) performed a follow-up study on infants seen at 6, 7 and 8 months. He followed their behaviors in situation of reaching for a toy out of reach placed on a cloth which was next to hand. It was observed that 6 month infants performed transitional reach (with “partial intention”), while 7 month infants reach for the toy with clear intention (intentional pull of cloth without other exploratory behavior). Also, one more example of this goal-directed behavior was studied by Bruner and

Koslowski (1972) in infants from 12 to 24 months in task of reaching for a toy positioned on a lever in which infants had to push the lever in order to reach for a toy. It was shown that infants applied more efficient strategies with ages, and between 16 and 24 months they were able to integrate more steps in sequence of action making them more successful than in earlier stages.

Some other studies followed the progression in the use of strategies with the first tool that infant systematically uses, namely the spoon (Connolly & Dalgleish, 1989; McCarty, Clifton, and Collard, 1999). Connolly & Dalgleish (1989) followed-up infants from 11 to 17 months in which they observed a change in efficiency in used strategies relating to hand preference, trajectory control and type of grasp. Similar results were reported by McCarty, Clifton, and Collard (1999) on spoon use in 9, 14 and 19 month-old infants. These two studies demonstrate improvement in planning strategies in use of tool, concerning more the motor aspect of tool use than the conceptual one.

The conceptual aspect of tool use was the focus of studies in which a tool was used to act on another object in condition with spatial gap. The use of tools to bring an object placed out of reach was first described by Piaget on his son Laurent at the end of first year (Piaget & Cook, 1952). As we will see below, infants in the period from 12 to 18 months start to combine and relate two objects together such as banging a toy with a tool (e.g. stick). However, to discover, during random spontaneous manipulation, that combining two objects may lead to an interesting result is one thing; to understand that in order to obtain this result one has to use one of the objects and apply it in a specific way to the other object is more difficult. This is referred to as the “inverse problem”. Indeed, before 18 months, infants are not successful in using tools when there is a spatial gap between them and the target (Bates, Carlsonluden & Bretherton, 1980; Brown, 1990; van Leeuwen et al., 1994).

Tool use in spatial gap situation

For instance, in the study by Bates et al. (1980) 10-months-old infants were subject to task in which an out of reach toy was placed next to different tools (mini-hoop, hook or stick). The toy was placed in different positions relative to the hoop (against or in the middle), the hook (within its curved part or to the side) and next to the stick. The authors also used two means-end conditions in which toy was placed on a cloth or attached to the end of a string. The results show that the percentage of success is higher in means-end situation, slightly lower when the connection between toy and tool is dissociable (e.g. toy placed against the tool), and that success is rare in the absence of connection (e.g. toy placed beside the tool).

Similar results were observed in study by van Leeuwen et al. (1994), in which a hook within hand reach and a ball out of reach were placed in different positions in relation to hook and presented to infants between 8 months and 3,8 years. It was shown that not only spatial discontinuity, but also the number of steps involved in the action influenced the success in the task. Some other studies (O'Regan et al., 2011; Rat-Fischer, O'Regan & Fagard, 2012) also found earlier success in spatial contiguity condition than in non-contiguity condition but they stressed that early successes appear due to the contingency between toy and tool and should not be over interpreted as infants' full understanding of tools function. For instance, Rat Fischer et al. (2012) followed tool-use development in infants aged 14, 16, 18, 20, and 22 months, which were presented with an attractive toy and a neutral rake-like tool in five conditions of spatial relationships between the toy and the tool (e.g. from toy and tool being connected to the large spatial gap between them). Results show that even some of the youngest infants could spontaneously retrieve the toy when it was presented inside and touching the top part of the tool. In contrast, in conditions with a spatial gap, the first spontaneous successes were observed at 18 months, suggesting that a true understanding of the use of the tool has not been fully acquired before that age.

Mechanisms responsible for tool use development

Most of the mentioned studies have tried to describe progress of manual skill in use of a tool, or the factors influencing the success, such as spatial gap between the tool and the object. Some studies were interested in the development of understanding of tools function. In same vein, studies on tool-use development also tried to explain how infants overcome tool use difficulties by investigating two learning strategies: observational learning (cognitive components) and spontaneous manipulation (motor component) (Greif & Needham, 2011; O'Regan, Rat-Fischer & Fagard, 2011; Rat-Fischer, O'Regan & Fagard, 2012; Esseily, Rat-Fischer, O'Regan, & Fagard, 2013).

Rat Fischer et al. (2012) and O'Regan et al. (2011) evaluated at what age infants who spontaneously fail the task can learn this complex skill by being given a demonstration from an adult. It is not before 18 months that infants began to benefit from a classic demonstration in the conditions with a spatial gap. This is fairly coherent with the findings of Chen and Siegler (2000) on a group of 18- to 26-month-olds, but on task of choosing between alternative tools, including one similar to tool used in Rat-Fischer, O'Regan and Fagard studies (2012). The absence of effect of the demonstration before 18 months was focus of a study by Esseily et al. (2013), in which the effect of demonstration was evaluated based on a

way it was provided. Esseily and colleagues (2013) investigated whether understanding the experimenter's intention enables 16-month-olds to use observation to perform a tool-use task. Infants were assigned to a spontaneous condition (no demonstration) or to one of four demonstration conditions. In the first two conditions (*classic demonstration* condition and *prior intention* condition) the intention of the demonstrator was shown, while the second two conditions (*hand enhancement* condition and *stimulus enhancement* condition) were used as control conditions. Infants who were presented with information about the adult's intention before the demonstration made a connection between the tool and the toy significantly more frequently than did those not presented with this information. Infants did equally poorly in all other conditions in which no information was provided about the adult's intentions. Connections between the rake and the toy were almost exclusively observed in the prior intention condition and not in the other conditions meaning that understanding prior intention enabled infants to gain at least some understanding of new tool affordances at 16 months of age.

Studies focusing on effect of spontaneous manipulation have evaluated the impact of active experiences on early development of tool use. In studies that used object retrieval tasks, children rarely succeed before 2–3 years of age in selecting the appropriate tool for retrieving a toy (Brown, 1990), and success increased over trials as children learn about the tools through their own interactive experience with them (Chen & Siegler, 2000).

Only few studies (Flynn & Whiten, 2010; Whiten & Flynn, 2010; Cutting, Apperly & Beck, 2011; Somogyi, Ara, Gianni, Rat-Fischer, Fattori, O'Regan, & Fagard, 2015) have compared the roles of observation and manipulation in tool-use development, stressing the advantage of observational learning over object manipulation. For instance, Somogyi et al. (2015) investigated how repeated, five-minute familiarization sessions over a 6-week period influenced infants' knowledge about the functional properties of a rake-like tool and their ability to use it for retrieving an out of reach object by 16 months of age. It was found that infants who were not allowed to touch the rake, but only to observe an adult retrieve an object with it, improved their performance. On the other hand, infants who were allowed to manually manipulate the rake and touch and move other objects with it did not improve their performance. The results suggest that, although both motor and cognitive limitations affect performance, it is rather cognitive limitations that prevent infants from understanding the functional properties of the tool and from succeeding in such tool-use tasks.

In conclusion, these results suggest that the development of tool use emerges from a continuous and gradual process. Also, they emphasize more the importance of cognitive

rather than motor experience in making infants successful at a tool use task, already at a young age. Tool use development so far has not been studied in preterm population, which is not the case for general development of visual-manual coordination in this population.

2.4. Development of visual-manual coordination in low risk preterm born infants

The developmental implications of preterm birth are rather complex and far from being fully revealed (Medgyes, 1991). The information available about low risk preterm infants is particularly puzzling as most of the research has focused on the population of a high-risk group in which the role of prematurity is confounded with the effects of various perinatal complications (Vohr et al., 1989). Although there is a relatively high inter-individual variety of neonatal behavioural and autonomic organisation in the low risk preterm group, this population is often considered clinically similar to full-term infants. Studies prove different as we will see below.

Neonatal period

Neurobehavioral follow-up studies have shown that low risk preterm infants have more variable and delayed neurobehavioral development than full-term infants (Ferrari et al. 1983, Piper et al. 1985, Als et al. 1988). For instance, they differ from full-terms in acquisition of motor capacities such as postural control (van der Fits et al., 1999), kicking movements (Jeng, Chen & Yau, 2002; Piek & Gasson, 1999), head control and suction (Howard, Parmelee, Kopp & Littman, 1976). Low risk preterm infants may manifest weak motor responses, such as decreased flexion in limb traction, weaker head extension in prone position, head lag in traction movement, weaker sucking responses and absence of reflex of rooting and grasping (Kurtzberg et al., 1979, Ferrari et al., 1983). Also, it was observed that preterm infants have poor organization of state, attention and autonomic regulation (Ferrari et al., 1983; Als et al., 1988). One question of interest is how does this relative immaturity of central nervous system in neonatal period, caused by low risk preterm birth, have an effect on future development of early reaching and grasping skills.

Functional reach emerges in preterm infants around 4.5 months corrected age, as in full-term infants (Clearfield et al., 2001; Heathcock et al., 2008). Despite this normal onset of reach, low risk preterm infants demonstrate poorer reaching skills development than full-term

infants (Guimaraes et al., 2013). For instance, kinematic studies in preterm infants showed less velocity at 4 and 6 months, more corrections and less rectilinear trajectory compared with full-terms (de Toledo & Tudella, 2008; Grönqvist, Strand Brodd & von Hofsten, 2011). Specifically, low-risk preterm infants performed poorly when regulating muscle strength of the upper limbs during reaching (Plantinga, Perdock & de Groot, 1997). Some studies stress the oscillation in muscle tone regulation as important factor that affects the axial musculature and, consequently, postural control for upper limb-related functions (Plantinga et al., 1997; de Groot, 2000; Pin et al., 2010). In addition, de Toledo & Tudella (2008) found a negative correlation between mean velocity and successful grasping in preterm group (e.g. lower velocity-higher success of grasping), making them more careful in performing movements compared to full-terms. These results, as authors interpret, point to the fact that preterm infants adopt a strategy in order to overcome inherent limitation (e.g. low muscle tone) by increasing deceleration time before touching the object. In the same vein, other studies also observed specific reaching strategies in preterm infants (de Toledo et al., 2011; Grönqvist, Strand Brodd & von Hofsten, 2011). For instance, Grönqvist et al. (2011) found that very preterm infants at 8 months corrected age were equally successful as full-terms in task of reaching for a moving object but they performed more bimanual reaches than their full-term peers. It is not clear whether this increase in bimanual reaches reflects a less adapted strategy to the physical properties of the objects to be grasped (Newell, Scully, McDonald & Baillargeon, 1989; Fagard & Jacquet, 1996), or an increased need for postural compensation during reaching. Some studies focusing on the distal adjustment of reach in preterm infants showed indeed that they show sometimes a less adapted strategy to the physical properties of the objects to be grasped than full-terms.

In the study by de Toledo and colleagues (2011), late preterm infants compared to full-term infants, at 6 months corrected age, performed significantly more reaches with open hand than full-terms (Thelen, 1995; de Toledo & Tudella, 2008; de Toledo et al., 2011). As authors note, possibly due to low muscle tone (Plantinga et al., 1997). Following this point of view, some authors studied the effect of short training intervention on reaching behavior performance in low risk preterm infants (Heathcock, Lobo & Galloway, 2008; de Almeida Soares et al., 2014). It was found that shortly after training, preterm infants presented greater motor variability of proximal adjustments (e.g. greater proportion of unimanual reaches than the full-term infants), but less distal control (e.g. lower proportion of reaches with open hand compared to the full-term infants) and less successful grasping outcomes compared to the full-

term group. The authors concluded that prematurity limits the infant's ability to benefit from short training intervention in more refined manual tasks at the onset of goal-directed reaching.

Perception - action studies

As opposed to a certain number of reaching and grasping studies, fewer studies focused on perception and information processing in low risk preterm infants. Studies presented below, although only few in number, indicate that perception and information processing in low risk preterm infants is somehow different than in full-term group. For instance, a series of papers based on behavioural tasks demonstrated that visual information processing is affected by preterm birth; such as processing speed (Rose et al., 2005), visual attention (Ricci et al., 2010; Grönqvist, Brodd & Rosander, 2011) and visual recognition memory (Rose, 1983; Rose, Feldman & Jankowski, 2001). In particular, preterm infants required about 20% more trials and 30% more time than full-terms to perform following tasks equally: fixation shifts (measured by tracking the direction and latency of saccadic eye movements in response to a peripheral target), smooth pursuit eye movements (measured by tracking of a small happy face) or recognition of a visual stimulus after familiarization. However, conflicting results have been reported by some other studies (Ricci et al., 2008), showing that low-risk preterm infants tested at 35 weeks and 40 weeks had significantly more mature ocular movements, better vertical and arc tracking and, at 40 weeks, better stripe discrimination than full-term infants tested 48h after birth. As authors explain it, this relative lack of visual impairment may reflect accelerated maturation of aspects of visual function correlated with ocular stability and tracking with early extrauterine experience. Some other studies focused on development of tactile perception in preterm infants and showed that they can memorize by touch specific features of shape and detect differences when another shape is presented few days after birth, same as full-term infants (Marcus et al., 2012).

These differences in perceptual processing may explain some specificity of object exploration observed in preterm infant. For instance, de Almeida Soares and colleagues (2012) followed-up the development of exploratory behaviors in late preterm infants at age of 5 up to 7 months (de Sores, von Hofsten & Tudella, 2012). Preterms' performances were similar to those of full-terms in some of the exploratory behaviors such as: fingering, banging-on-the-object, banging-the-object, transferring, rotating and alternating. In other behaviors, such as mouthing the object and waving the object, they significantly differed from full-term group, performing these behaviors less often. However, as the authors pointed out, the

difference may also partly be due to differences in muscle tone observed between the groups (Ricci et al., 2008).

Despite observed differences in performance in preterm infants comparing to full-terms in perception-action studies, majority of studies focused on the follow-up of psychomotor development of preterm infants (in which both cognitive and motor tasks are integrated) using standardized assessment inventories (e.g. Bayley Scale of Infant Development, Griffith Scale etc...). The results of the studies using standardized norms are intriguing. Preterm infants, by correcting their age for prematurity, have a similar mental developmental index (MDI) to full-term infants at 12 and 18 months (Romeo et al., 2012; Morag et al., 2013). Contrary to this, results of studies on preschool and school age low risk preterm children show a lack of visual-manual coordination (Goyen, Lui & Woods, 1998; Luoma et al., 1998; Caravale et al., 2005; Vicari et al., 2004; Baron et al., 2009; Caravale et al., 2012). Based on the results of these studies, there is a certain loop in performance seen in this population on trespass from infancy to preschool period. Due to this, a longer follow-up is needed in order to investigate which preterm infants will developmentally “catch up” or benefit from early intervention to prevent motor, attentional, visual, and other developmental, cognitive and learning disabilities frequently reported at later ages.

Altogether, these results show some immaturity in the perception-action system of preterm infants when reaching for, grasping or manipulating objects. One important component in the development of object grasping and bimanual manipulation is the emergence of handedness. In the next section, we will examine how this emergence is affected by prematurity.

2.4. Development of handedness in low risk preterm born infants

Atypical handedness is often reported in developmental disorders. For instance, studies showed less evident handedness in children with developmental disorders such as Down syndrome (Groen et al., 2008), autism spectrum disorder (Cornish & McManus, 1996) and fetal alcohol syndrome (Domellöf et al., 2009). Since preterm born children are at risk for developing disorders in motor functioning such as cerebral palsy (CP), more evident in high-risk preterm group, and more “subtle“ motor deficits such as developmental coordination disorder (DCD), more present in low risk preterm group (Williams, Lee & Anderson, 2010;

Fawke, 2007; Bracewell & Marlow, 2002), it is worth investigating the development of handedness in children born preterm.

There is a great variability in reported outcomes of handedness development in preterm children. Some studies reported more NRH in the preterm than full-term group, but without statistical significance (Luciana et al., 1999; Harding et al., 2001; Feder et al., 2005; Curtis et al., 2006; Allin et al., 2006; Schafer et al., 2009; Soria-Pastor et al., 2009). For instance, Harding et al. (2001) studied a sample of 7- to 10-year-old preterm children of similar gestational age and low birth weight and although failing to prove a significant difference in hand preference between preterm and full-term children in general, the authors reported high prevalence (32%) of NRH in the extremely low birth weight group. These results are in line with those by Luciana et al. (1999) in a study on 7- to 9-year-old extremely/very low birth weight preterm born group.

