Delayed Development of Visuomotor Capacity in Very Preterm Infants

KATARINA STRAND BRODD
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Abstract

To coordinate visual perception and motor control in daily life where we are constantly surrounded by motion, we are dependent on normal visuomotor capacity. One essential prerequisite for normal visuomotor capacity is smooth pursuit eye movements (SP). Infants born very preterm (VPT = born <32 gestational weeks) are at high risk of developing disabilities in higher brain functions i.e. perception, cognition, concentration and coordination.

In this thesis visuomotor capacity was investigated in a cohort of VPT infants (n = 113) and compared to control groups of full term (FT) infants. Levels of SP were measured at 2 and 4 months’ corrected age (CA). At 8 months’ CA reaching capacity toward a moving object was evaluated as this represents an executive activity guided by vision that develops at an early age.

Lower levels of SP were found in the VPT infants compared to FT controls. The VPT boys showed higher levels of SP compared to the VPT girls.

In VPT infants without major neonatal morbidities lower levels of SP was found compared to the FT controls. No difference in total capacity of gaze tracking was found, although the VPT infants lagged the object more at 4 months’ CA and used more saccades at 2 months’ CA.

With age the VPT infants’ SP levels increased, but with a wider dispersion compared to the FT controls, and the levels of SP at 4 months’ CA corresponded to the levels of the FT infants at 2 months.

A number of perinatal risk factors were found to be negatively associated to lower levels of SP, and this effect was more pronounced in VPT infants with multiple risk factors.

When evaluating the capacity to reach a moving object at 8 months’ CA, the VPT infants showed significantly more bimanual reach and more curved reaching paths to catch the object as compared to the FT control group.

In conclusion, a delayed visuomotor capacity was found in VPT infants compared to FT control infants at 2, 4 and 8 months’ CA. Some VPT infants with perinatal risk factors did not develop in levels of SP between 2 and 4 months’ CA.

Keywords: preterm infants, visual development, neurosensory development, smooth pursuit eye movements, perinatal risk factors, reaching movements

Katarina Strand Brodd, Department of Women's and Children's Health, Pediatrics, Akademiska barnsjukhuset, ing. 95 nbv, Uppsala University, Uppsala, Sweden.

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To all the LOVIS children and their families

“From little things big things grow”
(P. Kelly)
List of papers

I. Katarina Strand Brodd, Uwe Ewald, Helena Grönqvist, Gerd Holmström, Bo Strömberg, Erik Grönqvist, Claes von Hofsten, Kerstin Rosander

II. Helena Grönqvist, Katarina Strand Brodd, Kerstin Rosander

III. Katarina Strand Brodd, Helena Grönqvist, Erik Grönqvist, Gerd Holmström, Kerstin Rosander, Uwe Ewald
“Development of Smooth Pursuit Eye Movements in very preterm born infants. 3. Association with perinatal risk factors.” Accepted in *Acta Paediatrica 2011*

IV. Helena Grönqvist, Katarina Strand Brodd, Claes von Hofsten
“Reaching strategies of very preterm infants at 8 months corrected age”. *Experimental Brain Research 2011, Volume 209, Number 2, Pages 225-233*
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#### Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BPD</td>
<td>bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>BW</td>
<td>birth weight</td>
</tr>
<tr>
<td>CA</td>
<td>corrected age</td>
</tr>
<tr>
<td>FT</td>
<td>full term</td>
</tr>
<tr>
<td>GA</td>
<td>gestational age</td>
</tr>
<tr>
<td>Gain</td>
<td>gain of smooth pursuit eye movements</td>
</tr>
<tr>
<td>GW</td>
<td>gestational week</td>
</tr>
<tr>
<td>IUGR</td>
<td>intrauterine growth restriction</td>
</tr>
<tr>
<td>IVH</td>
<td>intraventricular haemorrhage</td>
</tr>
<tr>
<td>LOVIS</td>
<td>LOnitudinal VISual follow-up of visuomotor development</td>
</tr>
<tr>
<td>NEC</td>
<td>necrotizing enterocolitis</td>
</tr>
<tr>
<td>PDA</td>
<td>persistent ductus arteriosus</td>
</tr>
<tr>
<td>PMA</td>
<td>postmenstrual age</td>
</tr>
<tr>
<td>PPROM</td>
<td>preterm premature rupture of membranes</td>
</tr>
<tr>
<td>propSP</td>
<td>proportion of smooth pursuit eye movements</td>
</tr>
<tr>
<td>PVL</td>
<td>periventricular leukomalacia</td>
</tr>
<tr>
<td>ROP</td>
<td>retinopathy of prematurity</td>
</tr>
<tr>
<td>SDS</td>
<td>standard deviation score</td>
</tr>
<tr>
<td>SGA</td>
<td>small for gestational age (weight)</td>
</tr>
<tr>
<td>SP</td>
<td>smooth pursuit</td>
</tr>
<tr>
<td>VPT</td>
<td>very preterm</td>
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</table>
Introduction

For normal development of perception, coordination, concentration and cognition we are dependent on normal visuomotor capacity. Infants born < 32 gestational weeks (GW) are at high risk of developing later disabilities in these higher functions. Measuring and calculating smooth pursuit eye movements (SP) is a method to evaluate the capacity to follow, maintain attention on and predict the direction of moving objects with the eyes.

In view of this background, the studies in this thesis were performed to investigate early visuomotor development by measuring and evaluating smooth pursuit eye movements and reaching capacity in a population of infants born < 32 GW.

Visuomotor capacity

Visual perception is essential to the interpretation of visual stimuli into a meaningful whole in order to create adequate action on the stimuli. Normal visual perception is dependent on normal vision, e.g. visual acuity, visual fields, stereopsis, eye movements and as a consequence of this, normal development of the eye, the retina and the visual pathways and connecting nucleus in the brain (1-4).

Visuomotor capacity may be described as the ability to coordinate visual perception and motor control, or in other words, the capability to perform motor activities guided by visual perception (1). This implies that visuomotor capacity and visual perception are mutually dependent of each other.

Impairment in visuomotor capacity

Impaired visuomotor capacity can lead to difficulties in performing motor activities that are guided by visual perception. Specific symptoms of impaired visuomotor capacity could be described to be of four major types; a: impaired eye-hand-coordination including reaching, b: difficulties in movement and spatial orientation due to relative inability to discriminate, maintain attention on, and follow moving surroundings, c: difficulties in coordinating and executing movements that are guided by vision (1-3, 5, 6) and d: difficulties in following facial expressions, a variant of prosopagnosia (facial blindness) (7, 8). Examples of situations where deficiencies can appear in
daily life are the capability to react and act properly in traffic situations, in
sports, in the classroom and the playground. These impairments may also
lead to difficulties in following moving pictures on TV, computers etc, and
pronounced social disability due to the difficulties in following facial ex-
pressions.

Development of visuomotor capacity
Development of vision starts prenata lly although the visual system is the
single sensory system not exposed to patterned stimuli before birth. Synap-
togenesis in the primary visual cortex is found from 28 GW in human foet-
tuses and increases threefold until 40 GW (9), and spontaneous retinal activ-
ity before birth has been shown to produce connectivity patterns in the visual
pathways of the brain (10). At term age healthy infants are able to track,
fixate, discriminate and maintain attention at different distances, as reported
by Ricci et al 2008 (11). Postnatal development of vision continues to be
rapid during early childhood, although myelinisation and network building
between visual pathways is not completed until adult age (1, 12-15). At birth
and during the first two postnatal months infants uses saccades and head
movements, as well as a smaller amount of smooth pursuit eye movements
(SP) to track moving objects (1, 12, 16, 17). From two months SP develops
quickly and becomes one of the main prerequisites for normal visuomotor
capacity (1, 12, 18).

Smooth pursuit eye movements
Smooth pursuit eye movements (SP) are essential for focusing gaze on mov-
ing objects and are also considered an important part of our capacity to
maintain attention on a moving object and discriminate it from the back-
ground (17, 19). In order to visually track moving objects, the gaze in human
adults consists of more than 90% SP and the remaining 10% consists of head
movements and saccades (16, 17). Horizontal gaze tracking is reported to be
smoother than vertical tracking in adults (20, 21).