In contrast, other studies reported an approximately equal presence of NRH in preterm and control group considering preschool children at 5 to 7 years (Ehrlichman et al., 1982; Sagnol et al., 2007), but due to insufficient description of the study sample (the preterm participants were specified as “less than 34 weeks“ or “lower than 2490 g”) we can only presume that their sample included full range of low birth weight sample. Similar results were found in study by Zuazo et al. (1999) in 3 and 5 year olds.

Some studies observed the relation of handedness and neurological abnormalities accompanying preterm birth using etiological risk factors (O’Callaghan et al., 1993), neurological examination (Ross et al., 1992; Saigal et al., 1992) or cerebral ultrasound scanning (Marlow et al., 1989). For instance, O’Callaghan et al. (1993) found an association between prevalence of left-handedness and increasing neonatal risk score (based on the sum of 10 risk factors and considered as an indirect measure of brain injury). Saigal et al. (1992) noted an evident relationship between NRH and brain injury (defined as abnormalities in tone and posture with hypertonicity, hydrocephalus, and/or $IQ < 70$), particularly so in male children with extremely low birth weight. With respect to birth weight, Ross et al. (1987) observed that preterm children with extremely/very low birth weight at 4 years were more likely to have mixed hand preference compared to full-term peers. Similar results were found in study by Marlow et al. (1989) in which the prevalence of NRH was higher in sample of extremely/very low birth weight preterm children at 2–8 years old compared to their full-term siblings from 3–24 years old. These results are also in line with some other studies (Saigal et al., 1992; O’Callaghan et al., 1993).

Other studies assessed handedness in relation to other developmental areas using a range of various standardized tests (e.g. Wechsler Intelligence Scale for Children-Revised, NEPSY, Movement Assessment Battery for Children) to explore the link between handedness and neuropsychological performance in preterm children (Ross et al., 1992; Saigal et al., 1992; O’Callaghan et al., 1993; Zuazo et al., 1999; Luciana et al., 1999; Marlow et al., 2007). O’Callaghan et al. (1993) found that increase in left hand preference was associated with lowered intelligence quotient (IQ), lowered motor abilities and more difficult temperament style with the preterm children at 4 years old. Adding to this, Ross et al. (1987) found that 4-year old NRH very low preterm group had lower IQ scores and delayed language development compared to full-term infants. Marlow et al. (2007) noted a linear relationship between hand preference score (especially NRH) and cognitive development in 6-year-old extremely low preterm children. Contrary to this, Zuazo et al. (1999) found that NRH was not related to IQ in 3- and 5-year-old preterm children with low birth weight. Similar results were found in study by Luciana et al. (1999) who failed to relate handedness to cognitive performance in extremely/very low birth weight preterm children at 7–9 years old.

Finally, one study used kinematic analysis in assessment of handedness in preterm group (Johansson, Domellöf & Rönnqvist, 2014). They found that only full-term group expressed evident side differences characterized by smoother movements with the preferred hand compared to the preterm children (moderately and very preterm born) from 4-8 years.

One of the possible explanations for the variability of the handedness in premature children’s results is to be found in differences in used methodological approach ranging from: sample size (small sample size), heterogeneity of sample (e.g. extremely/very low gestational age vs. moderate/late gestational age, low birth weight vs. normal birth weight, low risk preterm vs. high risk preterm), variables observed (behavioral, kinematic or neurological), assessment protocols (experimental tasks vs. standardized assessment inventories).

As opposed to the many studies on preschool preterm group, only few studies observed development of handedness in preterm infants (see for instance Fox, 1985; Rönnqvist & Domellöf, 2006). Rönnqvist & Domellöf, (2006) using kinematic analysis found that compared to full-terms, preterm group showed temporary deviation from the typical development of right-side reaching specialization (e.g. less side consistent) at 6 – 12 months. Fox (1985), on the other hand, observed handedness in preterm and full-term infants at 2 years in relation to their medical complications at birth. Results of the handedness tasks revealed an increased incidence of use of the left hand among the „healthy“ preterm infants (as well as among the term infants who underwent birth asphyxia).

Some theories, directly or indirectly, addressed the phenomenon of increased frequency of left-handedness or lack of right-handedness in preterm born children (Domellöf Johansson & Rönnqvist, 2011). In the right shift theory (Annett, 1985) presence or absence of a single right shift gene (RS+) increases or decreases the probability for a dominant left hemisphere for speech and subsequent right handedness. Within this theory, it is postulated that preterm delivery interrupts this typical development of cerebral asymmetry and handedness (Domellöf, Johansson & Rönnqvist, 2011). However, the likelihood that a single gene is responsible for asymmetries is increasingly disputed (Fagard, 2013). In the Bakan theory (1971) NRH is considered pathological and is seen in preterm born children due to brain injury caused by perinatal hypoxia affecting the left motor cortex. According to a third theory, NRH may be of either a natural or pathological origin due to brain injury, such as those seen in preterm birth (Soper & Satz, 1984; Bishop, 1990).

To summarize, the studies presented here show an association between preterm birth and increased NRH in preterm born children aged 3–19 years, despite high level of heterogeneity of samples in conducted studies. Also, there is more evidence that preterm children differed from the full-terms by being more often NRH rather than by being more left-handed. Adding to this, NRH seems to be more evident in preterm children with lower gestational ages, although a cautious interpretation needs to be taken into account due to unreliability of sample integrity (e.g. birth weight and gestational age used without separation). Still, future research is needed in long term follow-up of handedness in preterm group starting from sensorimotor period in order to gain understanding of development of trajectory in visual-manual performance. Given the role of early motor experience on gradual development of body schema and motor control, following is an overview of motor development in sensorimotor period.

Chapter III

Development of posture and locomotion

Preterm birth imposes a challenge on the development of motor control in low risk preterm infants due to immature and more vulnerable motor and sensory system starting from birth (Fallang & Hadders-Algra, 2005). As mentioned earlier in the part regarding the development of reaching and grasping in preterm infants, muscle tone oscillation seems to play an important role in preterms' motor performance, including gross motor one (Plantinga et al., 1997; de Toledo & Tudella, 2008; de Toledo et al., 2011). Following is a brief summary of the typical development of gross motor skills and what is known of this development in low risk preterm infants.

3.1. Gross motor development in full-term infants

Locomotion is one of the greatest achievements of early motor development. At birth, infants are bound to gravity and by the end of their first year, they master an array of locomotor movements: rolling, bum shuffling, belly crawling, hands-and-knees crawling, cruising sideways, supported stepping, independent walking and so on (Adolph, 2008). Infant motor development involves many important behavioral transitions (McMillan & Scholtz, 2000) required to increase mobility and maximize function, as we will see below.

Classic vs. Contemporary theories

Classic theories of motor development attribute transitions in motor behaviors primarily to the maturation of the central nervous system (McGraw, 1939; Gessell & Amatruda, 1947). McGraw, for example, identified seven stages in the assumption of an erect posture development compared to Gessell's twenty-three stages. Based on McGraw's and Gessell's studies, the practice of cataloging motor achievements and assigning motor stages to age continues with popular developmental inventories such as the Bayley Scales of Infant Development, Alberta Infant Motor Scale and others. Nowadays most developmental textbooks contain a chart that features infants' postural milestones (see Figure 1).

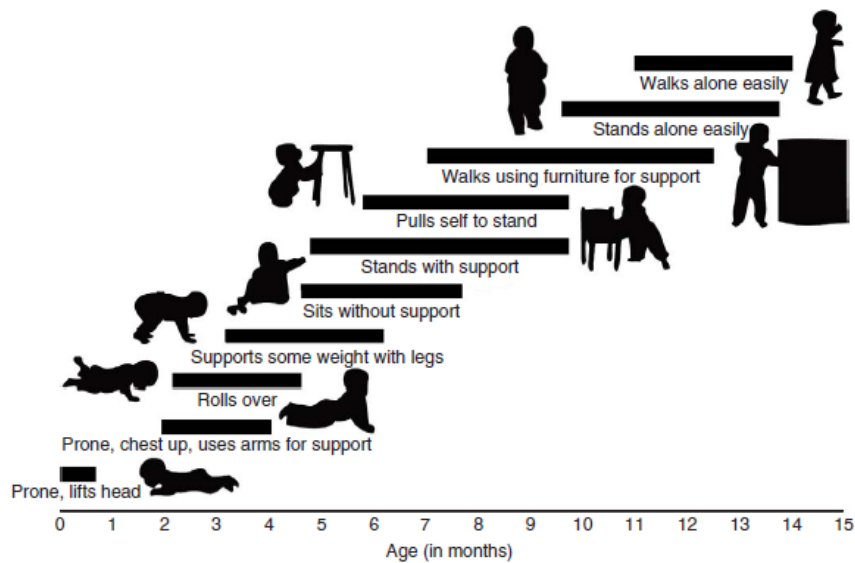


Figure 1 Developmental motor chart with age range for postural and locomotor milestones. Source: Adolph, K.E. (2008): Motor and Physical Development: Locomotion in M.M. Haith & J.B.Benson (eds): Encyclopedia of Infant and Early Childhood Development, San Diego: Academic press, pp: 359-373.

More contemporary theories emphasize the importance of factors such as musculoskeletal maturation, changes in body mass distribution, maturation of the postural control system and properties of the surrounding environment seen as additional constraints on motor performance (Kugler et al., 1982, Thelen et al., 1984, Thelen et al., 1987; Thelen, Ulrich & Wolff, 1991). Based on these assumptions, two contemporary views emerged: dynamic approach and perception-action approach. From a dynamic systems account new forms of movement emerge in development when all of the component subsystems are in a state of readiness. From a perception–action account, for locomotion to be adaptive, infants must select and modify movements to suit the affordances of the current situation. Thus, for infants to control locomotion, they must gather perceptual information about upcoming affordances to plan their next steps (Adolph, 2008).

Origin of locomotion

Since the early pioneers, researchers have thought that developmental precursors to independent locomotion can be observed in infants' first spontaneous limb movements. In human fetuses, small, slow, cyclic bending of the head and/or trunk are detected with 4D-ultrasonography at 5 weeks post-conception (Felt et al., 2012). Waxing and waning general movements can be observed slightly later, at 7 weeks, and persist throughout pregnancy and

the first months after term birth (de Vries, Visser & Prechtl, 1982; Hadders-Algra, 2007). General movements consist of complex, variable, flexion-extensions of the whole body and limbs, they are not triggered by external stimuli and lack distinctive sequencing of different body parts. In addition, human fetuses exhibit a rich repertoire of leg movements that includes single leg kicks, symmetrical double leg kicks and symmetrical inter-limb alternation with variable phase (Stanojevic et al., 2011). Spontaneous movements of the limbs evolve toward an increased coordination between the arms and between the legs, at 2–4 months after birth (Kanemaru, Watanabe & Taga, 2012). Newborn stepping is the best-known example of precursory locomotor limb movements. It can be elicited in an infant supported under the arms in an upright, slightly tilted forward posture, after contacting ground with the feet soles (Lacquaniti, Ivanenko & Zago, 2012). Infants respond with alternating leg movements that look like exaggerated marching. Stepping movements typically disappear by the time infants are 8 weeks old and then reappear at around 8 months of age when infants begin to walk with caregivers holding their hands to provide balance (Adolph, 2008). Some contemporary studies (Thelen & Fischer, 1982) have shown that stepping movements do not disappear; they are only masked when infants are held in an upright position due to differential effects of gravity. That is, throughout the first year of life, infants move their legs in an alternating pattern when they lie on their backs and at 8 months they have sufficient muscle strength to lift their legs in an upright position. Contrary to Thelen and Fischer's view, Barbu-Roth et al. (2015) in two experiments (air vs. surface stepping) showed that 2-month-old infants displayed significantly more stepping movements when supported upright in the air than when supported with their feet contacting a surface. In addition, more air steps and more donkey kicks were seen when infants were exposed to optic flows that specified backward compared to forward translation, stressing the role of visual control in control of stepping.

The role of posture in locomotion development

Both classical and contemporary researchers view postural control as the central prerequisite for locomotion (Adolph, 2008). Every form of locomotion requires postural control, including the forms that typically precede walking (cruising, crawling, rolling, etc.) and the forms that follow it (running, skipping, sliding, stair climbing, walking backward, etc.). In any position except lying flat on the ground, postural control is required to fight the force of gravity.

According to Assaiante et al. (1998) and their model of balance control needed both for posture and locomotion, infancy period is characterized by the development of postural responses along a cephalocaudal gradient. Balance control appears first in the muscles of the neck, then trunk, and finally in the legs (Woollacott, Debu & Mowatt, 1987). Also, head control improves with emergence of reaching (Thelen & Spencer, 1998). In line with this, studies show that reaching freely from a sitting posture appears between 6 and 8 months when infants can keep their heads balanced between their shoulders and maintain equilibrium in the trunk with their legs outstretched along the floor in a “V” (van der Fits et al., 1999). These results, taken together, suggest an articulated operation of the head–trunk control during the first year of life.

Prone progression

Prone progression is the most variable and idiosyncratic of all of infants’ motor behaviors (Tecklin, 2008). Typically, the ability to change the whole body position and orientation without moving to a new location begins in the first 6 months of life (Bly, 1994). Infants roll front to back and vice versa, they transit from sitting to prone position, pivot in circles on their stomachs, swim in place and rock back and forth on hands and knees (Adolph, Vereijken & Denny, 1998).

Their first success at forward prone progression is when their abdomens are raised in the air during each crawling cycle (hands-and-knees crawling). From cycle to cycle, infants use their arms, legs, bellies and heads in various combinations (Adolph, 2008). For instance, infants move arms and legs on alternate sides of the body together like a trot, ipsilateral limbs together like a pace, lift front, then back limbs into the air like a bunny hop and so on. With time, crawling steps become larger and faster. In time and with experience, infants are more successful in stabilizing their torso while moving their extremities, which is important skill to acquire in order to reach upright position (Tecklin, 2008).

Upright position

Achieving an upright posture that precedes independent mobility can for infants take up to several months (Atun-Einy, Berger & Scher, 2011). This sequence of milestones starts between 7 and 10 months of age (8 months on average) with infants using furniture or another object for support to help them pull up to a standing position and continues with infants cruising along a surface of support, keeping balance without holding on, taking their first independent steps and, finally, between 11 and 15 months of age, walk independently (Capute

et al., 1985; Piper & Darrah, 1994). Typically, infants' first walking steps are shaky and inconsistent. Movements at the hip, knee and ankle joints are jerky and variable. Infants in the first 4–6 months of independent walking show the most rapid improvements in walking proficiency (Adolph, 2008; Lacquaniti, Ivanenko & Zago, 2012). Walking patterns continue to improve, although more slowly, until 5–7 years of age, when children's walking becomes truly adult-like.

3.2. Gross motor development in low risk preterm born infants

Despite the growing number of studies that observed gross motor development of preterm infants compared to those of full-terms (Palmer et al., 1982; Forslund & Bjerre 1985; Piper et al., 1989; Palisano et al., 1986; Allen & Alexander, 1990; Restiffe & Gherpelli, 2006), results are quite inconclusive, as we shall see below.

According to Piper et al. (1989), theoretically, motor development in preterm infants could follow one of four possible courses. If nervous system development is solely dependent on innate preprogrammed processes, similar motor developmental progression should evolve whether the infant was *in utero* or *ex utero*. If central nervous system maturation is affected by the environment, the extra-uterine stimulation experienced by preterm infants could either enhance or delay this process (Touwen 1980). The final possibility is that the sequence and quality of maturation, while not necessarily delayed or advanced, may differ from that of the full term infant.

Based on this theory, following hypothesis emerged regarding the trajectory of gross motor development in preterm infants. There are three possible ways of effect of prematurity on timing of gross motor development (Largo, 1993). If motor development is solely dependent on corrected age, its developmental course will be as shown in Figure 2A.

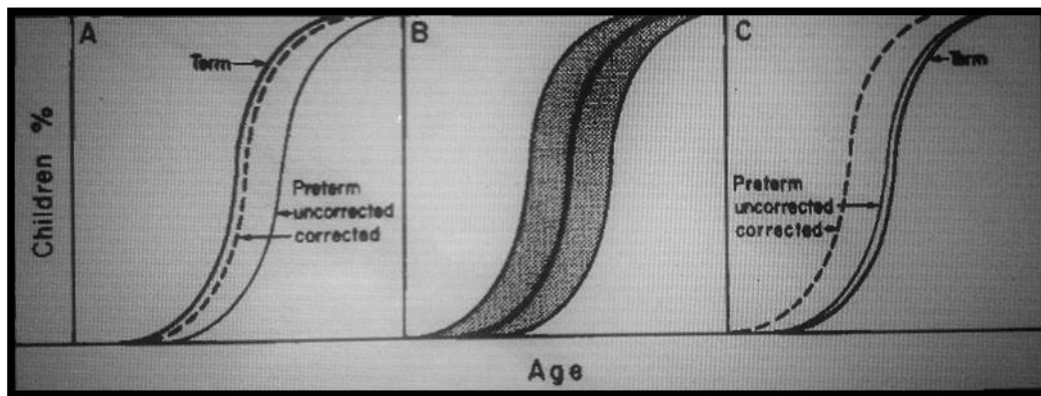


Figure 2 Possible effects of prematurity on motor development A: motor development dependent on corrected age; B: motor development dependent on maturational and environmental factors; C: motor development dependent on postnatal age Source: Largo, RH (1993): Early motor development in preterm children in Savelsbergh, GJP (eds): The Development of Coordination in Infancy, Netherlands: North-Holland, pp: 425-443

Data not corrected for prematurity will show delay in motor development, while corrected data will be close to that of term group. If motor development is exclusively dependent on postnatal age, developmental curve will be as shown in Figure 2C. Developmental curve of the uncorrected data would fit that of the term, while the corrected data would indicate advance motor development. Finally, third way would be that if there is an interaction between maturation and developmental factors, result would lie on the curve as shown on Figure 2B.

Delayed or not?

In respect to these three ways, most studies on motor development have taken into account both chronological (postnatal) and corrected age when observing low risk preterm infants in order to counterbalance the disadvantages of under- (when solely chronological age is used) and overestimation (when only corrected age is used) when compared to full-terms (Siegel, 1983; Miller, Dubowitz & Palmer, 1984; Palisano, 1985; Blasco, 1989). Despite the use of both corrected and chronological age, studies using standard assessment inventories (e.g. Alberta Infant Motor Scales...) yielded contradictory results. Results of some early (Largo et al., 1985; Piper et al., 1989; Ouden et al., 1991) and more recent studies (Mancini et al., 2002; Restiffe & Gherpelli, 2006) show that when using chronological age, motor development of low risk preterm infants is underestimated during the first year of life leading to false negative diagnostic of motor delay, while when corrected age is used they show a similar motor development to full-terms. Cited authors concluded that low risk preterm

infants gross motor development seems to mature according to corrected, rather than chronological age. Contrary to this, other studies (Jeng et al., 2000; Bartlett & Fanning, 2003; van Haastert et al., 2006) identified significant differences (lower scores) in early gross motor development of preterm infants compared with term infants from birth to 18 months, even after full correction for prematurity was used.

Due to these contradictory results, authors now question as to whether the gross motor development of preterm infants should be compared with the standardized norms of inventories obtained on full-term infants (van Haastert et al., 2006; Formiga & Linhares, 2010).

Mechanisms of delay/difference

Some studies focused on mechanisms that could contribute to deeper understanding of different developmental trajectories seen in preterm infants. One of the biological factors possibly influencing motor development in preterm infants is insufficient postnatal growth (weight & height). Studies show a relation between body weight and gross motor performance, especially in extremely and very low birth weight infants which are often put in high risk preterm group (prone to severe levels of neurological impairments leading to motor disorder such as cerebral palsy) (Wood et al., 2000; Kohlhauser et al., 2000; Marlow et al., 2004). Some studies (van Haastert et al., 2006) on low risk preterm infants found a significant association between birth weight and gross motor scores in which infants with lower birth weight had lower motor scores. Accompanying lower body weight, studies show that small muscle size and lower proportion of fast-twitch muscle fibers which can lead to reduced intramuscular high-energy phosphate, and physical hypoactivity that may cause anaerobic performance, were also seen more often in preterm children than in their full-term peers (Keller et al., 2000).

Inferior intermuscular coordination, poor muscle strength, poor muscle power regulation and, as a result, inadequate postural control, can affect the quality of movement and result in a delayed onset of antigravity activities in preterm infants (De Groot et al., 1992; Barlet & Fanning, 2003; Mercuri et al., 2003). For instance, Mercuri et al. (2003) found that low risk preterm infants few weeks after birth do not behave in the same way as newborn term infants. Most of the differences were accounted to muscle tone. Preterm infants tended to have less flexor tone than term infants, with less marked flexion in the limbs. This oscillation in muscle tone (also called transient dystonia) was shown to have an effect on postural behavior in preterm infants (Fallang & Hadders-Algra, 2005). For instance, preterm infants

show a reduced amount of rotation during crawling, delayed dynamic balance, delayed onset of independent walking and a poor quality of early walking behavior (Gorga et al., 1988; de Groot et al., 1997; Bylund et al., 1998). Also, kinematic studies show that preterm infants have a relatively immobile postural behavior during reaching task (very small travel path of the total body center of pressure (COP)) and non-optimal hand functions seen as incoordination of flexor–extensor muscles in the hand compared to full-term infants (Georgieff et al., 1986; Plantinga et al., 1997; van der Fits et al., 1999; Fallang et al., 2000). Some authors stress the role of cerebellum in respect to lower coordination of muscle power in preterm group (Barinaga, 1996; Allin et al., 2004; Limperopoulos, Soul & Gauvreau, 2005).

To summarize, studies on gross motor development of low risk preterm infants yielded contradictory results, but they emphasize the need for use of corrected age. They also seem to stress the role of body weight and muscle tone as one of the factors influencing the performance on gross motor tasks and the role of cerebellum in the development of motor coordination.

Chapter IV
Problem and presentation
of the population

We have seen that, whereas preterm born children in general have often been observed to have a delay in visual-manual development, little is known about the early development of this skill in low risk preterm infants.

We have seen previously, in part regarding visual-manual coordination development of this manuscript, that low risk preterm infants, starting from birth, show more variable and delayed neurobehavioral development than full-term infants. Also, despite the fact that their first functional reach and grasp develops at the same age as in full-term infants, they demonstrate poorer reaching skills development than full-term infants. This difference in performance seen in low risk preterm infants can also be seen in visual information processing, which makes us question whether visual-manual coordination development in this population is affected by preterm birth. More specifically, is their visual-manual coordination developmentally „on track“, is it different but still „on track“, or is it delayed when compared to full-term infants. Thus, we decided to conduct series of studies in which we observed the development of visual-manual coordination in low risk preterm born infants from 6 to 24 months of chronological age.

4.1. Participants

A total of 22 infants (14 girls and 8 boys) participated in our studies, including 12 preterm infants (8 girls and 4 boys) and 10 full-term infants (6 girls and 4 boys). All the preterm infants included in the studies had no IVH above grade I, no evidence of visual or auditory impairment and no major neurological complications. Five infants were born vaginal and seven by cesarean. Preterm infants were recruited from a database of the Zagreb Special Hospital for Children with Neurodevelopmental and Motor Disorders where they were followed by a physician on a monthly basis. After approval of the Hospital Ethical Committee, the families were sent an information leaflet about the study. The families who expressed interest in taking part in the study signed a parental consent form. The infants in the control group (full-term infants) were recruited through a list of local families from several kindergartens. We ensured that all control infants were born full-term, with a normal weight and no medical history. Nine infants were born vaginal and 1 by cesarean. The families interested in taking part in the study also signed a parental consent form prior to the study. By chance, four families of preterm twins offered to participate in the study. We did not turn them down, but type of pregnancy (single birth vs. twins) was included as independent

variable in all analyses. The preterm infants were compared to the full-term infants according to their corrected age.

Clinical description of participants

The mean gestational age of the preterm infants was 35 weeks. The category of late preterm birth (35-37 weeks) included 58.3% of the infants, whereas the category of moderate preterm birth (32-34 weeks) included 41.7% of the infants. The birth weight of the preterm infants was 2260.83 gr. Half of the preterm infants were considered low birth weight and half were considered normal birth weight. Seven infants had been in incubators (58.3%). 66.7% of preterm infants were born from twin pregnancy. Half of the preterm infants had intraventricular hemorrhage (IVH) grade I, whereas 50% had no IVH. Finally, all preterm infants had either a tendency towards higher muscle tone (83.3%) or a tendency towards lower muscle tone (16.7%, see Table 2 for a summary of information for the two groups).

	Preterm infants		Full-terms
Type of pregnancy:	Single birth: 33.33%	Twin birth: 66,66%	Single birth: 100%
Muscle tone:	Hypertone: 75%	Hypotone: 25%	Normal tone: 100%
IVH (intraventricular hemorrhage):	IVH grade I: 50 %	No: 50%	no IVH: 100%
Number of weeks of gestation (SD)	35 (1.279)		40.2 (0.42)
Category of gestational age at birth:	Moderate birth 33 weeks: 16.7% 34 weeks: 25%	Late birth 36 weeks: 58.3 %	
Birth weight (SD)	2260.83 gr (382.01)		3350 gr (329.10)
Category of birth weight:	Low birth weight: 50% 1975 gr	Normal birth weight: 50% 2546 gr	
Incubator after birth (SD):	4.33 days (5.95)		0 (0)

Table 2: Medical information about preterm/full-term infants

4.2. Specific goals of the studies

The goal of the **first study** was to investigate the development of visual-manual coordination, including handedness, in low risk preterm born infants from 6 to 12 months of chronological age. We also checked whether visual perception and gross motor development were within normal range. We wanted to ensure that a deficit in either domain was not responsible for an abnormal development of visual-manual coordination, in case we found one. In order to investigate the underlying mechanisms of development of visual-manual coordination in low risk preterm infants, we targeted the following goals in which we observed performance of low risk preterm infants in comparison to full-terms:

- Evaluating visual-manual coordination
- Evaluating visual function and its relation to visual-manual coordination development
- Evaluating the development of handedness and its relation to visual-manual coordination development
- Investigating bimanual coordination development
- Evaluating the gross motor development and its relation to visual-manual coordination development

The goal of the **second study** was to investigate at what age a child can use perceptual knowledge of an object in action planning and whether this differed between low risk preterm infants and full terms. For that purpose, we targeted the following specific goal:

- Evaluating the differences between low risk preterm and full-term infants in grasping a composite object

The goal of the **third study** was to investigate the development of tool-use in low risk preterm infant and the differences between low-risk preterm and full-term infants.

4.3. Questions and hypotheses

Through our studies and accompanying goals we investigated how low-risk prematurity can affect the development of visual-manual coordination, handedness, bimanual coordination, gross motor skills, object understanding, and tool use. Following most studies on the development of preterm born infants, as well as the suggestion of the reviewers of our first article, we used corrected age to compare the preterm infants with the full-terms. We hypothesised that at the same post-gestational age, low risk preterm infants, as a group, would have comparable performance on experimental tasks to the full-term infants'. We also raised the possibility that not all low risk preterm infants could have compensated the lack of maturation induced by the preterm birth with experience since birth. The question of interest was which of the functions tested would be the most sensitive to prematurity, and should be controlled in infants to prevent further delays.

Chapter V

Experimental studies

5.1. Study 1: Visual-manual coordination in preterm infants without neurological impairments

The goal of the first study was to investigate the development of visual-manual coordination, bimanual coordination and handedness in preterm infants born after 33-36 weeks gestation between the postnatal ages of 6 and 12 months, after having evaluated their visual functions.

Several tests and experimental tasks have been administered to preterm and full-term infants during this longitudinal study. The administration time sequence, according to postnatal age (PA) of both groups, is presented in Table 3. All infants were five months old at the time of the visual evaluation and six months old at the start of the visual-manual follow-up.

PRETERM (P) CONTROL (C)	PDMS-II	Tube/container bimanual task	BbHtest	Gross motor Questionnaire	BABE
5 months (PA)	-	-	-	-	P/C
6 months (PA)	P	-	P/C	P/C	-
7 months (PA)	P	-	-	P/C	-
8 months (PA)	P	-	P/C	P/C	-
9 months (PA)	P	-	-	P/C	-
10 months (PA)	P	P/C	P/C	P/C	-
11 months (PA)	P	P/C	-	P/C	-
12 months (PA)	P	P/C	P/C	P/C	-

Table 3: Time assessment protocol according to postnatal age (PA) (PDMS-II: Peabody Developmental Motor Scales 2nd edition; BbHtest: infant handedness test; BABE: Evaluation of visuo-attentional capacities in babies)

Visual perception

Methods

One month prior to the start of the visual-manual follow-up, thus at 5 months of postnatal age, we evaluated visual function in all infants with five tasks taken from the Evaluation of visuo-attentional capacities in babies (BABE) (Cavézian et al., 2010; Cavézian et al., 2013; Pawletko, Chokron & Dutton, 2015). The BABE battery is constituted of 13 subtests: (1) visual fixation, (2) light detection, (3) photomotor reflex, (4) blink reflex to threat, (5) visual tracking, (6) visual field integrity, (7) gaze orientation toward an auditory stimulus, (8) visual-motor coordination, (9) object prehension, (10) visual selective attention, (11) embedded figures, (12) visual memory, (13) visual matching. The subtests 1 to 7 can be administered to children from 3 months. The subtests constituting the BABE battery have been designed, standardized and normalized in order to be used separately if necessary. We choose to test the infants for photo motor reflex (2), blink reflex to threat (4), visual fixation (?), visual tracking (5), and visual field integrity (6).

Photomotor Reflex

The child and the experimenter are sitting in darkness. The experimenter successively switches on or off an electric lamp just in front of each pupil of the baby. The examiner observes for miosis (decrease in diameter of the pupil) when the light beam is directed toward the eye and mydriasis (increase in diameter of the pupil) when the beam moves away. Each infant was tested three times. The maximum score is two points. One point was awarded for each eye when the reflex was observed even once (miosis).

Blink reflex to threat

The examiner slowly approached a finger to the eye of the child, who should normally show a blink reflex. There were two trials, one for each eye. The maximum score was two points. One point was awarded for each eye when the reflex was observed.

Visual fixation

The examiner sat in front of the child at a distance of about 50 cm and drew the child's attention to her face. The examiner observed how long the child held its gaze fixed to the examiner's face. The examiner tested fixation successively at five positions (straight ahead, in the right or left hemisphere, above or below the child). The maximum score was five points.

One point was awarded when the child was able to keep his eyes fixed on the examiner for 10 seconds without moving eyes or head. No points were awarded when the child moved its eyes or head.

Visual Tracking

The examiner sat facing the child and silently moved a black-and-white disc in horizontal, vertical, and diagonal directions, always at a distance of about 50 cm from the child's face, approximately arm's length. The test ended after three successful trials or four trials. If the test was not successful after four trials, it was repeated again, but this time the examiner held a bell in the same hand as the disc. When the test with sound was successful on the first, second, or third trial, then the test was ended and considered successful. If the test was not successful after four trials, it was considered failed. In all directions, one trajectory lasted three seconds. The maximum score was thirty-two points: for each direction: if the child followed the target without any accompanying sound, two points were awarded (total: 16 points), and one point was awarded if the child followed the target with the addition of sound (total: 8 points). No points were awarded if the child lost or did not follow the target.

Visual Field Integrity

The examiner sat in front of the child and ensured that the child could see her face through a hole in a screen placed between them at a distance of about 50 cm from the child's face. The screen prevented the child from seeing the movements of the examiner's hand and arm as the examiner made an object (pencil with little bee on top) appear off to one side of the screen, and then the other, and then up, and then down, and noted whether the child detected each presentation of the stimulus. Three trials were given per position. If the child did not detect the appearance of the object in the visual field, the examiner performed the test a second time while holding a bell in the same hand as the pencil. The maximum score was 8 points. Two points were awarded if the child detected each presentation at the four locations on the first trial (no sound). One point was awarded for each target identified on the second trial (with sound). No points were awarded if the target was not detected.

Results

We first investigated whether there were any differences in vision at 5 months between preterm and full-term infants, using the BABE subtests (photomotor reflex, blink reflex, visual field integrity, visual tracking, and visual fixation). We calculated an ANOVA on each score with group (x 2, preterm and full-term) as a between-subjects factor. The results showed that there was no difference between preterm and full-term infants in photomotor reflex and blink reflex. Full-term group scores were almost equivalent for visual tracking and non-significantly better for visual field integrity ($p = .42$). Full-term infants' visual fixation scores were better than those of preterm infants, but the difference only approached significance ($p = .066$, see Table 4).