Development of Smooth Pursuit Eye movements
The development of smooth pursuit eye movements (SP) starts immediately
after birth, develops rapidly and is at an almost adult level at 4-6 months of
age (13, 16-18). Horizontal visual tracking with SP develops ahead of verti-
cal tracking with SP (22, 23). SP are essential in order to stabilise moving
objects on the retina and thereby predict the objects’ movement and this
predictive capacity is reported to be seen at 4-5 months of age, at which time
SP are almost fully developed (1, 16).
During the first sex weeks of postnatal life the main visual pathway for processing motion passes through the subcortical area of the brain via the superior colliculus (SC) and pulvinar nucleus (PU), bypassing the lateral geniculate nucleus (LGN) and the primary visual cortex (V1) direct to the human medial temporal cortex (+hMT). From 2 to 4 months’ postnatal age a rapid maturation of the LGN pathways takes place (24). After 4 months of age the primary visual pathway takes over as the main pathway of visual motion perception, passing through LGN to V1 and further to the +hMT and the dorsal pathways (1, 24-26). The dorsal pathway is the visual pathway responsible for our ability to identify “where” an object is, and it consists of magnocellular neurons, while the ventral pathway with mainly parvocellular neurons is responsible for the ability to identify “what” an object is (1, 2, 16, 17). (Fig. 1).

![Visual pathways in the brain](image)

**Figure 1.** Visual pathways in the brain. LGN=lateral geniculate nucleus, PU=pulvinar, SC=superior colliculus, V1=primary visual cortex, VENTRAL=the ventral pathway, DORSAL=dorsal pathway, hMT+=the human medial temporal cortex.

**Reaching capacity**

Reaching is an executive function of visuomotor capacity, where the capability of reaching is dependent on visual acuity, stereopsis, visual fields, eye movements and attention as well as coordination of the input and the motor activities performed (27, 28). This involves a number of cortical networks that are responsible for incoming stimulus, interpretation, executive guiding of activities and feedback systems (1). Reaching capacity is often assessed at
follow-up examinations (29-31), and side differences with postural adjustment at 4-6 months of age could be early signs of cerebral palsy (CP) as shown by Hadders-Algra et al (32).

Development of reaching

Eye and head movement are the earliest vision-guided systems to develop, while reaching develops somewhat later (1). Development of intentional reaching starts at around 3-4 months of age, although it has been found that infants from one week of age move their arms and hands in order to keep them in the visual field, and also that newborn infants use “prereaching” movements to approach a slowly moving object when they are fixating it (33-35). Between 3-4 and 9 months of age the intentional reaching and grasping develops with visual feedback to correct the direction of the reach, positioning of the hand and opening of the hand to catch the object. (33-36). When infants start intentional reaching they often use two hands (37), but during the first year of life the use of bimanual and unimanual reaching varies, also dependent on object size (38). At 5-6 months the use of a one-hand strategy increases, at the same time as self-sitting occurs. The dominance of unimanual reaching continues until 10-12 months of age at which time bimanual reaching again becomes more common. At this stage, the bimanual reach is less symmetrical than earlier, and is dependent on object size and complexity of the reach and grasp, similar to the reaching patterns of adults (1).

To reach for and catch an object that is moving requires the capacity to anticipate where the object will be when the hand meets it (28). This development has been found to start at around the same age as reaching for a stationary object i.e. at 4-5 months of age. At birth infants have been shown to be able to reach for and catch slowly moving objects (30 cm/s) while at 8 months this capacity had developed to faster moving objects (120 cm/s) (27, 39). Adult-like pattern of reaching and grasping for moving objects are not seen until 6-8 years of age (1).

Toledo et al and Fallang et al have reported that preterm-born infants used different motion patterns in reaching stationary objects compared to term-born infants as they used lower velocities and more adjustments during the reach (40, 41). It has also been shown by Fallang et al that inability to reach a stationary object at 4 months’ CA for the preterm infants was associated with adverse neuromotor development at 6 years of age (42). van der Meer et al and Kayed et al have described how preterm infants reaching for moving objects used a less efficient anticipatory strategy (velocity and distance instead of time) and later onset of reaching compared to full term infants at 5-12 months of age (28, 43, 44). van der Fits et al described in a group of preterm infants an excessive amount of postural activity that was temporally disorganized during reaching movements at 4-18 months of age compared to
a full term control group (45). In a recently published review article, Domellöf and Rönnqvist reported of a two-fold likelihood of non-right-handedness in preterm children compared to full term children (46).

Infants born very preterm

Care of infants born very preterm

The history of caring for newborn infants born before their estimated due date is quite short. VPT infants rarely survived until the 1930s at which time the first “premature units” were set up with gynaecologists in charge. The care was provided by nursing staff and focused on keeping the babies warm using incubators and feeding them with breast milk substitute (formula). Mothers were separated from their children during the hospital stay except for visiting hours. During the 1950s neonatal care units were opened in major paediatric clinics and therapeutic interventions such as oxygen therapy and exchange transfusions were introduced. In the late 1960s new medical technologies including continuous positive airway pressure (CPAP), ventilators, electronic monitoring, phototherapy, intravenous infusions and diagnostic methods such as ultrasound were introduced (47). The 1990s ushered in evidence-based therapies, e.g. surfactant therapy and prenatal steroid administration, that were based on randomized controlled studies with proven effect on survival (48, 49). Recently the importance of adequate growth and minimizing damage to the retina and the brain has focused interest on improved nutritional intake, strict monitoring and stabilization of oxygen saturation, carbon dioxide levels, blood pressure and fluid balance (50, 51).

A major change in the neonatal intensive care units (NICU:s) over the last ten years is that the parents have been re-introduced into the care of their babies with the goal of empowering them, encouraging the attachment process and also reducing the stress and pain that the infants experience by limiting stressful/painful care interventions as much as possible. This is also reflected in the increased implementation of the Newborn individualized developmental care and assessment program (NIDCAP) (52), Kangaroo mother care (KMC) (53) and family centred care (FCC) (54).

Survival rates

The mortality rate of VPT infants in Sweden decreased from almost 40% in 1973 to below 7% in 2009. (Fig. 2).
In the MOSAIC cohort from 10 European regions consisting of VPT infants born in 2003, the reported mortality rates differed from 7.3% to 21.5% (55). The recently reported neonatal survival rates from the NICHD neonatal research network (USA) with extremely preterm infants (EPT i.e. born before 28 GW) 2003-2007 ranged from 6% after 22 GW to 92% after 28 GW (56). In Japan 2005 the neonatal survival rates of infants with a birth weight (BW) of less than 1000 g ranged from 47% in the < 400 g BW group to 78% in the 500-599 g BW group and 91% in the 800-899 g BW group (57). In the Swedish EXPRESS study of infants born at less than 27 GW during 2004-2007 the survival rates were 9.8% at 22 GW, 53% at 23 GW, 67% at 24 GW, 82% at 25 GW and 85% at 26 GW (58).

Neonatal and long term outcomes

As the survival rate of VPT infants has increased, it has become increasingly obvious how important it is to study the outcome regarding neonatal as well as long-term morbidities of this vulnerable population.

VPT infants are at major risk of neonatal morbidities including bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), and necrotising enterocolitis (NEC). Even though the incidences of these major neonatal complications have decreased they are still high for the extremely preterm-born infants (< 27 GW) e.g. BPD = 25%, ROP > stage 2 = 34%, IVH > grade 2 = 10% and cystic PVL = 5.7% in the Swedish EXPRESS study (59, 60).
The incidence of later disabilities, often referred to as “major handicaps” i.e. cerebral palsy (CP), mental retardation (IQ < 70), blindness and deafness has not increased in spite of the fact that the survival of infants born < 28 GW has increased. The Victorian Infant Collaborative Study Group, Australia, reported 1991 on the 8-year outcome of infants born 1979 and 1980 with a birth weight < 1000 g. The incidences of handicaps were 8.9% for CP, 6.5% for mental retardation, 6.7% for blindness and 5.6% for deafness. The Swedish National Prospective Study of infants born 1990-1992 with a birth weight < 1000 g reported an overall incidence of 7% regarding these “major” handicaps (61, 62).

Symptoms of disturbances in concentration, coordination, cognition and perception are subtle, and become more obvious later in childhood compared to major handicaps – sometimes not until school age. When reviewing studies of outcome at school age from the 1990s and 2000s, impairments of these “higher functions” seem to be more common and are more in focus.