BABE subtest	<u>Preterm infants</u>	<u>Full-terms</u>	
	Mean (SD)	Mean (SD)	<i>p</i> of difference (ANOVA)
Psychomotor reflex	1.00 (0)	1.00 (0)	-
Blinking reflex to threat	1.00 (0)	1.00 (0)	-
Visual fixation	7.33 (0.89)	8.00 (0)	0.066
Visual tracking	15.92 (0.29)	16.00 (0)	0.46
Visual field integrity	1.92 (1.44)	2.43 (0.98)	0.42

Table 4: Results of preterm and full-term infants on BABE subtests

We checked if there was any relation between muscle tone and performance on the visual fixation, visual tracking and visual field integrity tests. A Mann-Whitney test showed no relation for visual fixation or visual tracking, but preterm infants with hypotonia had significantly lower visual field integrity scores than those with hypertonia, $z = -2.16$, $p = .03$.

Conclusion

The preterm group performance did not differ significantly on any of the subtests, although the difference between preterm and full-term infants on the visual fixation test (in favor of the latter) nearly reached significance. Preterm infants with hypotonia had significantly lower visual field integrity scores than those with hypertonia. But this should be interpreted with caution since only three preterm infants had hypotonia.

Visual-manual coordination

Methods

Visual-manual coordination was assessed using the Visual-Motor Integration and Grasping subtests of the Peabody Developmental Motor Scales, Second Edition (PDMS-2) (Folio & Fewell, 2000) in 6- to 12-month-old preterm infants seen every month. No testing of the control group was necessary since the test is standardized. The Visual-Motor Integration subtest consists in 72 items which measure the child's ability to use his or her visual perceptual skills to perform complex eye-hand coordination tasks such as reaching and grasping for an object, building with blocks, and copying designs. The items used were the following: at 6 months: extending arms, approaching midline; at 7 months: fingering hands, bringing hands together, extending the arm; at 8 months: retaining cubes, transferring cubes; at 9 months: touching pellet, banging cup; at 10 months: poking finger, removing pegs, combining cubes, clapping hands; at 11 months: retaining cubes, manipulating string; and at 12 months: removing pegs, releasing cube. The Grasping subtest consists of 26 items which measure the child's ability to use his or her hands, first starting with holding an object with one hand and slowly progressing to controlling the use of fingers of both hands. We calculated an index of the infants' motor development, the Fine Motor Quotient (FMQ), which is sum of their standard scores on the Visual-Motor Integration and Grasping subtests.

Results

On the PDMS-2, we analyzed the Fine Motor Quotient (FMQ), derived from the standard results on the Visual-Motor Integration and Grasping subtests. When correction for prematurity was used, across all testing sessions, a large majority of preterm infants showed

average or even (at 12 months) above-average fine motor performance (between 100% at 6 months and 83.3% at 12 months). Between 8.3% and 22.2% of the infants showed below-average performance depending on age, with 16.7% still below average at 12 months postnatal age even when correction for prematurity is used (see Table 5).

Corrected age/FMQ	Poor	Below average	Average	Above average
6 months			100%	
7 months			100%	
8 months		8.3%	91.7%	
9 months		22.2%	77.83%	
10 months		16.7%	83.3%	
11 months		16.7%	83.3%	
12 months		16.7%	75%	8.3%

Table 5: Percentage of preterm infants in categories drawn from the Peabody Developmental Motor Scales' Fine Motor Quotient (FMQ)

We tested whether performance on the Visual-Motor Integration subtest, as measured by raw scores, was correlated with performance on the Grasping subtest, also using raw scores. At each session, there was a strongly positive and significant correlation between Visual-Motor Integration and Grasping scores ($r = 0.66, 0.72, 0.87, 0.91, 0.87, 0.81, \text{ and } 0.81$, at 6, 7, 8, 9, 10, 11, and 12 months, respectively, $p < .05$ for all correlations). This means that preterm infants who had better results on the Visual-Motor Integration subtest also performed better on the Grasping subtest. Infants with hypotonia had lower FMQ. A Mann-Whitney test indicated that the difference was significant at all ages (see Table 6).

Corrected age	Hypotonic FMQ (SD)	Hypertonic FMQ (SD)	Mann-Whitney <i>p</i>
6 months	95 (1.73)	100 (2.6)	0.021
7 months	95 (4.56)	101 (2.18)	0.022
8 months	93 (7.54)	100 (2.5)	0.055
9 months	89 (7.55)	101 (1.22)	0.012
10 months	88 (7.94)	99 (3.67)	0.052
11 months	88 (5.2)	99 (4.85)	0.026
12 months	89 (4.58)	99 (6.44)	0.033

Table 6: Fine Motor Quotient (FMQ) by muscle tone and corrected age

Since, in the preterm group, there were more twins than singletons, and more late than moderate preterm infants, we again used a Mann-Whitney test to check whether these factors influenced FMQ. In addition, we checked the effect of birth weight category. We found no significant difference for any of these parameters. We also checked whether Fine Motor Quotient (FMQ) was correlated with BABE results. As can be seen in Table 7, we found positive correlations between FMQ and visual field integrity, which were significant at 7, 10, 11, and 12 month postnatal age. Infants with higher scores on the visual field integrity test had higher FMQs as measured by the Peabody Developmental Motor Scales.

FMQ/BABE	Visual field integrity	Visual fixation	Visual tracking
FMQ 6 months postnatal	0.38	0.41	-0.13
FMQ 7 months postnatal	0.58*	0.23	-0.16
FMQ 8 months postnatal	0.45	0.20	-0.26
FMQ 9 months postnatal	0.60	0.14	-0.29
FMQ 10 months postnatal	0.63*	0.21	-0.16
FMQ 11 months postnatal	0.77*	0.46	-0.12
FMQ 12 months postnatal	0.70*	0.36	-0.19

Table 7: Correlations between Fine Motor Quotient (FMQ) and scores on BABE tests of visual fixation, visual tracking, and visual field integrity by postnatal age (* = $p < .05$)

Conclusion

Tests of visual-manual coordination (two subtests of the Peabody Developmental Motor Scale) indicated that a large majority of preterm infants, when corrected age is used, showed average or above average (at 12 months) fine-motor performance. Some preterm infants did not seem to catch up from 6 to 12 months, and the percentage of infants with below-average coordination increased rather than decreasing over this period. Preterm infants with low muscle tone (hypotonia) showed less visual-manual coordination on the Peabody Developmental Motor Scale than preterm infants with high muscle tone (hypertonia), significantly so at 9 months and almost significantly at 10 to 12 months.

Also, we found no relationship between visual fixation and FMQ score in preterm infants. In contrast, we observed that visual field, which only tended to be lower in preterm than in full-term infants, was related to FMQ. Infants with higher scores on the visual field test had higher FMQs, significantly so at some sessions.

Handedness

Methods

Handedness was assessed with the baby handedness test (BbHtest) (Sacco, Moutard & Fagard, 2006) which consists of seven items (five to test simple grasping and two to test precision grasping). The objects used to test simple grasping were small baby toys: three Playmobil figurines, one musical toy (maracas), and a teeter. For precision grasping, one of the tasks consisted in removing a very thin red tube (6 mm in diameter) from a slightly shorter transparent tube into which it was inserted with only the top protruding, and the other task consisted in grasping a small horse inserted in a container 30 mm in height. All infants were tested every two months starting from 6 months until 12 months of postnatal age.

For the handedness test, a laterality index (LI) was calculated as follows: $[\text{number of right hand grasps} - \text{number of left hand grasps}] / [\text{Total number of grasps}]$. An absolute LI was also calculated to evaluate the degree of handedness, independently of its direction. We used the laterality index, rather than the z-score sometimes used with infants (see for instance, Nelson, Campbell & Michel, 2013) or with non-human primates (see for instance Hopkins, 2013) in order to take the bimanual grasps into account, and not only the percentage of right-hand grasps over the number of right-hand + left-hand grasps. However, given the small number of data, we used a Wilson z-score Interval suitable for small data (Brown, Cai, & Das

Gupta, 2001; Wallis, 2013). Thus, the confidence interval was calculated using Wilson's

formula: $\frac{1}{1 + \frac{1}{n}z^2} \left[\hat{p} + \frac{1}{2n}z^2 \pm z\sqrt{\frac{1}{n}\hat{p}(1 - \hat{p}) + \frac{1}{4n^2}z^2} \right]$. Children with Wilson score (WS) $> 50 - \text{CI}$ (confidence interval) were considered as right-handers. Children with WS $< 50 + \text{CI}$ were considered as left-handers. In accordance with Nelson et al. (2013), values that were within 5% of the 50% level were also considered lateralized. All children with WS falling between these values were considered as non-lateralized.

Results

The LI of full-term infants in a given session was compared to that of preterm infants in the following session. We first calculated an ANOVA on the LI with Age (6FT/8PT, 8FT/10PT, and 10FT/12PT; repeated measures), and Group (preterm vs. full-term infants) as independent variables. It showed a significant Group effect, $F(1,18) = 6.21, p = .023$, and a significant Age effect, $F(2,36) = 4.19, p = .023$. When both groups are considered, a post-hoc LSD test showed that LI significantly increased between the age of 6 and 12 months, $p = .003$. As a group, the preterm infants had a significantly lower LI over the three sessions (8, 10, and 12 months; LI = .22) than the full-terms (6, 8, and 10 months; LI = .52). The Group x Age interaction did not reach significance, $p = .154$. However, a post-hoc LSD test indicates that, when each age is considered separately, the difference between preterm infants and full-terms was significant only when 10-month-old preterm infants were compared to 8-month-old full-terms, $p = .002$. Thus, at 10 months postnatal age preterm infants were less right-handed than 8-month-old full-terms, thus even with a 2-month correction for corrected age (see Figure 3).

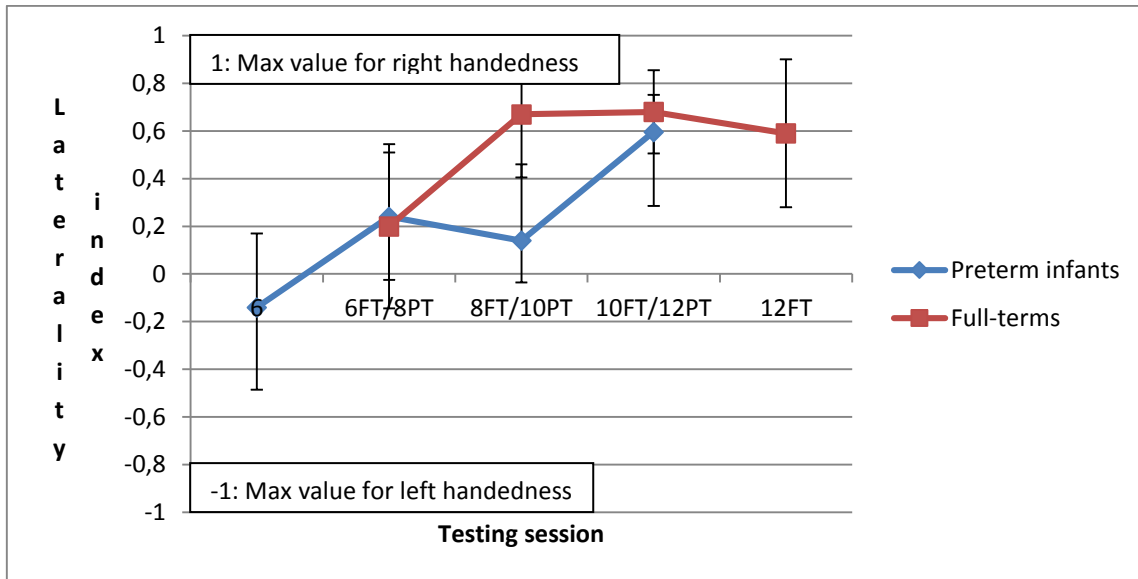


Figure 3: Laterality Index (LI) as a function of age (6, 8, 10, 12 months) and group (FT: full-terms; PT: preterm infants)

The same ANOVA on the absolute LI showed that full-terms had a significantly higher score (mean absLI = 0.70) than preterm infants (mean absLI = 0.47), $F(1,18) = 9.06$, $p = .007$, with no main effect of Age ($p = .26$) and no Age \times Group interaction ($p = .41$).

When infants were categorized from their Wilson z-score, chi-square tests showed no significant difference between preterm and full-term infants in the frequency in each category when each session was considered separately. When the z-score was calculated from all presentations across the three sessions the percentage of right-handers was 33.3% among the preterm infants and 70% among the full-terms. The rest of the infants were categorized as non-lateralized (preterm infants: 66.7%; full-terms: 30%). Although a chi-square test did not reach significance ($p = .08$), these results show that the preterm infants tend to be less right-handed than full-terms by being more often non-lateralized rather than by being more often left-handed.

We checked whether the laterality index of preterm infants varied with type of pregnancy (singleton vs. twins), birth weight (normal vs. low), gestational age at birth (33 weeks, 34 weeks, or 36 weeks), and muscle tone (hypertonia vs. hypotonia). For this purpose, we calculated a Mann-Whitney test on the LI on all these variables. Type of pregnancy, birth weight, and number of weeks of pregnancy had no significant effect on LI. At 6 and 8 months, there was no relationship between muscle tone and LI. At 10 months, hypotonic infants had a significantly lower LI (-0.61) than hypertonic infants (0.38), $z = -2.22$, $p =$

.0265. At 12 months both groups had a similarly positive LI (0.61 and 0.63 for hypotonic and hypertonic infants, respectively).

LI was not correlated with the BABE and FMQ or with bimanual performance.

Conclusion

Handedness evaluation showed that preterm infants, as a group, had a lower laterality index (LI) than full-terms, even when using a corrected age comparison which more than compensated for prematurity (since handedness was only tested every two months). However, when all sessions were considered, the preterm infants differed from the full-terms by being more often non-lateralized rather than by being more left-handed. Both groups' LIs increased between the age of 6 and 12 months, but at 8 months, the full-terms were significantly more right-handed than the preterm infants at 10 months. At 10 months hypotonic infants were less right-handed than hypertonic. At 12 months, the preterm infants were as likely as full-terms to be right-handed. Thus it appears that handedness takes longer to emerge among preterm infants than among full-terms, but that it finally settles with a large majority of right-handers.

Bimanual coordination

Methods

Bimanual coordination was assessed using a bimanual task, the tube/container task. The task consists in extracting a plastic tube from a wooden container into which it is partly inserted. It requires the spatio-temporal coordination of complementary movements of the hands, a capacity that develops toward the end of first year (Fagard, 1998). The behavior was coded as successful if the infant grasped the wooden container with one hand and pulled the tube out with the other hand. It was coded as failed when infants simply manipulated the toy, put the protruding part of the tube into their mouth, or shook the container. If the random manipulation of the container caused the tube to fall out by chance (which rarely happens, but can, for instance if an infant vigorously shakes the container, or pulls the container while holding the tube in his or her mouth), then the test was given a second time to check whether the infant was able to repeat the extraction of the tube. If the infant succeeded with the same unimanual strategy on this second attempt, it was coded as half-success. We gave only a second trial in case of failure at the first trial because we observed that when infants are ready

to succeed, they do it at the first or the second trials. When they keep failing at the second trial, repeated trials and even a demonstration by the adult do not help (Esseily, Nadel & Fagard, 2010). The tube/container task was given at 10, 11, and 12 months to preterm and full-term infants.

Results

Performance on the bimanual task was coded 0 (failure), 1 (half-success) or 2 (full success). There were very few half-successes and only at 10 months. Corrected age comparisons using a chi-square test showed a non-significant tendency toward lower performance in preterm infants at 11 months postnatal age in comparison to 10-month-old full-term infants. Twelve-month-old preterm infants had a significantly lower performance than 11-month-old full-terms, $\chi^2(1) = 4.02, p = .04$ (see Figure 4).