Increased risk for attention deficit hyperactivity disorders (ADHD), developmental coordination disorders (DCD) and autism spectrum disorders have been reported e.g. from Sweden by Lindström et al (63) from USA by Hack et al (64), from Australia by Davis et al (65) and from England and Ireland by Johnson et al (the EPICure study) (66). Children with these disorders have also been reported with impaired use of SP (6, 67).

Visual dysfunction were reported at 10 years of age in children born very preterm by Holmström et al (68), when assessing visual acuity, strabismus, stereopsis, contrast sensitivity astigmatism, visual fields, colour vision and refraction. Hellgren et al (5) found significantly lower visual acuity and stereo acuity and higher prevalence of astigmatism in adolescents born very preterm, while Langaas et al (6) reported on impaired smooth pursuit eye movements in 5-7 year old children born preterm.

When looking at neurosensory and cognitive outcome in early school age for children born preterm, the PIIPARI study group described poorer neuro-psychological functions, except for verbal memory, compared to the control group at 5 years of age (69). Marlow et al in the EPICure study group (70) showed that impairment of motor, visuospatial, and sensorimotor function contributes independently to poor classroom performance at 6 years of age and Pritchard et al (71) reported about lower academic results at 6 years of age, most pronounced in mathematics.

Saigal described the outcome at 8 years of age in a population of VPT children (BW < 1000 g), where children born very preterm did less well on the reading, spelling and mathematics tests, and motor performance and visual-motor integration were also poorer compared to the control group (72). Finnström et al (73) reported on a Swedish cohort of very preterm children (BW < 1500 g) where these children performed less well in most academic achievement tests and on some behavioural subscales compared to term-born control children at 9 years of age.
Studies that were investigating outcome in high school and in young adulthood after being born preterm reported of long-time sequel. Hack et al have described persistent educational disadvantage associated with BW < 1500 g, more pronounced for men than women (74). From Norway Lohaugen et al described a cohort of 19 year old young adults with a BW of < 1500 g, showing a global and lasting impact on cognitive ability where the subtest profile indicated problems on all subtests, but especially on those related to arithmetic and visual–perceptual tasks (75). From Sweden Gäddlin et al (76) showed poorer academic results at 15 years of age in a population with BW < 1500 g, and Finnström et al (73) reported on hyperactivity in the classroom, but no adverse social behaviour. Saigal and Doyle (77) reported in a review an increased risk of developing ADHD for children with a BW < 1500 g. Hack et al (74) could not find risk-taking and externalizing behaviour in their group of 20-year-old adults born preterm. Boyle et al from Canada described higher prevalence of internalizing problems (i.e. depression, anxiety, avoidant personality problems) but not externalizing problems (ADHD and antisocial personality problems) in a population of young adults with a BW < 1000 g when compared to term born controls (78).

Risk factors for subsequent disability

IVH > grade 2 and cystic PVL have been shown to be significant risk factors not only for major handicaps, but also for neurodevelopmental difficulties such as impairments in cognition, concentration, coordination and perception. Other major neonatal complications such as ROP, BPD, persistent ductus arteriosus (PDA), NEC, and neonatal infections have been shown to be associated with impaired development, particularly in combination with IVH and/or PVL (51, 79). The degree of prematurity, preterm premature rupture of membranes (PPROM), lack of treatment with prenatal corticosteroid, being born small for gestational age (SGA) and poor postnatal growth have also been reported to be significant risk factors for the development of impairments in cognition, coordination, concentration, perception and autism spectrum disorders (50, 69, 79-82).

It may be assumed that the causes of later neurodevelopmental disabilities are multifactorial and also include psychosocial factors related to maternal health and socioeconomic background, male gender, foetal and postnatal growth, complications during pregnancy and delivery, exposure to stress and painful neonatal environment. This has been reported from the Nordic countries by Finnström et al, Lind et al, Lohaugen et al, Munch et al and Farooqi et al (62, 69, 75, 80, 83), from United Kingdom and Ireland by Marlow et al (the EPICure study) (84), from France by Fily et al (the EPIPAGE study) (85), from USA (Cleveland, Rainbow Hospital) by Hack et al (74) and also in an overview article from Saigal et al (77).
The LOVIS project

Considering that VPT infants are at high risk of developing disabilities in cognition, perception, concentration and coordination, and the knowledge that normal visuomotor capacity is an important prerequisite to the development of these capacities, the LOVIS (LOngitudinal VISual) project was initiated in 2004 as a cooperative study between the Departments of Psychology, Neuroscience and Women’s and Children’s Health at Uppsala University, Sweden. The multidisciplinary composition of the group was intended to ensure a comprehensive view in this study of visuomotor development of VPT infants.

Ethical approval

The Human research Ethical Committee of the Medical Faculty at Uppsala University (nr Ups 03-665) has approved this project.
The general aim of the LOVIS project
To develop instruments for early identification of VPT infants with affected visuomotor capacity that might imply later impaired perceptual and cognitive development and also to investigate any associations between perinatal risk factors and visuomotor capacity.

Study I
To investigate the impact of preterm birth on early visuomotor development by measuring smooth pursuit eye movements (SP) at 2 and 4 months’ CA in a cohort of VPT infants and compare to a group of healthy term-born infants at the same corrected postnatal ages.

Study II
To investigate the impact of preterm birth on visual tracking a moving object at 2 and 4 months’ CA in a subgroup of VPT infants in the LOVIS cohort without severe neonatal complications or being born small for gestational age, and compare the results with a control group of healthy term-born infants.

Study III
To investigate if a number of defined perinatal risk factors in VPT infants were associated with early visuomotor development measured as SP at 2 and 4 months’ CA in the LOVIS cohort and to investigate if having more than one risk factor implied lower levels of SP.
Study IV

To investigate if very preterm birth in a subgroup of the LOVIS cohort had an impact on the infants’ ability to reach and catch a moving object at 8 months’ CA when compared to a group of full-term infants. A second aim was to investigate if the capacity to reach at 8 months was associated with the findings from neuromotor examinations performed at 2 and 10 months’ CA.
Subjects and methods

The LOVIS study in general

Subjects
A cohort of 113 out of all 145 live-born infants born before 32 GW in Uppsala during the time period 2004-2007 and treated at the Neonatal Intensive Care Unit at Uppsala University Children’s Hospital, Uppsala constitutes the entire LOVIS population. Gestational age was estimated by ultrasound in GW 16-18. Due to late neonatal mortality, 111 infants were available for follow up. (Fig. 3)

Figure 3. Flow chart over study population in the LOVIS cohort.

All infants were recruited into the study after the most intensive postnatal period, parental written consent was obtained after written and oral information given by the same neonatologist. Healthy term-born infants constituted
two different control groups, (see below for each study). For clinical characteristics of mothers and infants in the study group, see table 1.

Table 1. Clinical characteristics of mothers and infants

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of mothers’ (n = 95), mean and range (years)</td>
<td>31.8 (18.3 - 46.5)</td>
<td></td>
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<tr>
<td>Caesarean section, mothers (n = 95)</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>Infants delivered by caesarean section</td>
<td>68</td>
<td>60</td>
</tr>
<tr>
<td>Prenatal steroids</td>
<td>78</td>
<td>69</td>
</tr>
<tr>
<td>PPROM</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Boys/girls</td>
<td>61/52</td>
<td>54/46</td>
</tr>
<tr>
<td>Twins and triplets</td>
<td>35</td>
<td>31</td>
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<tr>
<td>Gestational age (n = 113) mean and range (GW)</td>
<td>28+5 (22+0 - 31+6)</td>
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<tr>
<td>Gestational age &lt; 28 GW</td>
<td>35</td>
<td>31</td>
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<tr>
<td>Birth weight, mean and range (gram)</td>
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<tr>
<td>SGA</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>deltaSDS, mean and range (SD)</td>
<td>-1.73 (-5.39 - +0.95)</td>
<td></td>
</tr>
</tbody>
</table>