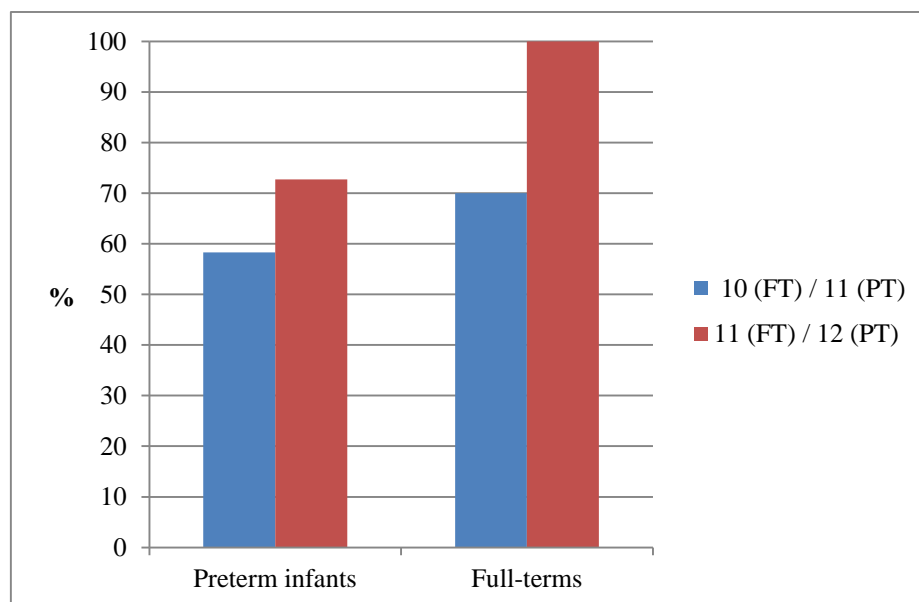


Figure 4: Success on the bimanual task as a function of group and age

We checked whether the bimanual performance of preterm infants varied with birth weight (normal vs. low), number of weeks of pregnancy (33 weeks, 34 weeks, or 36 weeks), and muscle tone (hypertonia vs. hypotonia). Fisher exact test showed that at 10 months, there was no significant difference in bimanual performance according to these factors. At 11 months, normal-weight preterm infants tended to be more successful (83.3% success) than low-weight preterm infants (33.3% success), but the difference did not reach significance ($p = .12$). At that age, late preterm infants were significantly more successful (85.7% success) than

moderate preterm infants (20% success), $p = .0455$. Similarly, hypertonic 11-month-old infants were significantly more successful (70%) than hypotonic infants (0%), $p = .0455$. At 12 months, the difference according to birth weight and number of weeks of pregnancy was much reduced and not significant. But also at that age, hypertonic infants were significantly more successful (100%) than hypotonic infants (0%), $p = .0061$.

Preterm infants who were successful at the bimanual test at 11 and 12 months had also a larger visual field than infants who failed. A Mann-Whitney test showed that the difference did not reach significance at 11 months, $z = -1.62$, $p = .104$, but was significant at 12 months, $z = -2.04$, $p = .041$. No other relation was found between the BABE and bimanual success. In addition, bimanual performance was not correlated with the laterality index.

Finally, we checked whether the bimanual performance was related with FMQ at 10, 11 and 12 months. At 11 months, but not at 10, the FMQ score was significantly higher in infants having succeeded on the bimanual task (FMQ = 101.3) than in infants having failed (FMQ = 90.4), $F(1,10) = 17.06$, $p = .002$. Similarly, at 12 months, the FMQ score was significantly higher in infants having succeeded on the bimanual task (FMQ = 101.3) than in infants having failed (FMQ = 89), $F(1,10) = 8.7$, $p = .002$.

Conclusion

Bimanual coordination was delayed in preterm infants in comparison to full-term infants, and the former were less successful than the later on the bimanual task when compared by corrected age, significantly so at 11 months (12 months postnatal age for preterm infants).. In addition, hypotonia was also associated with lower bimanual coordination, significantly so at 12 months postnatal age: at that age all hypertonic preterm infants succeeded whereas all three hypotonic infants failed. We observed that visual field, which only tended to be lower in preterm than in full-term infants, was correlated with bimanual coordination. Infants with higher scores on the visual field test were significantly more successful at bimanual coordination at 12 months, and to a lesser extent, at 11 months. Finally, the bimanual performance was related with FMQ at 11 and 12 months, FMQ score was significantly higher in infants having succeeded on the bimanual task than in infants having failed.

Gross motor development

Methods

The gross motor development of the infants in both groups was followed from 6 to 12 months. Parents were given a questionnaire with developmental gross motor milestones. The questionnaire is a short version of the questionnaire used by Garrett, McElroy, & Staines (2012). On a monthly basis parents were asked to circle the milestones that their child had accomplished and at what age, until the child began to walk independently. Infants received a score of 1 for being able to rotate their body, 2 for the ability to sit independently, 3 for crawling, 4 for standing with support, 5 for walking with support, and 6 for walking independently.

Results

When the two groups were compared using corrected age, an ANOVA with Group (x 2) as a between-subjects factor and corrected Age (x 6: 6FT/7PT, 7FT/8PT, 8FT/9PT, 9FT/10PT, 10FT/11PT and 11FT/12PT) as a within-subjects repeated variable, showed a significant effect of Age, $F(5,100) = 221.19$, $p = .00000$, but no effect of Group (see Figure 5). There was no Age x Group interaction.

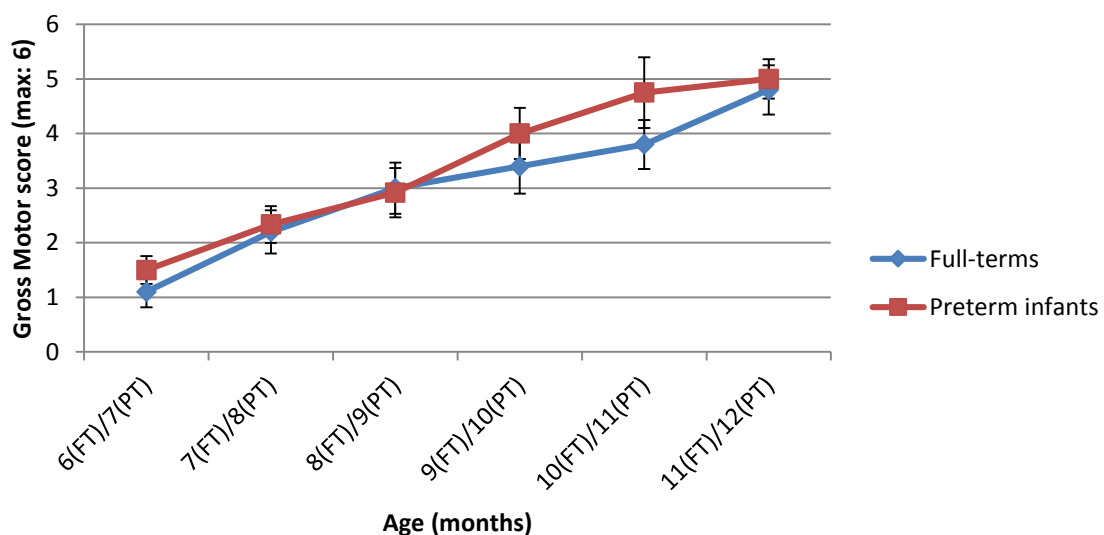


Figure 5: Gross motor score as a function of group and age (1: Rotates; 2: Sits independently; 3: Crawls; 4: Stands with support; 5: Walks with support; 6: Walks independently)

Since the preterm group included more twins than singletons, and late than moderate preterm infants, we used a Mann-Whitney test to check whether these factors influenced gross motor development. In addition, we checked the effect of category of birth weight and muscle tone. We found no significant difference for any of these parameters.

There was no correlation between the score of gross motor development and vision estimated at BABE. Except at 6 months, gross motor development was positively correlated with the FMQ score, significantly so ($p < .05$) at 7, 9 and 10 months postnatal age ($r = -.48, .70, .46, .65, .63, .43, .29$, at 6, 7, 8, 9, 10, 11, and 12 months, respectively). Gross motor development was not correlated with handedness and there was no correlation between gross motor development and bimanual performance at the three ages tested.

Conclusion

Our results on gross motor development showed that it was not delayed in preterm group, when compared to full-term group according to corrected age. We did not present the results for postnatal age, for the sake of coherency with the other results. But let us mention that when compared according to postnatal age, the preterm infants caught up, and starting at 10 months the difference between the two groups disappeared and preterms infants even tended to be better.

General conclusion for Study 1

The goal of our first study was to evaluate visual-manual coordination, bimanual coordination, and handedness in preterm infants without neurological impairments from 6 to 12 months of postnatal age in comparison to their full-term peers, after having checked, prior to the start of the longitudinal study, their visual functions. In addition, gross motor development was also evaluated and compared to all other evaluations.

Thus, we first evaluated whether 5-month-old preterm and full-term infants were comparable for vision. The preterm group performance did not differ significantly on any of the subtests, although the difference between preterm and full-term infants on the visual fixation test (in favor of the latter) nearly reached significance. These results are in line with others indicating that visual fixation may be less mature in preterm infants (Ricci et al., 2011;

Romeo et al., 2012). This point is of importance given the preponderant role of visual fixation in the development of grasping and reaching, but also in the establishment of early relationships, joint attention and imitation (Dutton, 2014). However, we found no relationship between visual fixation and FMQ score in preterm infants. In contrast, we observed that visual field, which only tended to be lower in preterm than in full-term infants, was correlated with FMQ and with bimanual coordination. Infants with higher scores on the visual field test had higher FMQs, significantly so at some sessions, and were significantly more successful at bimanual coordination at 12 months, and to a lesser extent, at 11 months. The fact that we did not observe a performance difference between the two groups on the visual tracking test is not in line with findings reported in other studies (Ricci et al., 2008; Grönqvist, Brodd & Rosander, 2011). This relative lack of visual impairment may reflect accelerated maturation of aspects of visual function correlated with ocular stability and tracking with early extrauterine experience: for instance, Ricci and colleagues (2008) found that low-risk preterm infants tested at 35 weeks and 40 weeks had significantly more mature ocular movements, better vertical and arc tracking, and, at 40 weeks, better stripe discrimination than full-term infants tested 48h after birth. Preterm infants with hypotonia had significantly lower visual field integrity scores than those with hypertonia. But this should be interpreted with caution since only three preterm infants had hypotonia.

Regarding the comparison of visual-manual coordination, bimanual coordination, handedness, and gross motor development, preterm infants were compared to full-term infants using corrected age.

Tests of visual-manual coordination (two subtests of the Peabody Developmental Motor Scale) indicated that a large majority of preterm infants showed average or above average (at 12 months) fine-motor performance. It is intriguing that some preterm infants did not seem to catch up from 6 to 12 months, and that the percentage of infants with below-average coordination increased rather than decreased over this period. These results are in line with other studies showing a lack of visual-manual coordination in preschool and school-age preterm group (Goyen, Lui & Woods, 1998; Luoma et al., 1998; Caravale et al., 2004; Vicari et al., 2004; Baron et al., 2009; Caravale et al., 2012). They are not in line with the findings reported in some other studies which observed similar performance in preterm and full-term population compared according to corrected age (Romeo et al., 2012).

Bimanual coordination was delayed in preterm infants in comparison to full-terms, and the former were less successful than the later on the bimanual task when compared by

corrected age, significantly so at 11 months (12 months postnatal age for preterm infants). To our knowledge, this is the first time bimanual coordination has been evaluated in preterm infants. We tested this because of the role played by the corpus callosum in the bimanual coordination of complementary movements (Preilowski, 1972) and the white matter abnormalities found in preterm infants (Marlow, Hennessy, Bracewell, Wolke, & EPICure Study Group, 2007; Narberhaus et al., 2008; Braddick & Atkinson, 2013). This lower performance of our group of preterm infants may reflect lesser maturation of the corpus callosum and correspondingly weaker interhemispheric communication. One study has observed less efficient interhemispheric transfer in very preterm born 8-year-old children compared to full-term born children (Schneider et al., 2008).

Handedness evaluation showed that preterm infants, as a group, had a lower laterality index (LI) than full-terms, even when using a “corrected” comparison which more than compensated for prematurity (since handedness was only tested every two months). However, the preterm infants differed from the full-terms by being more often non-lateralized rather than by being more left-handed. Both groups’ LIs increased between the age of 6 and 12 months, but at 8 months, the full-terms were significantly more right-handed than the preterm infants at 10 months. These results are in line with previous studies showing less lateralization in preterm than in full-term infants (Fox, 1985; Rose & Feldman, 1987; Marlow, Roberts & Cooke, 1989; Saigal et al., 1992; Schafer, Lacadie & Vohr, 2009; Soria-Pastor et al., 2009; Domellöf, Johansson & Rönnqvist, 2011). At 12 months, the preterm infants were as likely as the 10-month-old full-terms to be right-handed. This is interesting to compare with observations that 7-8 year-old preterm-born children were still more often mixed-handed than same-age full-term born children (Ross, Auld, Tesman & Nass, 1992). The lack of correlation between handedness and visual-manual skills is in agreement with other results showing no relationship between handedness and motor skills, although this has been observed in extremely low birth weight infants (O’Callaghan et al., 1993).

Our results on gross motor development showed that it was not delayed in the preterm group, when compared to the full-term group according to corrected age. These results are coherent with previous results showing that preterm infants catch up in gross motor development during the first year (O’Callaghan et al., 1993; Saigal et al., 1992).

The preterm group included twins, contrary to the full-term group. However, twinning was never a significant factor in variability among preterm population. The other factors

tested to account for the variability among preterm group, and thus to explain why some preterm infants have a delayed visual-manual development compared to full-term infants, were muscle tone, number of weeks of pregnancy, and birth weight. All these comparisons should be interpreted with caution due to the small size of each subgroup.

Muscle tone in our study sample seems to be the main factor that accounts for this variability. Hypotonicity has often been observed in preterm infants (Pineda et al., 2013). Here we observed that preterm infants with low muscle tone (hypotonia) showed less visual-manual coordination on the Peabody Developmental Motor Scale than preterm infants with high muscle tone (hypertonia), significantly so at all ages. In addition, hypotonia was also associated with lower bimanual coordination, significantly so at 11- and 12-month postnatal age. A lack of regulation of muscle tone could lower infants' level of arousal, slow their motor execution and make them more prone to motor fatigue. One way of explaining visual-motor impairment in the preterm group is with reference to the cerebellum. The development of the cerebellum, which is involved in dynamic feedforward motor control, has been found to be impaired in preterm infants (Allin et al., 2004; Limperopoulos, Soul & Gauvreau, 2005). The cerebellum is important in muscle tone regulation (Shah et al., 2006) which could explain why muscle tone modulated performance in our study. We also found an interaction between muscle tone and visual field integrity, with hypotonic preterm infants showing significantly lower visual field score. One possible explanation for this finding would be the connection of eye movements and muscle tone with the cerebellum, which is important for eye and head movements (Prsa & Their, 2011). Still future research is needed to confirm the effect of muscle tone on performance of preterm infants on large sample size.

Gestational age at birth did not significantly influence scores on the Peabody Developmental Motor Scales, but it influenced performance on the bimanual test at 11 months, when this type of bimanual coordination normally emerges (Fagard, 1998). This finding is interesting to compare with Schneider et al. (2008)'s observation that degree of prematurity influences interhemispheric transfer. Even though no statistics could be made, it is worth noting that the two 33-week preterm infants had a very low LI compared to the 34- and 36-week preterm infants up to 12 months when they finally had a normally high LI (Michel, Ovrut & Harkins, 1985; Fagard & Lockman, 2005). Thus, degree of prematurity seems to partly account for the preterm group's results on the emergence of a new skill such as bimanual coordination or of new movement organization such as having a preferred hand. These results should be confirmed with a larger sample of preterm infants, but similar

findings on the effect of degree of prematurity on movement organization have been reported in other studies (Domellöf, Johansson & Rönnqvist, 2011). Birth weight did not influence significantly any of the results.

To summarize, our results indicate that, although the preterm infants in our study were without neurological impairment, as a group they had delayed visual-manual development, including visual-manual integration, grasping, bimanual coordination, and handedness even though corrected age was used for comparison with full-term infants. Muscle tone and, to a lesser extent, number of weeks of pregnancy and visual field integrity, accounted for some of the differences between preterm and full-term infants, and for the variability among preterm infants. Because of the small sample of preterm infants of this study, we should be careful in our conclusions.