**Methods**

*Perinatal risk factors and neonatal complications*

Prenatal steroid treatment was defined as treatment with one or two doses of corticosteroids > 12 hours before delivery. Preterm premature rupture of membranes (PPROM) was defined as rupture of the membranes > 24 hours before delivery. SGA was evaluated in accordance with the national foetal weight-based growth standard (86) and expressed as standard deviation scores below the mean (SDS; actual value minus mean/standard deviation). Infants with birth weights of more than 2 SDs below the mean were classified as SGA. Standard deviation scores for growth (deltaSDS) were related to the intrauterine growth standard (87) and compared the SDS at birth corrected for GA and the weight at 36 weeks postmenstrual age (PMA). BPD was defined as the need for at least 25% oxygen treatment to achieve a satu-
ration of > 90% at 36 weeks PMA, due to lung complications (88). ROP was defined according to the International Classification of ROP (89), and screening for ROP was performed by pediatric ophthalmologists weekly from 5 weeks’ postnatal age until the retina was fully vascularised i.e. around term age or until regression of ROP (60, 90, 91). IVH was defined according to Papile (92) and PVL was defined in size (mm), laterality and as cystic or diffuse (93, 94) and these investigations were performed at 2-7 days postnatally and at 35 weeks’ PMA by a pediatric radiologist using an ultrasound machine (Acuson Sequoia 512, Siemens Medical™, California, USA) and a 10 Hz probe. Necrotizing enterocolitis (NEC) was defined according to criteria defined by Bell (95). Neonatal septicemia was defined as clinical symptoms requiring treatment with intravenous antibiotics, positive blood culture and/or CRP > 30 mg/l. PDA was defined in accordance with the Swedish EXPRESS study as symptomatic ductus arteriosus necessitating pharmacological treatment, surgical ligation or both (59).

**Neuromotor development**

Neuromotor development examinations (NME) of the study population were performed at the outpatient unit, Uppsala University Children’s Hospital at 2 and 10 months’ corrected age (CA). They were performed by a neonatologist using a modified version of Touwen and Amiel-Tison and a physiotherapist using the Structured Observation of Motor Performance (SOMP) instrument that estimates both the infants’ level of motor development and the quality of the achieved motor function level (29-31). After the examination the neonatologist and the physiotherapist together made an overall evaluation of the infant’s performance and expressed the result as 1 = normal for CA, 2 = possibly abnormal for CA and 3 = abnormal for CA.

**Visuomotor capacity**

All examinations for visuomotor capacity were performed at Babylab, Department of Psychology Uppsala University. The measurements explored the infants’ capacity to visually track a moving object.

Smooth pursuit eye movements (SP) were recorded for the VPT and control infants at 2 and 4 months’ CA (16, 17). A specially designed apparatus was used, consisting of a cylinder 1 m in diameter and height with an opening sector. An infant chair was placed in the centre of the cylinder and a narrow horizontal slit faced the infant. In the slit, an object (a bright orange happy face, 7 cm diameter, see fig. 4 and cover picture) could be moved according to a triangular or sinusoidal pattern and two different amplitudes, 10 or 20 degrees. An opto-electronic motion recording system (Qualisys, Proreflex, Gothenburg, Sweden) was used to measure the object motion and the motion of the infants head. The horizontal eye movements were measured in synchrony with these measurements by using Electro Oculographic (EOG) recordings, using an amplifier system designed by G.Westling (De-
Head movements, saccades (defined as periods of the eye velocity recorded higher than 50°/s of the tracking velocity amplitude), SP and raw eye movements (the sum of saccades and SP) were measured. The ratio between the amplitude of smooth pursuit and the object (Gain), as well as the ratio between the amplitude of smooth pursuit and the total (“raw”) eye movement (propSP) was calculated. The ratio between the gaze amplitude and the object amplitude (Gain of gaze) was calculated for study II where the gaze amplitude is the sum of head movements and raw eye movements. Timing was evaluated as how much the eyes lagged or were ahead of the object motion.

Figure 4. Photography from inside the drum.

Study I

Subjects
113 VPT infants were included and background data including neonatal complications were recorded. Of the VPT infants in the LOVIS cohort 81 infants, 45 boys and 36 girls, with a mean GA of 28+4 weeks and a mean BW of 1083 g were investigated for propSP and Gain at 2 and 4 months’ CA. The dropouts consisted of 10 infants not called to the Babylab due to reduced resources and 20 infants not able to come due to logistic reasons or
being too fussy or tired during the examinations. There was no significant
difference between the investigated infants and the dropouts regarding gen-
der, age, BW or perinatal risk factors. Thirty-two healthy term-born infants,
17 boys and 15 girls, constituted the control group.

Methods
Neonatal clinical data, complications and perinatal risk factors were re-
corded as mentioned above for the LOVIS study in general.

Smooth pursuit eye movements were measured and calculated as the
mean values of both motion patterns (sinusoidal and triangular) and two
amplitudes (10 and 20 degrees) regarding propSP and Gain at 2 and 4
months’ CA, using the previously mentioned method and equipment.

Study II
Subjects
VPT infants without severe neonatal complications (no BPD, ROP, PVL,
IVH or NEC) and not born SGA constituted a “low risk” study group (N=37,
mean GA 29+6). The control group was the same as in study 1.

Methods
Neonatal complications i.e. IVH, PVL, ROP and presence of SGA were
defined as described above. Gain of gaze, propSP, head movements, sac-
cades and timing between eye movements and object were measured and
calculated at 2 and 4 months’ CA, using the methods described previously.
In this study both motion types and amplitudes were analysed separately.

Study III
Subjects
The same VPT infants as in study I were investigated regarding propSP and
Gain at 2 and 4 months’ CA and the results were analysed with respect to
perinatal risk factors.

Methods
Maternal and infant clinical data and perinatal risk factors were registered
and defined as described previously.

The associations between smooth pursuit eye movements measured as
propSP and Gain at 2 and 4 months’ CA and perinatal risk factors were
evaluated.
Study IV

Subjects
Of the 113 VPT infants in the LOVIS cohort 47 (23 girls, mean GA of 28+2 and 24 boys, mean GA 28+5 weeks) and a control group of 20 full-term infants (12 boys and 8 girls with a mean GA 39+5 weeks and mean BW 3535 g) were investigated in a study of reaching capacity at 8 months’ CA.

Methods
Neuromotor examinations of VPT infants were performed as described above. The overall evaluation (described previously) of the results from investigations at 2 and 10 months’ CA was used.

Reaching strategies and capacity were examined at 8 months’ CA (96). To investigate reaching capacity, the infants were presented with small toys moving on a semicircular path in the vertical plane (fig 5).

The trajectories of the target and the hands of the infant were measured using a 3D motion analysis system. 3D coordinates of the target motion and the movements of the hands of the infant were sampled at 240 Hz using five ProReflex cameras (Qualisys, Gothenburg Sweden). Relative length (ratio between the length of the trajectory of the hand and a straight line between
the starting and ending coordinates) \((37)\), \textit{max jerk} (maximal change of acceleration \((\text{mm/s}^3)\)) and \textit{point of peak velocity} (the percentage of the movement time from the start where the peak velocity occurred) were calculated in a computer program designed in MATLAB (P. Nyström, Department of Psychology, Uppsala). Furthermore, the \textit{number of bimanual reaches, number of movement units} (a movement unit (MU) was defined as the region between two adjacent local minima that contained a velocity peak greater than \(2.3 \text{ cm/s} \) above the minima), \textit{mean and maximum speed of the whole reach and the transport unit} (the transport unit (TU) was defined as the longest MU of the reach) and \textit{aiming} (where a positive aiming value indicates that the hand is lagging behind the object and perfect aiming results in zero) of the reaches were calculated.
Statistical analysis

The statistical analysis was performed with SPSS 16.0 and 18.0 (SPSS Inc, IBM, Illinois, USA) and Stata/SE 11.0 (StataCorp LP, College Station, TX, USA).

In study I independent $t$-tests were used to test for differences between the study group and the control group in mean propSP and Gain. Regression analysis was used to test for any interaction effects between group and age.

In study I and II the distribution of data for propSP and Gain was displayed using an estimated Kernel density (97) where the contribution of each data point is smoothed out nonparametrically over a local neighbourhood around that data point to create a density curve. To test whether the proportion of very preterm infants reaching different parts of the distribution for full-term infants changed between 2 and 4 months, an indicator of whether the very preterm infant reached the 10th or the 50th percentile of the full-term group was regressed on the age indicator.

In study II a linear regression model was used to estimate how Gain of gaze and propSP for the various tracking variables were associated with (i) the age at examination (2 respective 4 months); (ii) the infant being very preterm or full-term; (iii) whether any change between 2 and 4 months differed between very preterm and full-term status.

In study III independent $t$-test (for dichotomous variables) and linear regression (for continuous variables) were used for univariate analysis of the association between risk factors and mean propSP and Gain at 2 and 4 months’ CA. These risk factors were also correlated to each other in order to display any interrelation across factors. All risk factors found to be significantly related (10% level) to propSP and Gain at 4 months’ CA in the univariate analysis were included in multiple regressions aimed at assessing each factors independent relation to propSp and Gain, respectively. These risk factors were also bundled together in variables counting the number of early risks and the number of late risks and included in multiple regression analyses.

In study IV independent $t$-tests and one-way-ANOVA tests were used to estimate mean differences between study and control groups in relative length, the number of movement units, speed, max jerk, point of peak velocity and the ratio between unimanual and bimanual reaches between the study group and the control group.
Results

When compared to healthy FT control infants, visuomotor development for VPT infants in these studies was delayed or impaired at 2 and 4 months’ CA when measured as levels of SP. The boys in the VPT group showed higher levels of SP at both 2 and 4 months’ CA compared to the VPT girls. Both the VPT and the FT infants developed between 2 and 4 months, although the distribution curve at 4 months’ CA became narrower for the FT group but more dispersed for the VPT group. The levels of SP were even lower for VPT infants with presence of perinatal risk factors. When reaching a moving object at 8 months’ CA the VPT infants used more bimanual reach and less straight reaching path compared to the control infants.

Study 1

The LOVIS population consisted of 113 infants with a mean GA of 28+5 GW. Incidences of neonatal complications are shown in table 2. None of the infants were diagnosed as having NEC. In 84 (74.4%) of the 113 VPT infants, no major neonatal morbidities i.e. BPD, IVH > grade 2, PVL, NEC and/or ROP > stage 2 were found.

Table 2. Incidences of neonatal complications

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>ROP total</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>ROP stage 1-2</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>ROP &gt; stage 2</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>ROP treated</td>
<td>6</td>
<td>5.3</td>
</tr>
<tr>
<td>NEC</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IVH total</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>IVH grade 1-2</td>
<td>20</td>
<td>17.5</td>
</tr>
<tr>
<td>IVH grade 3-4</td>
<td>4</td>
<td>3.5</td>
</tr>
<tr>
<td>PVL total</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>PVL diffuse, noncystic</td>
<td>4</td>
<td>3.5</td>
</tr>
<tr>
<td>PVL cystic</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>PDA</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Septicaemia</td>
<td>22</td>
<td>19.5</td>
</tr>
</tbody>
</table>
The 81 VPT infants with a mean GA of 28+4 and a mean BW of 1083 g who were investigated at 2 and 4 months’ CA showed significantly lower propSP (p<0.001) and Gain (p<0.001) compared to the control group (fig 6).

Both groups developed in propSP and Gain between 2 and 4 months towards adult levels but the VPT infants at 4 months’ CA reached the level for the FT infants at 2 months while the FT infants at 4 months approached the level for adults. A higher proportion of the VPT infants had reached the 10th and 50th percentile for the FT infants regarding Gain at 4 than at 2 months’ CA. The VPT infants showed a more dispersed distribution curve for both propSP and Gain at 4 than at 2 months’ CA while the FT control group showed the opposite development. (Fig 7a and 7b).

Figure 6. Gain and propSP in VPT (circle) and FT (square) infants at 2 and 4 months’ CA.

Figure 7a. Density distribution of propSP at 2 and 4 months’ CA for the VPT and FT infants.
The VPT boys showed higher Gain compared to VPT girls at 2 months’ CA and at 4 months the levels of both propSP and Gain was higher for the VPT boys compared to the VPT girls. (fig 8). This difference in gender was not found in the FT infants.

Figure 8. propSP and Gain in VPT girls and boys at 2 and 4 months’ CA.
Study 2

Despite the absence of major neonatal morbidities or being born SGA these VPT infants showed lower propSP than the FT infants at both 2 and 4 months’ of age. Both the VPT and the FT infants improved their ability to smoothly pursue a moving object, evaluated by propSP (fig 9).

Figure 9. propSP at 2 and 4 months’ CA for the VPT (open) and FT (filled) infants separated by the two types of motion; sinus (circle) and triangular (triangle).
Furthermore, the smooth pursuit eye movements lagged the object motion more in the VPT group at 4 months’ CA. The groups did not differ with respect to Gain of gaze (fig 10) or head movements, but the saccade frequency was higher at 2 months and the saccades decreased more between 2 and 4 months’ CA for the VPT infants in some of the conditions calculated.

![Figure 10. Gain of gaze at 2 and 4 months’ CA for the VPT (open) and FT (filled) infants separated by the two amplitudes; small (circle) and large (square).](image)

As shown in fig 11, the VPT infant group had a more dispersed distribution curve of propSP at 4 months’ compared to 2 months’ CA, in contrast to the FT group which had a more narrow distribution curve of propSP at 4 compared to 2 months’ CA.

![Figure 11. Density distribution of propSP in VPT and FT infants at 2 and 4 months’ CA.](image)
Study 3

Among the 15 tested perinatal risk factors, 8 showed significant negative association in univariate analysis with the levels of SP at 4 months’ CA namely administration of prenatal corticosteroids, GA, BW, BPD, ROP, ROP > stage 2, PVL, and PDA (table 3).

Table 3. Associations between perinatal risk factors and SP

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>PropSP Difference between mean (95% CI)</th>
<th>Gain Difference between mean (95% CI)</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r = 0.213</td>
<td>r = 0.361</td>
<td>0.069</td>
<td>0.002</td>
</tr>
<tr>
<td>Gestational age (mean = 28+4)</td>
<td>0.165 (0.068-0.263)</td>
<td>0.163 (0.061-0.266)</td>
<td><strong>0.002</strong></td>
<td>0.002</td>
</tr>
<tr>
<td>BPD (n = 18)</td>
<td>0.102 (0.011-0.193)</td>
<td>0.143 (0.050-0.235)</td>
<td><strong>0.003</strong></td>
<td>0.003</td>
</tr>
<tr>
<td>ROP (n = 26)</td>
<td>0.202 (0.072-0.331)</td>
<td>0.263 (0.133-0.393)</td>
<td><strong>0.000</strong></td>
<td>0.000</td>
</tr>
<tr>
<td>ROP &gt; stage 2 (n = 9)</td>
<td>-0.019 (-0.131-0.093)</td>
<td>0.736 (0.029-0.146)</td>
<td>0.616</td>
<td></td>
</tr>
<tr>
<td>IVH (n =15)</td>
<td>0.107 (-0.091-0.304)</td>
<td>0.285 (0.184-0.387)</td>
<td>0.076</td>
<td></td>
</tr>
<tr>
<td>IVH &gt; grade 2 (n = 4)</td>
<td>0.227 (0.358-0.419)</td>
<td>0.021 (0.188-0.015)</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>PVL (n = 4)</td>
<td>0.227 (0.358-0.419)</td>
<td>0.188 (0.188-0.015)</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>PDA (n = 15)</td>
<td>0.193 (0.091-0.295)</td>
<td>0.211 (0.106-0.317)</td>
<td><strong>0.000</strong></td>
<td>0.000</td>
</tr>
<tr>
<td>Septicaemia (n = 17)</td>
<td>0.077 (-0.028-0.183)</td>
<td>0.148 (0.087-0.229)</td>
<td>0.119</td>
<td></td>
</tr>
<tr>
<td>PPROM (n = 10)</td>
<td>-0.013 (-0.145-0.118)</td>
<td>0.841 (-0.055-0.191)</td>
<td>0.429</td>
<td></td>
</tr>
<tr>
<td>SGA (n = 17)</td>
<td>-0.048 (-0.154-0.059)</td>
<td>0.373 (-0.003-0.109)</td>
<td>0.959</td>
<td></td>
</tr>
<tr>
<td>deltaSDS</td>
<td>r = 0.200</td>
<td>0.869</td>
<td>0.216</td>
<td></td>
</tr>
<tr>
<td>Prenatal steroids (n = 51)</td>
<td>0.085 (-0.025-0.195)</td>
<td>0.126 (0.100-0.001)</td>
<td><strong>0.047</strong></td>
<td>0.047</td>
</tr>
<tr>
<td>Twins/triplets (n = 20)</td>
<td>-0.023 (-0.123-0.078)</td>
<td>0.656 (-0.078-0.182)</td>
<td>0.139</td>
<td></td>
</tr>
<tr>
<td>Primipara (n=42)</td>
<td>0.008 (-0.098-0.083)</td>
<td>0.864 (-0.076-0.169)</td>
<td>0.110</td>
<td></td>
</tr>
<tr>
<td>Sectio (n=45)</td>
<td>0.047 (-0.044-0.138)</td>
<td>0.309 (0.003-0.093)</td>
<td>0.951</td>
<td>0.003</td>
</tr>
<tr>
<td>Birthweight (mean = 1083 g)</td>
<td>r = 0.197</td>
<td>0.092</td>
<td>0.338</td>
<td></td>
</tr>
<tr>
<td>Age of mother (mean = 31.5 year)</td>
<td>r = 0.039</td>
<td>0.447</td>
<td>0.146</td>
<td></td>
</tr>
</tbody>
</table>