Nevertheless, we thought interesting to investigate if delays in grasping, visual-manual coordination and handedness within first year of life would have an influence on infants' development of the notion of object cohesiveness. We believed that studying development of this skill within first year through means-end tasks (e.g. composite object task) could bring us closer to understanding neuropsychological deficits seen later in preschool and school age period.

5.2. Study 2: The development of cohesiveness in preterm infants

As mentioned in the introduction, full-term infants integrate the notion of object cohesiveness into their action plan between 6 and 8 months of age (Fagard et al., 2015). This allows them to understand that they can grasp a composite object by any part. The goal of the second study was to investigate whether preterm infants would develop this skill normally or not.

Methods

The same 10 full-term and 12 preterm infants as in study 1 were given the composite object task at 6, 8, and 10 months. Preterm infants were given an additional session at 11 months so that they could be compared with 10-month-old full-terms. Infants were presented with a brightly decorated ball attached to the end of a featureless white cardboard handle (see Figure 6). The handle was either straight or L-shaped. In all conditions the ball was presented out of reach and the handle was presented within reach. In the “composite object” condition

(C1), the bright ball was attached to the end of the handle. In the “invisible disconnection” condition (C2), the ball was placed next to the handle so that it looked like it was attached to the handle, but actually was not.

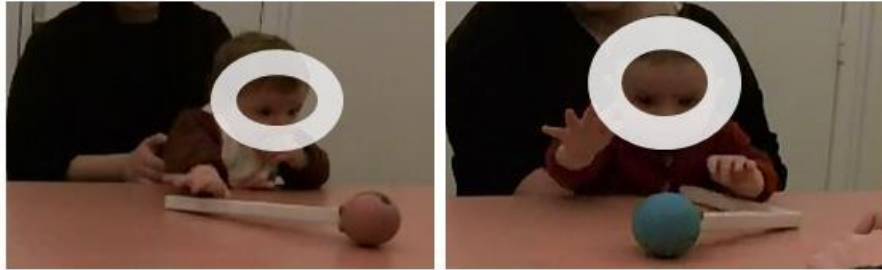


Figure 6: (a) Straight object, handle to the right (infants grasp the handle while looking at the ball, level 3); (b) L-shaped object, handle to the left (infant points to the ball, level 1)

To facilitate coding, objects were presented obliquely with the handle on one side and the ball on the other. All infants received four trials, two in the composite object condition (one with the straight object and one with the L-shaped object), and two corresponding trials in the invisible disconnection condition. The experimenter first placed the objects behind an occluder, and the trial began when the occluder was removed. Because we wanted to know the infant’s expectation after simply viewing the object, that is, before manually interacting with the object, we could only present each configuration (Straight and L-shaped) once. The “invisible disconnection” condition (C2) was always presented after the normal, “composite” condition (C1) so that it would not contaminate the composite condition.

Data analysis

All trials were videotaped. Analysis of the video recordings allowed us to code which part of the object – the ball or the handle – the infant was looking at while grasping. From the looking and grasping behavior of the child at each trial, we assigned him/her to one of three different levels of understanding of the composite object. The criteria were different for the composite object condition (C1) and invisible disconnection condition (C2), but in both cases they were designed to assess the degree to which the infant understood the link between the handle and the ball.

In the composite object condition (C1), the main criteria used to define the different levels were the relation between what the child does and where it looks:

Level 1: The child demonstrates no understanding of the link between handle and ball. This level is coded if one of the following behaviors is recorded: Child points only toward ball but does not grasp handle; Grasps handle after pointing to ball but without looking at ball anymore; Grasps handle without looking at ball at all; Ball's movement immediately triggers eyes' movement toward it; Looks at ball but does not grasp the handle.

Level 2: Transitional. We attributed this level if criteria for neither Level 1 nor Level 3 were present. An example would be if the child begs repeatedly for the ball before grasping the handle, or if the child grasps the handle after touching it by chance. Though defined by negation of levels 1 and 3, we assume that level 2 corresponds to the existence of real transitional mechanisms coming into play.

Level 3: The child clearly understands the link between handle and ball. This level is coded if one of the following behaviors is recorded: Grasps handle directly while looking at ball; Stretches second hand toward ball while pulling handle.

In the invisible disconnection condition (C2), the criteria used to distinguish the levels of comprehension involved the degree of surprise manifested by the child:

Level 1: The child demonstrates no understanding of the link between handle and ball. This level is coded if one of the following behaviors is recorded: Shows no surprise that the ball doesn't come; Does not look at the ball when it moves the handle.

Level 2: Transitional, neither clearly Level 1 nor Level 3.

Level 3: The child clearly understands the link between handle and ball. This level is coded if one of the following behaviors is recorded: Shows surprise that the ball doesn't come; Stops or changes the grasping movement after seeing that the ball doesn't come; Alternates looking between ball, handle and experimenter; Opens mouth; Opens eyes wide.

Since this kind of evaluation of how infants integrate the perception of a composite object in their grasping movement is relatively new and unfamiliar, we will first give a full account of the full-terms' results. Then we will compare these results to those of the preterm infants.

Results

Full-term infants

Composite object condition (C1)

In condition C1 the ball is connected to the handle. As one can see in Figure 7, the most frequently coded level at 6 months was Level 1, whereas at 8 and even at 10 months, Level 1 was the least frequently coded.

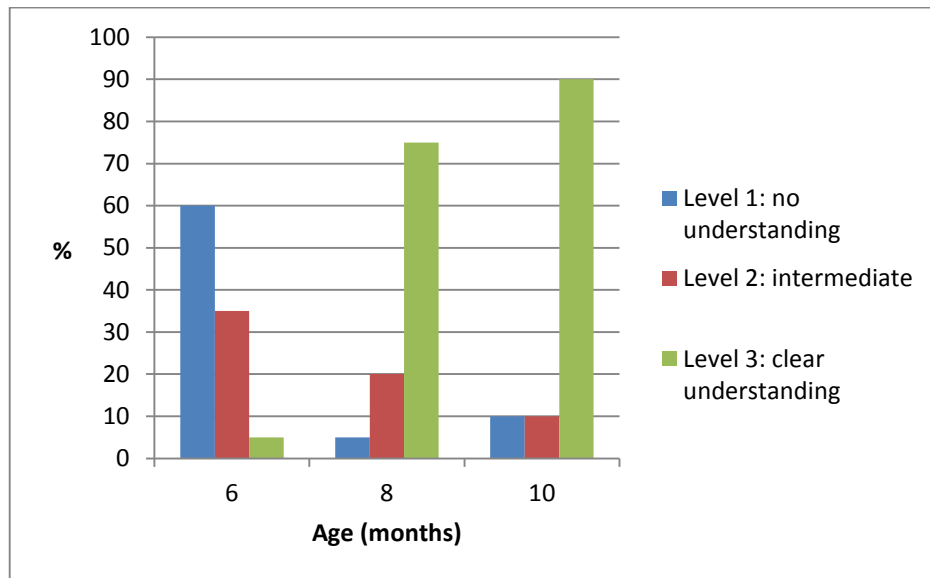


Figure 7: Frequency of each level of performance at each age at C1 (both objects pooled) in full-term infants

To check whether the performance changed significantly with age and differed according to the object, we calculated an ANOVA for repeated measures on the level of performance (1 to 3) taking Age (x 3, 6, 8, 10), and Object (x 2, Straight, L-shaped) as independent variables. The results show a significant main effect of Age ($F(2,18) = 47.97$, $p < .000001$). A LSD post-hoc test shows that the effect is due to the difference between 6 months and the two other ages ($p < .00001$ for both). Thus, infants showed a significantly better level of performance at eight than at 6 months, but they did not change significantly between 8 and 10 month ($p = .23$). There was no significant effect of Object. There was no Age x Object interaction.

Invisible disconnection condition (C2)

In this condition, the ball and the handle appeared connected. However, in fact they were only placed one against the other but not attached, so that when the infant pulled the handle, the ball did not come along. We expected to find an order effect in this condition. We expected that infants would show less surprise at the second presentation than at the first one, and so, that Level 1 would be obtained more often at the second trial than at the first one. But since in this second study the straight object was always given first, order effect is confounded with object effect. To check whether the level changes with age at Condition 2, and differs according to the object/ order, we calculated an ANOVA for repeated measures on the level of performance (1 and 3) with Age (x 3, 6, 8, 10), Object/Order (x 2, Straight, L-shaped) as independent variables. The results show a significant main effect of Age, $F(2,16) = 41.7, p < .000001$. A LSD post-hoc test shows that the effect is due to the difference between all three ages ($p < .0001$ for all comparisons). As can be seen in Figure 8, the level of performance increases with age, which means that as they grew older, infants were more surprised than before. There was no main effect of Object/Order and no significant interaction with Age.

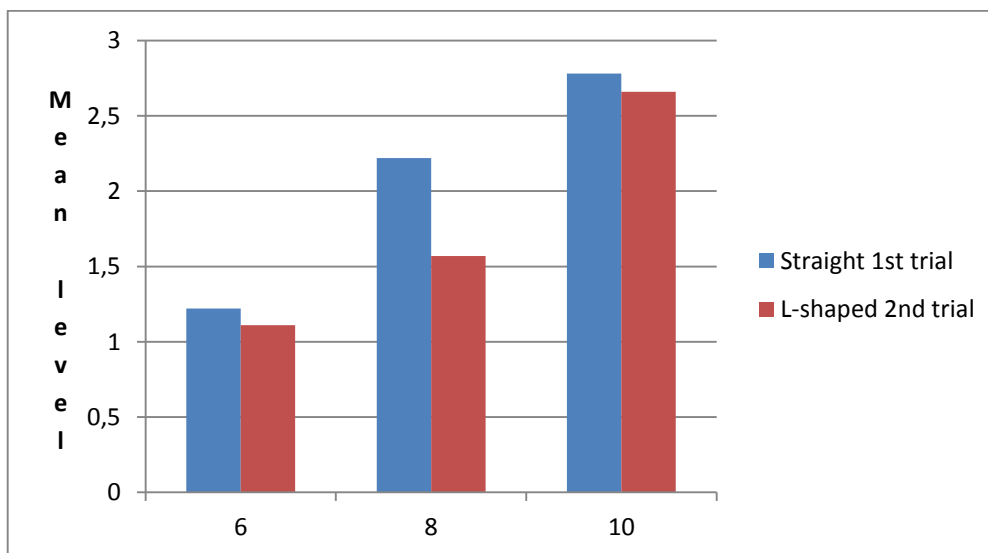


Figure 8: Mean level at C2 as a function of Age and Object / Trial in full-terms (the lower the level, the less surprised infants are)

Comparison between classifications in C1 and C2

We expected that infants who seemed unaware of the notion of composite object in C1 would show less surprise in C2 than those who seemed to understand that they could retrieve

the ball by grasping the handle in C1. To check this hypothesis, we calculated the correlation between the levels of performance in C1 and C2 for each age separately. There was a positive and significant correlation between the levels of performance in C1 and C2 at six months ($r = .64$), a positive but not-significant correlation at eight months ($r = 0.46$), and a positive and significant correlation at 10 months ($r = .93$).

Comparison between preterm and full-term infants

Composite object condition (C1)

The performance at C1 condition of full-term infants in a given session was compared to that of preterm infants in the following session. Since we found no effect of shape of the handle (straight vs. L-shaped), we took the mean between the two trials (one with straight shape and one with L-shaped). We calculated an ANOVA on the performance at condition C1 with Age (6FT/8PT, 8FT/10PT; 10FT/11PT; repeated measures), and Group (preterm vs. full-term infants) as independent variables. The results showed no significant effect of group ($p = .22$) but a significant effect of Age ($F(2,40) = 55.1, p = .0000$). A T-test for independent samples calculated separately for each age showed no significant difference between the two groups even at 6 months (Full-terms) compared to 8 months (Preterm infants) (see Figure 9).

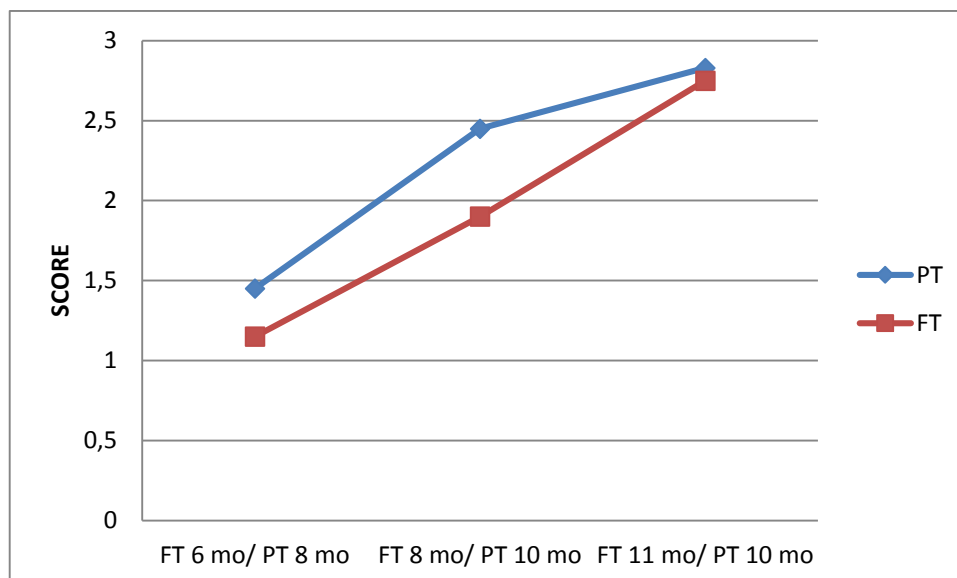


Figure 9: Score at composite object (C1) as a function of age and group

Invisible disconnection condition (C2)

The performance at C2 of full-term infants in a given session was compared to that of preterm infants in the following session. Since we found no effect of shape of the handle (straight vs. L-shaped), we took the mean between the two trials (one with straight shape and one with L-shaped). We calculated an ANOVA on the performance at condition C2 with Age (6FT/8PT, 8FT/10PT; 10FT/11PT; repeated measures), and Group (preterm vs. full-term infants) as independent variables. The results showed no significant effect of group ($p = .08$) but a significant effect of Age ($F(2,38) = 75.2, p = .0000$). A T-test for independent samples calculated separately for each age showed no significant difference between the two groups (see Figure 10).

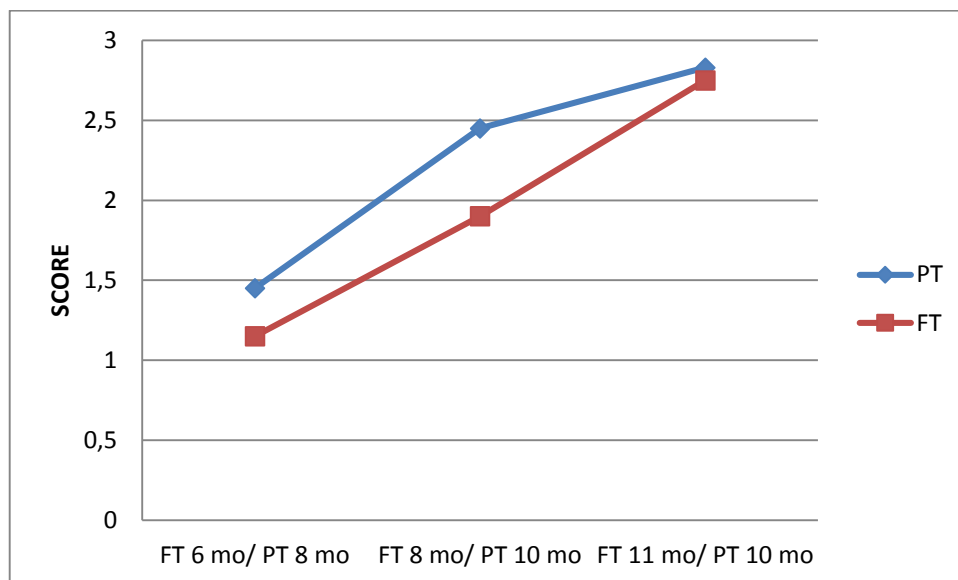


Figure 10: Score at composite object (C2) as a function of age and group

Finally we checked whether the performance at the composite object task differed with muscle tone, gestational age at birth and birth weight. We first calculated an ANOVA on the performance with Age (repeated measures) and Tonicity (Hypotonic vs. hypertonic preterm infants) as independent variables. At C1, besides the Age effect already mentioned, we found that hypotonic preterm infants had a significantly lower performance than hypertonic preterm infants ($F(1,10) = 14.1, p = .004$). There were no Age x Tonicity significant interaction. At C2, besides the Age effect already mentioned, we found that hypotonic preterm infants had a significantly lower performance than hypertonic preterm infants ($F(1,10) = 5.4, p = .04$). There

was no Age x Tonicity significant interaction. Birth weight and number of weeks of gestation had no effect on performance, neither at C1 nor at C2.