Note: Bold values indicate significant associations.
At 2 months’ CA only ROP > stage 2 was associated with SP. The risk factors associated with propSP and Gain were strongly associated to each other’s except prenatal corticosteroid treatment and PVL. BW was excluded from further analyses as it was strongly correlated with GA ($r = 0.982$, $p = 0.001$).

When all factors significant (at the 10% level) in the univariate tests were included in multiple regressions the only significant independent factor associated with SP was PVL, and this was only found for propSP.

When investigating the VPT infants with more than one risk factor significant at the 10% level, we found that when adding 2-5 risk factors using multiple regression analysis the levels of SP became lower (table 4 and fig 12).

Table 4. Relations between SP and the two groups of risk factors (“late” and “early”) when added. (*=significant at the 10% level, ** = significant at the 5% level).

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>propSP</th>
<th>Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early 1</td>
<td>0.035(-0.047-0.117)</td>
<td>-0.010(-0.104-0.083)</td>
</tr>
<tr>
<td>Early 2</td>
<td>-0.288(-0.401- -0.175)**</td>
<td>-0.250(-0.379- -0.122)**</td>
</tr>
<tr>
<td>Early 3</td>
<td>-0.093(-0.328-0.141)</td>
<td>-0.212(-0.479-0.054)</td>
</tr>
<tr>
<td>Late 1</td>
<td>-0.026(-0.128-0.076)</td>
<td>-0.003(-0.099-0.106)</td>
</tr>
<tr>
<td>Late 2</td>
<td>-0.153(-0.308-0.001)*</td>
<td>-0.193(-0.349- -0.038)**</td>
</tr>
<tr>
<td>Late 3</td>
<td>-0.231(-0.356- -0.106)**</td>
<td>-0.262(-0.388- -0.136)**</td>
</tr>
</tbody>
</table>
Study 4

Evaluating reaching strategies for a group of VPT infants and a group of FT infants reaching for a moving object showed no differences in how often the infants encountered the target. However, the VPT infants used bimanual strategies more often \((p = 0.033)\) and had more curved reaching paths (measured by numbers and directions of motor units \((p = 0.007)\)) than the FT infants. When dividing the VPT group in two subgroups where one group was born < 28 GW (=extremely preterm (EPT)) and one was born 28+0 - 31+6 GW, the infants born < 28 GW showed more curved reaching paths and bimanual reach compared to the infants born 28+0 – 31+6 GW. When correlating the reaching performance to the results from the neuromotor examinations, infants with abnormal neuromotor examinations at 2 months’ CA showed a jerkier movement profile with faster accelerations and higher maximum speed as they reached for moving objects (table 5), while VPT infants assessed as abnormal at 10 months’ CA aimed further ahead of the object compared to the VPT infants assessed as possibly abnormal (table 6).
Table 5. Reaching results (means and SD) for the VPT infants, grouped according to
the results from the neuromotor examinations (NME) at 2 months’ CA and for com-
parison the results of the FT controls.

<table>
<thead>
<tr>
<th>NME 1</th>
<th>NME 2</th>
<th>NME 3</th>
<th>FT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole reach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>max speed (mm/s)</td>
<td>503.7</td>
<td>94.7</td>
<td>93.9</td>
</tr>
<tr>
<td>mean acceleration (mm/s²)</td>
<td>31.2</td>
<td>9.3</td>
<td>25.9</td>
</tr>
<tr>
<td>Transport unit (TU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>max speed (mm/s)</td>
<td>462.2</td>
<td>86.0</td>
<td>421.9</td>
</tr>
<tr>
<td>max acceleration (mm/s²)</td>
<td>21.4</td>
<td>5.05</td>
<td>17.9</td>
</tr>
<tr>
<td>max jerk (mm/s³)</td>
<td>9.00</td>
<td>4.17</td>
<td>5.89</td>
</tr>
</tbody>
</table>

Table 6. Aiming of reaches (means and SD) for the VPT infants, grouped according
to the results from the neuromotor examination (NME) at 10 months’ CA and for com-
parison the results of the FT controls.

<table>
<thead>
<tr>
<th>NME 1</th>
<th>NME 2</th>
<th>NME 3</th>
<th>FT</th>
</tr>
</thead>
<tbody>
<tr>
<td>aiming</td>
<td>-5.58</td>
<td>8.20</td>
<td>-0.29</td>
</tr>
</tbody>
</table>
Discussion

With the aim of evaluating visumotor capacity in a population of VPT infants compared to a control group of FT infants, smooth pursuit eye movements (SP) at 2 and 4 months’ CA and reaching capacity at 8 months’ CA were measured.

Several studies have reported on visual impairment in child- and adulthood regarding acuity, stereopsis and visual field in VPT infants (2, 5, 6, 68, 98, 99). Langaas et al showed reduced Gain and predictive capacity in a group of children born VPT at 5-7 years of age while tracking a moving object (6) and Atkinson and Braddick (2) showed delayed development of visually evoked response potentials (VERP; measures the electrical response of the brain's primary visual cortex to a visual stimulus) when the stimulus was moving. However, I am not aware of any studies that have reported on impaired visuomotor capacity in early infancy in VPT infants. Ricci et al have developed a validated test battery for assessment of spontaneous ocular movements, fixation, tracking, reaction to coloured targets, discriminating stripes and attention at distance. In a cohort of infants born very preterm (< 31G W) examined at 35 weeks PMA and at term age, the preterm infants showed a more mature visual capacity compared to the term-born control infants in the aspects of ocular movements, vertical and arc tracking and stripe discrimination (11, 100). In a recent paper Ricci et al have also shown that a normal assessment with this test battery at term age was a good predictor of normal neurodevelopmental outcome at 12 months of age (101). However, the method used cannot discriminate for different types of eye movements. Furthermore, the development of SP starts at 6-8 weeks of age, and is not a meaningful parameter to measure before this age. The investigation and evaluation of SP development could therefore provide another tool for early evaluation of visuomotor capacity (1, 12, 17, 19).

Infants born very preterm and smooth pursuit eye movements at 2 and 4 months’ CA

In paper I in this thesis the capacity of VPT infants to visually follow a moving object at 2 and 4 months’ CA was measured and the results showed a significant delay in the development of SP regarding both propSP (defined as the ratio between SP and total eye movement) and Gain (defined as the
ratio between SP and object amplitude) when compared to the FT control infants. In a follow-up study of 14 year old children with a BW < 1500 g, Lindqvist et al (102) reported a normal capacity to track smoothly. However, this examination was performed by ocular observation of gaze and not by actually measuring SP, thereby not differentiating between head movements, microsaccades and SP. We have not found any studies that have measured SP in infants born preterm.

Another method to evaluate the capacity of the visual pathways responsible for motion is to measure directional-reversal visual event-related potentials (DR-VERP), and Atkinson and Braddick found in a study (2) that VPT infants at 2-5 months’ CA revealed a delayed development of DR-VERP compared to FT infants. In contrast, Ricci et al (100) reported more mature vision in infants born VPT, measured as spontaneous ocular movements, tracking and discriminating stripes at term compared to term-born infants. Their results indicate that postnatal visual experiences in VPT infants may accelerate development of visual function related to ocular stability and tracking, although in aspects other than visuomotor capacity controlled by the cortical pathways in the visual brain responsible for SP (1, 12, 17, 26).

In the present study there was a greater proportion of VPT infants that reached the 10th and 50th percentile of the results for the FT infants at 4 months’ CA than at 2 months’ CA. The levels of propSP and Gain at 4 months’ CA of the VPT infants corresponded to the levels of the FT infants at 2 months of age while the FT infants approached the adult levels of SP at 4 months’, verifying earlier reports (1, 12, 13). The infants born VPT also exhibited a wider range in the results of SP at 4 months’ than at 2 months’ CA. Together, this indicates that some of the VPT infants were delayed at 2 months’ CA and demonstrated a catch up in SP while others did not. This could reflect the fact that we measured the capacity of two different pathways at the two ages, where the pathways at 2 months are mainly subcortical (12, 17, 25, 26), implying that measurements of SP until this age might be an evaluation of the subcortical pathways, as well as of the retinal neurons, acuity and visual fields (1). Instead, at 4 months’ of age the primary cortical visual pathways have evolved to be the main pathways for SP, and measurements of SP more accurately reflect the capacity and development of these pathways (12, 17, 19, 24). The primary visual cortical areas are also reported to be the most vulnerable to diffuse as well as cystic PVL and severe IVH lesions in VPT infants (93, 99, 103-106).

Another aspect of the differences between the results at 2 and 4 months’ of age could be that at 2 months’ of age the development of SP has just started, which implies that any impact on the development of SP has not yet became apparent, while at 4 months SP should have reached almost adult level and injuries affecting SP capacity are more evident (13, 17).

The results in this study cannot definitively reveal whether SP development was delayed, or if the capacity to smoothly track, maintain attention on
and predict objects in motion was permanently impaired, as the infants until now only have been followed until 4 months’ CA.

Gender and smooth pursuit eye movements at 2 and 4 months’ CA

The results in paper I also showed that the boys in the VPT group performed better than girls with respect to Gain at both 2 and 4 months’ CA and to propSP at 4 months’ CA. There were no differences in the prevalence of perinatal risk factors between girls and boys that could explain these results. This was a somewhat unexpected finding as many previous studies show that VPT boys are more likely than VPT girls to develop disabilities in perception, coordination and cognition later in childhood. This has been reported from the PIIPARI study group in Finland and the EPICure study group in the UK and Ireland when examining VPT children at 5 – 6 years of age (69, 70). In Sweden Farooqi et al (107) and Gäddlin et al (76) showed that academic achievement at 10-12 and 15 years of age was better for preterm-born girls than boys, and in the USA, Hack et al (74) reported of a similar situation for adolescents at 20 years of age. However, Finnström in Sweden, the EPI-PAGE group in France and Saigal in Canada could not find any gender differences regarding outcome in adolescence, school age and 5 years of age respectively (73, 85, 108). One study of speech and language skills at 6.5 years of age showed that boys performed better compared to girls in a Swedish cohort of VPT children born in 1986-89 (109). Differences in interaction and emotional expressivity between mothers and 6 month old infants have also been reported by Weinberg et al, where the mother-boy dyad showed higher synchrony than the mother-girl dyad (110). Against this background, one could hypothesize that eye contact and early communication between mother/father and infant differed as a factor of the infant’s sex, which could be reflected as an advantage in early development of SP for the VPT boys in this study. When reviewing these studies on gender differences for VPT children, the picture is not homogenous, which implies that there could be not yet identified factors that may affect differently between genders.

Gaze tracking of moving objects at 2 and 4 months’ CA

In paper II a subgroup of the VPT infants with no major neonatal complications were investigated in order to further evaluate the impact of preterm birth without associated neonatal morbidities on development of gaze tracking, including SP, saccades and head movements. We could not find that development of SP was promoted by the earlier visual experience for the VPT infants compared to the FT infants. This was demonstrated at both ages measured – at 2 months when SP is processed through the subcortical path-
ways and at 4 months when the primary visual cortical pathways are almost fully developed. This again contrasts to the results from Ricci et al, where low risk VPT infants showed a more mature visual capacity concerning ocular movements and tracking at 35 weeks PMA and term age (100).

A greater proportion of the VPT infants reached the 10"th and 50"th percentile of the results for the FT infants at 4 months. This indicates that even in this low risk group, some of the infants did catch up in propSP, while others did not. The generally lower propSP for the VPT infants at 2 months’ CA might be explained either by a general delay in a time period where SP just started to develop, or by impact on the subcortical pathways responsible for processing SP at this age (17, 25, 26). A reasonable explanation for the catch up for some VPT infants at 4 months’ CA could be that they developed normally, as did the FT infants, during the time period between 2 and 4 months when the primary visual cortical pathways takes over as the main pathways for SP processing. The VPT infants that did not develop in levels of SP may be delayed in this respect. At 4 months of age SP should be at an almost adult level and it is reasonable to surmise that impairments in these pathways might be revealed at this time (1, 12, 17).

The VPT infants used more saccades at 2 months’ CA compared to the FT group when they were tracking the sinus motion with small amplitude, and decreased their use of saccades more between 2 and 4 months’ for the triangular motion. The VPT infants also lagged the object more at 4 months’ CA compared to the FT group for the large sinus and small triangular motion. These results may also indicate a delay in visuomotor development as timing developed in both groups between 2 and 4 months and saccades develop earlier than SP and are used to track moving surrounding together with head movements already at birth (12, 16, 17, 26, 111).

Gain of gaze did not differ significantly between the two groups in this study, which implies that saccades and head movements did compensate for impaired development of SP to track moving objects. However, the consequences of this will be less smooth tracking despite the normal gain of gaze. This compensatory mechanism could explain the results in a study by Lindqvist et al. that reported normal eye movements in teenagers born VPT (102).

Perinatal risk factors and smooth pursuit eye movement at 2 and 4 months’ CA

The associations between perinatal risk factors and propSP and Gain were analysed in paper III, and the results showed that the presence of PVL, severe IVH (only significant at the 10% level), BPD, ROP, PDA, low GA, low BW and lack of administration of prenatal corticosteroids associated negatively with development of SP at 4 months’ CA, but not at 2 months’ CA.
The background to the results at 2 months’ CA could be that SP have only started to develop at this age, implying that risk factors have not yet had time to demonstrate their detrimental action during the period between 2 and 4 months when development of SP are rapid (1, 13, 16-18). The low levels of SP at 4 months’ CA may be explained by further delay in SP development in VPT infants with risk factors, but could also reflect impaired SP, since SP should be close to adult levels at 4 months, as shown by the FT infants in this study (1, 12, 17).

Severe ROP (> stage 2) was negatively associated with SP at 2 months’ CA, which could certainly be explained by that severe ROP leads to impaired vision and thus reduced ability to visually follow a moving object.

It is important to clarify the difference between propSP and Gain as the identified risk factors associated differently with these outcomes. propSP is the ratio of SP and the raw eye movement, and is not influenced by head movements while Gain is the ratio between SP and the object’s movement and is influenced by head movements. If the infant uses considerable head movements during tracking, Gain tends to underestimate the level of smooth tracking. Instead, if Gain of gaze is poor, propSP can overestimate SP in relation to the object.

The only risk factor that in a multiregression model showed an independent negative association with SP at 4 months’ CA, was PVL. This may reflect the specific vulnerability of the visual pathways to PVL lesions, often situated in the areas of the dorsal pathways; i.e. the visual pathways that process SP and are responsible for movement identification (112). Further, Atkinson and Braddick, Jacobson et al, Hellgren et al, Ricci et al and Ramenghi et al (2, 5, 14, 99, 113) have reported that PVL is the main cause of impaired visual perception in children born preterm. PVL is also known to be a risk factor for disabilities in other higher brain functions (76, 82, 83, 114).

Severe IVH was only found in four infants, making it difficult to evaluate the results and somewhat unexpected, IVH was not significantly associated with Gain (p = 0.076).

GA and BW were strongly correlated with each other and are factors with general impact on outcome for VPT infants and later disabilities. GA and BW in this study were both associated with Gain but not with propSP. A reasonable explanation for this could be that the degree of immaturity as well as inflammatory and circulatory complications around the time of delivery may affect neuromotor development but not limited to the specific areas in the brain responsible for processing SP (3, 5, 98, 112, 115).