Conclusion

Whereas at six months, full-term infants often behaved as if they did not expect the handle and the ball to be connected, at eight and ten months most of them behaved as if they knew from visual inspection that the ball would come along with the handle. When compared with full-terms, preterm infants showed similar trajectory of development of understanding of composite object. Corrected age comparisons between preterm infants and full-terms showed no significant difference between the two groups. Full-term and preterm infants understanding of composite object notion was confirmed when we presented the infants with the trick, invisible disconnection condition, where handle and ball seemed connected but were only touching. In this condition infants looked more surprised that the ball did not come along with the handle as they grew older. Altogether, these results show that preterm infants improve their performance with age and “catch up” with time when compared to full-term infants. However, this is not true for all preterm infants: the hypotonic preterm infants had a significantly lower performance than hypertonic, at C1 as well as at C2, with no interaction with age of testing.

Based on these results it seems that preterm infants improve their performance within first year of life, but we can only hypothesize if the same can be said for later age stages. In our study 1 and study 2 we found that some preterm infants showed a delay on visual-manual development, bimanual development, handedness and development of notion of object cohesiveness (hypotonic infants and infants born after less than 34 weeks of gestation). One can wonder to what extent such a delay affects also the sensorimotor development during the second year of life. To answer this question we choose to observe the preterm infants from our longitudinal study on the emergence of tool use.

5.3. Study 3: The emergence of tool use in preterm infants

The goal of the third study was to evaluate how low risk preterm infants acquire tool use in their second year of life. Tool use is an important milestone in early sensorimotor period. In our longitudinal study on visual-motor development of low risk preterm infants between 6 and 12 months, preterm infants showed delayed visual-manual development, bimanual coordination, and handedness compared with full-terms. However, not all preterm infants from this study showed a delay: hypotonic infants and infants born after less than 34 weeks of gestation were more likely to have a delayed development than hypertonic infants or infants born after 36 weeks of gestation. One can wonder to what extent such a delay affects also the sensorimotor development during the second year of life. To answer this question we choose to observe the preterm infants from our longitudinal study on the emergence of tool use.

Methods

The twelve infants of the preterm group were the same that participated to the first two studies. Sixty infants were considered as a control group. All were full-terms. They were part of a cross-sectional study already published (Rat-Fischer, O'Regan, & Fagard, 2013). Five age groups of 12 participants were part of the control group: 14-month-olds (13 months 28 days to 14 months 13 days), 16-month-olds (15 months 28 days to 16 months 9 days), 18-month-olds (17 months 26 days to 18 months 4 days), 20-month-olds (19 months 27 days to 20 months 10 days), and 22-month-olds (21 months 25 days to 22 months 5 days). Infants were recruited from a list of local families who expressed interest in taking part in studies of infant development. Prior parental consent was granted before observing the infants.

For tool use the preterm infants were tested every two months from 15 to 23 months, thus at 15, 17, 19, 21, and 23 months. We choose to test them at these ages so that we could compare them to the full-terms tested at 14, 16, 18, 20, and 22 months. Thus, to correct for prematurity, the preterm infants were compared with full-terms a month younger.

Procedure

The apparatus was the same and the procedure was identical for the full-terms and the preterm infants. The experimental apparatus was designed to assess at what age and in which conditions infants are capable of using a tool to retrieve an out-of-reach toy. The desired toy was placed out of reach at different positions near a white cardboard rake-like tool designed to be visually plain (see Figure 11). During the whole experiment, infants sat in the lap of one of their parents in front of a table. The experimenter sat facing the infants behind the table. A digital video camera recorded the whole session.

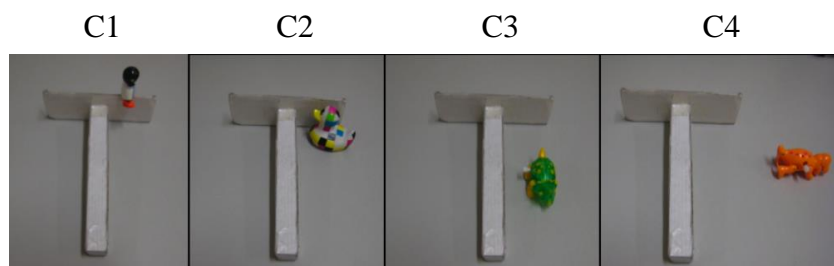


Figure 11: Five conditions of toy and tool placement

After the infants were familiarized with the surroundings and with the material, an attractive toy was placed in front of them successively in five conditions: toy attached to the rake part of the tool (C1: no spatial gap, attached), toy inside and against the rake part of the tool (C2: no spatial gap, unattached), toy inside the tool but not against it (C3: small spatial gap), toy to the side of the tool (C4: large spatial gap), and toy in the middle of the table with the tool directly held out to the infant by the experimenter (C5: effectively a very large spatial gap). The conditions were presented in order of increasing spatial gap from C1 to C5. All infants received one trial at C1, where they all immediately succeeded. They were then directly presented with two trials at C2. If both trials were successful, they received two trials at C3 (and so on until C5). If infants failed in one or both trials of a condition, they were given one or two additional trials of that condition. If infants failed to retrieve the toy on two of three trials, the parents or the experimenter gave two consecutive demonstrations of the failed condition. If infants failed in a condition after a demonstration, they were directly presented with the C5 condition. Thus, the C3 and C4 conditions were presented only if infants succeeded in the previous condition either spontaneously or after a demonstration; only the C1, C2, and C5 conditions were presented to all infants.

Data analysis

A trial was coded both for success or failure to retrieve the toy, and on the basis of a behavioral category for each infant. For this, a score of 0 was attributed when infants expressed no interest in the toy, the tool, or (more generally) the task; a score of 1 was attributed when infants were mostly interested in the out-of-reach toy, pointing toward it and possibly trying to retrieve it without using the tool; a score of 2 was attributed when infants were mainly interested in manipulating the tool itself, possibly alternating their attention between the toy and the tool but not in connecting the two; a score of 3 was attributed when infants systematically and repetitively brought the tool to bear on the toy but seemingly not with the purpose of retrieving the toy; a score of 4 was attributed when infants brought the tool to bear on the toy obviously with the purpose of retrieving the toy but failed. A score of 5 was attributed when infants succeeded in retrieving the toy with the tool.

The percentage of success was calculated in two ways: 1/ success (score of 1) or failure (score of 0) for the condition (success if the infant had been successful at both consecutive trials or at 2/3 of the trials of the condition; when infants were not tested at the following condition after repeated failure at the easier preceding condition, they were given a score of 0) and 2/ percentage of successful trials at the condition.

Results

Percentage of success and percentage of successful trials

Percentage of successful infants is shown on figure 12a and 12b. C1 is almost always successfully performed from the first session in both groups. In both groups there is a decrease of the percentage of success from C1 to C2 and to C3. There is a clear decrease in the percentage of success for the two most difficult conditions, C4 and C5, which do not differ much from each other.

An ANOVA for Group, Age, and Condition (repeated measures) was calculated on the percentage of successful trials. There was a significant effect of Age (x_5), $F(4, 68) = 31.3$, $p = .00001$; a significant effect of Condition (x_4 , C2, C3, C4, and C5), $F(3, 51) = 51.6$, $p = .00001$; a significant effect of Group, $F(1, 17) = 6.1$, $p = .024$. The interactions were not significant. A post-hoc test showed that C2 and C3 differ significantly from C4 and C5 ($p = .00001$ for all comparisons); C4 and C5 do not differ significantly ($p = .30$) and C2 differ

from C3 ($p = .009$). There was neither Group \times Age nor Group \times Condition significant interaction.

We calculated an ANOVA to test the difference between the two groups for each condition separately. There was no group difference at C1 and C2. For C3, the preterm infants were significantly better than the full-terms, $F(1, 19) = 7.7, p = .01$. A post-hoc LSD test shows that the difference is significant at 17-16 months, 19-18 months, and 21-20 months only. For C4 and C5 there was no significant difference between the two groups.

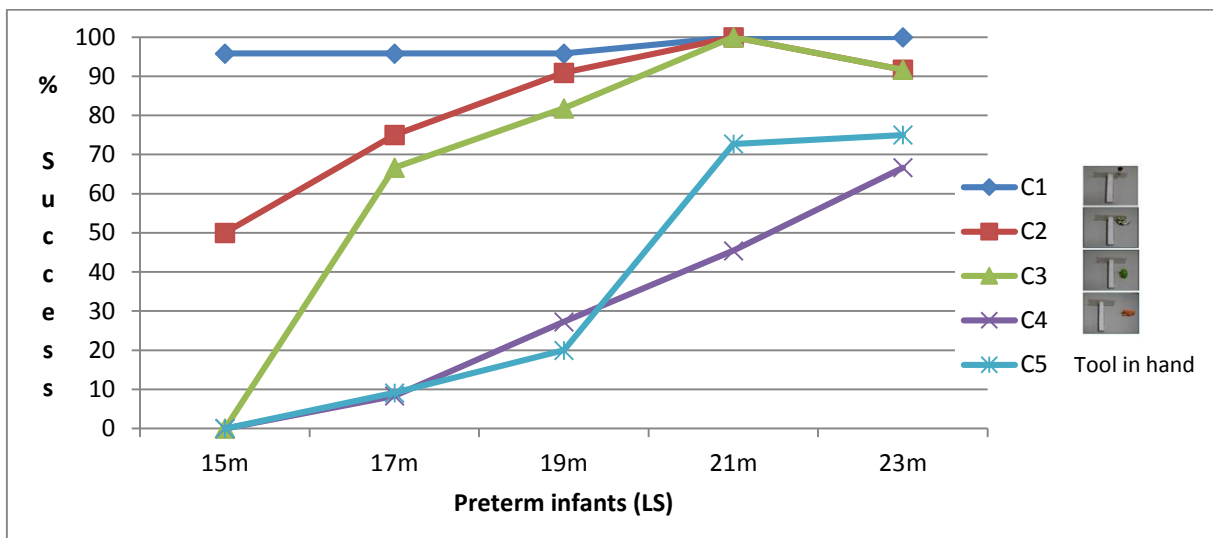


Figure 12a: Percentage of successful infants (Preterm infants)

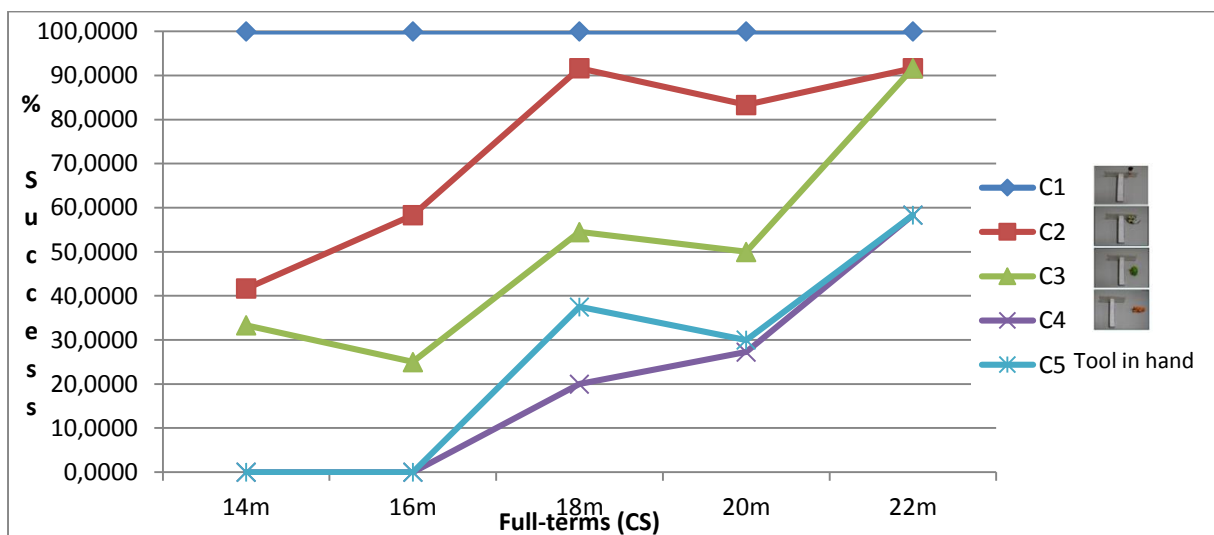


Figure 12b: Percentage of successful infants (Full-terms)

The influence of demonstration at C4 and C5

For the infants who did not succeed spontaneously, we gave a demonstration. We analyzed the effect of demonstration for C4 and C5 only because of small number of demonstrations at C2 and C3. We compared the mean score before and after the demonstration at C4 and C5. Before 18 months, there was no effect of the demonstration (see Figure 13). The level of performance increased significantly after demonstration at 21 months for the preterm infants, at 18 months and 22 months for the full-terms. We calculated an ANOVA for Group (x 2; Preterm infants, Full-terms), for Condition (x 2, Before Demo, After Demo, repeated measures) for each age separately. At 15-14 months, there was no effect of Group, no effect of Condition, and no Group x Condition interaction. At 17-16 months, there was no effect of Condition but a significant effect of Group, $F(1, 17) = 5.07, p = .04$. There was no Group x Condition interaction. The group of preterm infants has a higher mean score than the group of full-terms. At 19-18 months, there was no effect of Group but an effect of Condition, $F(1, 13) = 8.98, p = .04$. Infants had a higher score after than before demonstration. There was no Group x Condition interaction. At 21-20 months, there was an effect of Condition, $F(1, 12) = 12.8, p = .004$. There was also an effect of Group, $F(1, 12) = 10.8, p = .01$. The group of preterm infants has a higher mean score than the group of full-terms, and in both groups infants had a higher score after than before demonstration. There was no interaction. At 23-22 months, there was an effect of Condition, $F(1, 9) = 8.6, p = .017$, but no effect of Group and no interaction. In both groups infants had a higher score after than before demonstration. Thus, starting at 19-18 months, the effect of Condition was significant. Even though there was an effect of Group at 21-20 months, the absence of significant Group x Condition interaction indicates a comparable effect of demonstration for both groups.

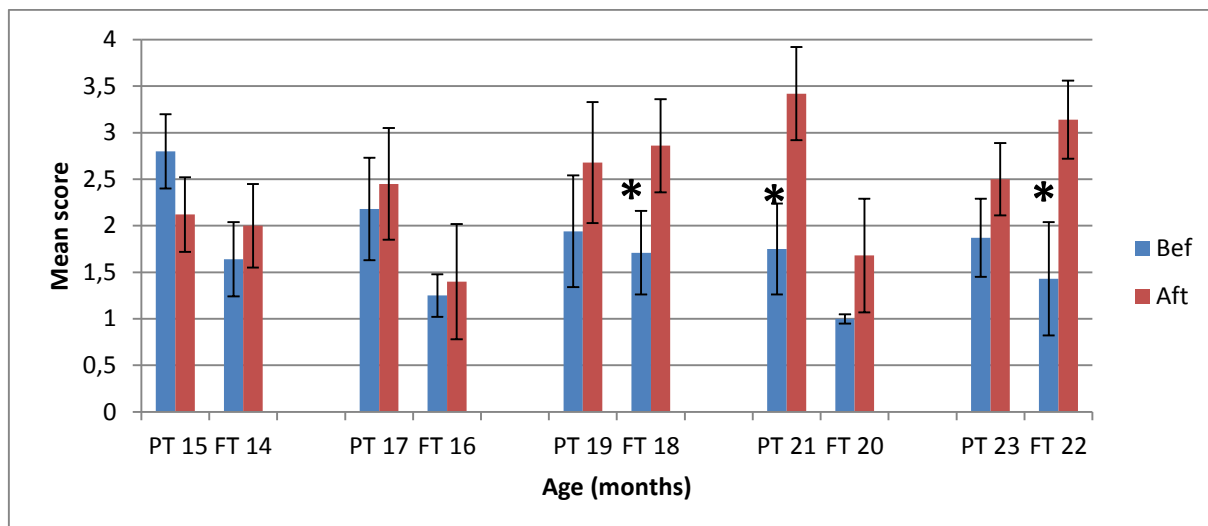


Figure 13: Mean score at C4-C5 Before versus After demonstration in Preterm (PT) and Full-term (FT) infants

Preterm infants' performance as a function of their characteristics (tonus, birth weight, prematurity)

We checked whether tool use performance varied with muscle tone (hypertonia vs. hypotonia), number of weeks of pregnancy (33 weeks, 34 weeks, or 36 weeks), and birth weight (normal vs. low). Given the lack of variance at 15 months, we could only compare the performance starting at 17 months. Globally, the three hypotonic infants were less successful at tool use than the nine hypertonic infants. The differences between hypotonic and hypertonic infants were small for C2 and C3 at 17 and 19 months and all preterm infants were successful at C2 and C3 at 21 and 23 months. For C4 and C5 none of the three hypotonic infants were successful, even at the last session (23 months) (see Table 8). Fisher exact test showed that the difference in percentage of success was not significant at 17 and 19 months. It was significant for C4 at 23 months, $X^2(1) = 8, p = .005$, and for C5 at 21 months, $X^2(1) = 6.5, p = .01$, and 23 months, $X^2(1) = 12, p = .0005$. An ANOVA calculated on the percentage of successful trials as a function of age (x 4: 17, 19, 21, 23 months; repeated measures), Muscle Tone (x 2), and Condition (x2: C4 and C5) showed a significant effect of Muscle Tone, $F(1, 9) = 7.6, p = .0122$. There was a significant effect of Age, $F(3, 27) = 5.2, p = .005$, but Condition was not significant. None of the interactions were significant.

Globally, the five infants born after 33 or 34 weeks (moderate preterm) were less successful at the two most difficult conditions (C4 and C5) of tool use than the seven infants born after 36 weeks (late preterms). Starting at 19 months, the late preterm had a higher

percentage of successful trials at C4 and C5 than moderate preterm. A Fisher exact test calculated at each age for C4 and C5 separately showed that the difference in percentage of success between moderate and late preterm infants was almost significant at 19 months for C4, $X^2(1) = 3.4$, $p = .06$, and significant at 21 months for C5, $X^2(1) = 4.9$, $p = .026$. An ANOVA calculated on the percentage of successful trials as a function of Age (x 4: 17, 19, 21, 23 months; repeated measures), Prematurity (x 2), and Condition (x2: C4 and C5) showed a significant effect of Prematurity, $F(1, 9) = 5.3$, $p = .050$. There was a significant effect of Age, $F(3, 27) = 11.05$, $p = .00006$, but Condition was not significant. The only significant interaction was Age x Prematurity, $F(3, 27) = 3.62$, $p = .027$. A post-hoc LSD test indicates that the difference of performance was significant only between 21 and 23 months for the moderate preterm infants, whereas it was significant between 17 and 19 months and 19 and 21 months for the late preterm infants. There was no difference of performance according to birth weight.

	Age (months)	17	19	21	23
Tonicity	Hypotonic	0	0	0	0
	Hypertonic	12.5	32.25	69.8	91.7
Prematurity	Moderate	16.7	0	30	46.7
	Late	3.3	45.8	77.9	89.4

Table 8: Percentage of success at C4-C5 (considered together) as a function of Age, Tonicity and Prematurity

Conclusion

Development of tool use in preterm infants emerges from a continuous and gradual process, as in full-term infants.

All preterm infants were successful at C1 (condition of composite object) from the first session. They were successful at the C2 and C3 (both conditions with no or small spatial gap), before being successful at the spatial gap conditions (C4 and C5). There was an increase in the frequency of success at C2 and C3 from 15 to 19 months when almost all infants were successful. However, at the C2 and C3 conditions, the toy was positioned so that it laid in the trajectory between the tool head and the infants. Thus, simply pulling the tool through a small distance would inevitably bring the toy into reach. Thus, in these conditions, successes could have been achieved by chance because infants could pull the tool and obtain the toy by pure spatial contingency. High scores in the C2 and C3 conditions with little or no spatial gap,

therefore, should not be considered as true indicators of infants' comprehension of the tool. In contrast C4 and C5 (both conditions with large spatial gap) could barely be succeeded by chance. Because of the spatial gap between the tool and the toy in these conditions, infants must understand the usefulness of the tool to succeed. Success at C4 and C5 occurred much later during development than success at C2 and C3. First spontaneous successes arose toward the end of the second year.

These results are close to the results obtained with the infants from a previous study that we used as full-term controls (Rat-Fischer, O'Regan, & Fagard, 2012). Preterm infants were compared with full-terms one month younger for correction for prematurity. The percentage of successful infants tends to be higher in the preterm than in the full-term group. The difference between the two groups is significant only for C3. This result indicates that, as a group, the preterm infants are not delayed in their acquisition of tool use. The tendency for them to be even better can be explained by the fact there was a correction for prematurity: it could be that at that age, the time spent after birth is more important than the total number of months since conception. Another reason for the better performance of the preterm infants, not exclusive of the first one, is that the preterm infants were tested longitudinally and therefore had the opportunity to practice, whereas the full-terms were seen only once. This is in line with the difference that was observed between a cross-sectional and a longitudinal study, the infants from the latter being clearly more advanced than the infants from the former (Rat-Fischer, O'Regan, & Fagard, 2012; Fagard, Rat-Fischer, & O'Regan, 2014).

When the infants failed, we gave them two demonstrations. The effect of the demonstration on the performance was analyzed for C4 and C5, by comparing the mean level of performance on trials before demonstration and after demonstration. In preterm infants, there was no effect of the demonstration before 19 months: starting at that age infants tended to have a higher mean score after demonstration. These results are close to those found with full-terms who start to score better after demonstration than before at 18 months. The absence of interaction between Group and Condition reveals that preterm infants are able to learn from observation of a model to the same extent and at the same age (corrected for the preterm infants) as full-terms.

Finally we checked whether, beyond the absence of group difference between the preterm infants and the full-terms, we would find individual differences within the group of preterm infants. Muscle tone was clearly associated with a lower performance within preterm infants. Hypotonic preterm infants were significantly less successful than hypertonic infants at 21 and 23 months for conditions C4 and C5. Our tool-use results indicate a persistence of the

effect of muscle tone during the second year.

Degree of prematurity also influenced the performance at tool use: the percentage of successful trials at C4 and C5 was significantly lower in moderate compared to late preterm infants. The significant interaction between age and prematurity indicates that late preterm infants start earlier to show some successful trials than moderate preterm infants.

In conclusion, our results indicate that, as a group, the preterm infants seem to have a normal development of tool use. However not all preterm infants developed tool use without delay. Hypotonic and moderate preterm children seemed delayed in their acquisition of tool use, in the same vein as they showed a delay in the acquisition of bimanual coordination and of handedness during their first year. Given the small number of infants, these results should be taken carefully and replicated on a larger population of preterm infants. However, they are interesting in that they confirm the first results obtained for visual-manual coordination on the same infants when they were younger. This should lead us to suggest some kind of early intervention programs on hypotonic preterm infants.

Chapter VI

General discussion and future directions

Introduction to importance of our research question

In the past decade, intellectual and neuropsychological performance of low risk preterm born children has been the focus of substantial number of studies due to observed negative impact of preterm birth on development of intelligence (Baron, Erickson et al., 2011), executive function (Baron et al., 2009; Baron, Kerns et al. 2011), attention (Huddy, et al. 2001; Linnet et al., 2012; Talge et al. 2010), language (Caravale et al., 2005; Nepomnyaschy et al., 2011), visual-motor and visual-spatial function (Baron et al., 2009; Caravale, et al., 2011) and overall academic achievement (Morse et al., 2009; Nepomnyaschy, et al., 2011). Although the deficits in visual-manual coordination in low risk preterm born children have been extensively studied in preschool and school age period the question of their emergence still remains open. In this thesis development of visual-manual coordination in low risk preterm infants in the first two years of life has been presented and discussed in details.

Our empirical findings

Results from our three studies indicate that, as a group, preterm infants seem to have a normal visual-manual coordination development during first two years of life when corrected age is used. However, not all preterm infants seem to develop visual-manual coordination without delay, showing no catch up from 6 to 23 months. Hypotonic and moderate preterm born infants seem delayed in their acquisition of visual-manual skills. Although very few hypotonic preterm infants participated in our studies, our conclusion has to be taken with care and should be replicated on a larger sample size. But also since the results are very coherent across the three studies, they might suggest implementation of special early intervention programs for hypotonic preterm infants in general practice. Indeed, hypotonicity has often been observed in preterm infants (Pineda et al., 2013) but its effect on action performance in preterm population has not gained significant attention. Here we observed that preterm infants with hypotonia already in first year showed less visual-manual coordination on the Peabody Developmental Motor Scale than preterm infants with hypertonia, lower bimanual coordination and less success than hypertonic infants in understanding the notion of object cohesiveness and in same vain less success at conditions C4 and C5 of tool use tasks. We also found an interaction between muscle tone and visual field integrity, with hypotonic preterm infants showing significantly lower visual field integrity score. As we already mentioned a lack of regulation of muscle tone could lower infants' level of arousal and by doing so slow their motor execution and make them more prone to motor fatigue. One way of explanations

for our results is with reference to the cerebellum which has been found to be important for muscle tone regulation and motor coordination, unfortunately the structure which seems to be impaired in preterm infants (Allin et al., 2004; Limperopoulos, Soul & Gauvreau, 2005; Shah et al., 2006).

Gestational age at birth influenced the scores on bimanual coordination and tool use performance making moderate preterm less successful when compared to late preterm infants. The interaction between age and prematurity indicates that late preterm infants start earlier to show success than moderate preterm infants. Thus, degree of prematurity seems to partly account for the preterm group's results on the emergence of a new skill such as bimanual coordination or that of a tool.

Theoretical implications

In this thesis we investigated possible ways prematurity affects trajectory of visual-manual coordination development, handedness, gross motor development and performance behavior on composite object and tool-use tasks, respecting maturational and environmental aspect (see for details Largo, 1993).

In our studies, we found that when using corrected age comparison (as such respecting maturational aspect) preterm as group show average development of visual-manual coordination (as seen on Peabody Developmental Motor scale), while there are preterm infants who seem to be delayed (e.g. in hypotonic infants) or show above average scores. The same can be said for performance on composite object/tool use task when compared to full-terms. One possible explanation of higher percentage of successful infants in preterm than in full-term group is due to correction for prematurity (which was not perfect in some tasks such as composite object task). Or that preterm infants were tested longitudinally and therefore had the opportunity to practice, whereas the full-terms were seen only once (as was the case for tool use task). The effect of practice on tool-use performance has also been observed in some other studies (Rat-Fischer, O'Regan, & Fagard, 2013; Fagard, Rat-Fischer, & O'Regan, 2015).

Nevertheless it seems that development of visual-manual coordination in preterm infants emerges from a continuous and gradual process, as in full-term infants. In addition preterm infants as a group improve their performance with time, stressing the role of environment on maturational aspect. Our results show that development of visual-manual coordination in preterm population is a result of integrative process of central nervous system

and infants dynamic interactions with the environment and by so preterm infants as a group are able to “catch up” in comparison to full-terms. Based on our results, there are preterm infants in which cases environmental experience seems insufficient in compensation for prematurity such as, in our study, moderate preterm born infants and those with hypotonia. These are the same infants who did not seem to catch up from 6 to 24 months. Since we were intrigued if our starting hypothesis about interaction of maturational and environmental factors was indeed correct, we performed (unpublished data) the analysis according to postnatal age comparison and found that between 8.3% and 31.7% preterm infants showed poor or below-average performance at 12 months on Peabody Developmental Motor Scale, also on the composite object tasks preterm infants were significantly worse when compared to full-terms on both conditions at 8 months.

Our results are in line with other studies showing a lack of visual-manual coordination in preschool and school-age preterm group (Goyen, Lui & Woods, 1998; Luoma et al., 1998; Caravale et al., 2004; Vicari et al., 2004; Baron et al., 2009; Caravale et al., 2012) but we can only hypothesize if lower gestational age or hypotonia accounted for variability in these studies. As such, following the development of preterm infants from our studies (especially those with hypotonia) in preschool period would bring us closer to answering this question. Our results are not in line with the findings reported in some other studies which observed similar performance in preterm and full-term population compared according to corrected age (Romeo et al., 2012).

Regarding the relation of visual-manual coordination with bimanual coordination, handedness, and gross motor development in terms of interaction of maturation and environment the results are following.

Examination of visual perception showed that even when postnatal age is used low risk preterm infants have similar performance when compared to full-terms. Although the difference between preterm and full-term infants on the visual fixation test (in favor of the latter) nearly reached significance. These results are in line with others indicating that visual fixation may be less mature in preterm infants (Ricci et al., 2011; Romeo et al., 2012). However we found no relationship between visual fixation and FMQ score in preterm infants. In contrast, we observed that visual field integrity, which only tended to be lower in preterm than in full-term infants, was correlated with FMQ and with bimanual coordination. This relative lack of visual impairment may reflect accelerated maturation of aspects of visual function such as visual tracking due to early extrauterine experience (Ricci et al., 2008).

Our results on bimanual coordination showed a significant delay in preterm infants at 11 months (12 months postnatal age) when compared to full-term infants even in both corrected and postnatal age comparison. To our knowledge, this is the first time bimanual coordination has been evaluated in preterm infants so future research is needed to confirm the results of our study.

Handedness evaluation showed that preterm infants have lower laterality index (LI) than full-terms at 12 months, making them more non-lateralized. In our postnatal age comparison this non-lateralization is even greater starting from 8 month. Our results are in line with previous studies showing less lateralization (Fox, 1985; Rose & Feldman, 1987; Marlow, Roberts & Cooke, 1989; Saigal et al., 1992; Schafer, Lacadie & Vohr, 2009; Soria-Pastor et al., 2009; Domellöf, Johansson & Rönnqvist, 2011). We found no correlation between handedness and visual-manual skills which is in agreement, although this has been observed in extremely low birth weight infants (O'Callaghan et al., 1993).

Our results on gross motor development are coherent with previous results showing that preterm infants catch up during the first year, also in same vain postnatal age comparison showed that difference between the two groups disappeared starting at 10 months. In addition we found no interaction between gross motor performance and visual-manual development (O'Callaghan et al., 1993; Saigal et al., 1992).

Future directions

Despite small sample size and subcategories of the sample our results should be confirmed with a larger sample of preterm infants. It would be interesting to continue to follow low risk preterm children in preschool period and evaluate which among the factors we observed in our studies (tonicity and gestational age) have an effect on visual-manual coordination development, cognitive development and sustained attention. We believe that this could bring us closer to understanding if one the important marker of neuropsychological deficits in low risk preterm children in preschool period is indeed hypotonicity.

Limitations

Despite our findings we should be careful in our conclusion. The reasons are following: small sample of preterm infants which was constituted from only 12 low risk preterm infants. Regarding the sample, half of the infants were from twin pregnancies, although twinning was never a significant factor in variability among preterm population. Subcategories of sample such as moderate/late or hypotonic/hypertonic, although accounted

for variability in analysis had only few participants (e.g. three infants with low muscle tone). One of the questions is medical documentation reliability, especially for muscle oscillation assessment, tested only by one physician.

Regarding the methodology, we systematically checked the results by comparing the performance of the preterm infants to the full-term infants during the previous session. Handedness test and composite object tasks were evaluated every two months but the corrected age was of two months instead of one. Thus the correction for age was not perfect except for the Peabody Developmental Motor Scale which includes correction for prematurity, tool use and bimanual coordination task. In addition, the BABE could only be compared according to the postnatal age of 5 months. Also in tool use study the preterm infants followed longitudinally were compared to 60 full-term infants which were a part of cross-sectional study and constituted the control group (Rat-Fischer, O'Regan, & Fagard, 2013).

Instead of conclusion

Despite limitations, this thesis adds new insight on development of visual-manual coordination and its underlying mechanisms in low risk preterm infants. Also, it is one of the first works which brings new information on development of bimanual coordination, handedness and object affordance in preterm population. Finally, it gives a detailed view from an action perspective approach how visual-manual coordination development is related to other developmental areas and experience.

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