BPD, PDA and ROP are neonatal complications of extreme prematurity and are late morbidities occurring weeks after preterm birth and are signs of a complicated neonatal period with accentuated illness severity (56, 59, 79). In this study these morbidities were significantly correlated to each other and all showed significant negative association with both propSP and Gain.
In this paper the risk factors were also bundled in one “early” (GA, prenatal corticosteroid administration, severe IVH and PVL) and one “late” group (BPD, ROP, PDA). This was performed to further investigate if “early” and “late” factors could have different effects on the development of SP as they occurred during different periods of brain development. The “early” risk factors appear around the time of delivery while the “late” risk factors appear later, several weeks after birth. The VPT infants with added risk factors of each group as well as when both groups were bundled together showed a more pronounced low level of SP at 4 months’ CA.

For the bundled “late” risk factors (BPD, ROP, PDA) both propSP and Gain were lower for each added complication and there was no difference in outcome between propSP and Gain. This could imply that these “late” risk factors when added as mentioned above, are expressions of vulnerable and multiply afflicted infants with high risk of later adverse neurodevelopmental outcome. This is in accordance with many other follow-up studies that report that VPT infants with multiple severe neonatal complications constitute a subgroup of the VPT population with an excessive risk of developing disabilities in neuromotor capacity, cognition, concentration and perception (73, 77, 79, 82, 83, 85, 99).

When the “early” risk factors (GA, IVH, PVL, lack of prenatal steroid administration) were bundled, we found that both propSP and Gain were lower for the infants with two “early” risk factors compared to those with only one. Infants with three “early” risk factors did not demonstrate significantly lower levels of SP, although this group consisted of only two infants (and no infant had four “early” risk factors). The high risk of adverse outcome among infants with two “early” risk factors is in accordance with other studies that have investigated perinatal risk factors with impact on neurodevelopmental outcome (81-83, 85, 108).

Reaching at 8 months’ CA

Paper IV estimated how well the VPT infants reacted to and reached toward a moving object. This study evaluated this vision-guided action system that appears early in development and reflects the infants’ input of information, reaction to this information and the capacity to act in accordance with the aiming (1, 39). The results showed that the VPT infants were as successful as the FT infants in catching the moving object, but they used significantly more bimanual reaching strategies. This result may reflect a delay in reaching capacity as unimanual reaching and grasping in full term infants have usually developed by the age of 5-6 months (1, 37). It could also imply that the VPT infants had poorer postural control of the trunk which has been shown by van der Fits et al (45) to be common among infants born preterm, as reaching with one hand is more dependent on stable trunk posture and the capability to sit independently. The VPT infants with deviant neuromotor
examinations at 2 months’ CA also showed a jerkier train of motion to catch the object at 8 months’ CA. This jerkiness may reflect difficulties in maintaining attention on the moving object while at the same time moving the arm and the hand in a controlled way. SP is highly involved in the capability to lock attention on moving objects (12) implying that impaired or delayed development of SP could contribute to jerky reaching movements. von Hofsten et al (37) have shown that reaching development includes longer transport units and less corrective movements with increasing age, making the reach pattern straighter, and a delay in this development may be shown by jerkiness. Toledo et al have also reported that when reaching for stationary objects, preterm infants used more adjustment movements in the reaching pattern compared to a full term control group (40). A tendency to aim ahead of the object was shown for the infants that had deviant results on the neuromotor examination at 10 months’ CA. One explanation for this could be that the capacity to brake the reaching movement, turn and open the hand to catch the object (the tau-dot strategy), which is essential for successful reaching, was delayed or disturbed, as described by Hopkins et al (116).

**Strengths and weaknesses**

The strengths in the LOVIS study are that it is a population-based cohort followed prospectively over a long period of time, minimizing the risk of selection bias and this also presents an opportunity to follow the same population in future studies. One limitation is that, although the SP investigations were performed on a considerably larger population than has ever been carried out previously, the number of infants was limited and demonstrated a wide range of GA, BW and perinatal complications, thus limiting the power of the statistical analyses. Another limitation is that not all VPT infants participated in the examination of visuomotor capacity at both 2 and 4 months’ CA, although the dropouts and the investigated VPT infants did not differ in GA, gender or prevalence of perinatal complications. Nevertheless, the SP investigations were performed on a considerably larger population than has previously been carried out, and the results could form the basis for future studies on specific risk factors in VPT populations. A third weakness in the study is that PVL was diagnosed only by ultrasound of the brain, which is known to be insufficient, which probably has underestimated the true incidence of PVL (117).
Conclusions

Delayed visuomotor development in infants born very preterm

Measuring and calculating smooth pursuit eye movements (SP) is a method to evaluate the capacity to follow, maintain attention on and predict the direction of moving objects with the eyes.

In a population of VPT infants we found delayed development of SP at 2 and 4 months’ CA compared to FT control infants. The VPT boys showed higher levels of SP compared to the VPT girls at both ages.

When excluding VPT infants with major neonatal complications there was still a delayed development of smooth eye tracking at 2 and 4 months’ CA for the VPT infants. Furthermore the VPT infants used saccades with higher frequency at 2 months’ CA.

The VPT infants developed in SP, and at 4 months’ CA approached the level of the FT infants at 2 months’ CA. The distribution of the results for the VPT infants became more dispersed at 4 months’ CA compared to 2 months’ CA.

Perinatal risk factors i.e. GA, birth weight, administration of prenatal steroids, BPD, ROP, PDA, IVH > grade 2, and PVL were associated with lower propSP and/or Gain at 4 months’ CA. The VPT infants with 2-5 of the risk factors, showed additional low levels of SP. PVL was the only risk factor that was independently associated to SP. Severe ROP was the only risk factor significantly associated to SP at 2 months’ CA.

When evaluating reaching strategy which is an executive function of visuomotor capacity at 8 months’ CA, the VPT infants used a reaching strategy to catch a moving object that was less efficient and less coordinated compared to the FT infants.
Future perspective

The visuomotor system is an activity-dependent system and the sources of impaired visuomotor capacity are multifactoral as motor development and cognition, concentration and perception are strictly linked together and not independent systems (36, 118). In these studies the VPT infants showed lower propSP and Gain at 2 and 4 months’ CA as well as less efficient reaching strategies at 8 months’ CA compared to the FT control infants. It is not evident whether this reflects a delay or a persistent functional limitation in visuomotor capacity among the VPT infants.

The VPT infants in the LOVIS study have undergone cerebral MRI at 2.5 - 4.5 years CA. These results are now beginning to be analyzed and evaluated, and will contribute to further insights into the association between perinatal brain injuries and early visuomotor development.

Neuromotor, EEG, visual and cognitive examinations have been performed on the VPT infants, but have not yet been analysed.

If low levels of SP in infancy as shown in this thesis are found to be predictive of later visuomotor impairment, studies should focus on intervention programs to promote visual development as the existing publications are both rare and quite outdated (119). The plasticity of the dorsal pathways where SP are processed, is at its highest level between 2 months’ and 2 years of age, indicating that it is crucial to detect impairments and initiate interventions during this time period (1, 4, 17, 120).

It is also of great importance to further develop tools in order to support the infants, their parents and teachers in their daily life in order to minimize the effects of functional limitations caused by impaired visuomotor capacity.
Försenad utveckling av visuomotorisk kapacitet hos mycket för
tidigt födda spädbarn.

För att kunna samordna visuell perception och motorisk kontroll i vardagen
där vi ständigt omges av rörelse, är vi beroende av normal visuomotorisk
kapacitet. En förutsättning för normal visuomotorisk förmåga är att ögonens
mjuka följrörelser är normala.

Barn som föds mycket för tidigt (< 32 graviditetsveckor) löper stor risk
att utveckla funktionsnedsättningar inom högre hjärnfunktioner dvs. perception,
kognition, koncentration och koordination.

I denna avhandling undersöktes visuomotorisk kapacitet i en population
av mycket för tidigt födda spädbarn och jämfördes med kontrollgrupper av
fullgångna spädbarn. Vid 2 och 4 månaders korrigerad ålder mättes nivåer
av ögonens mjuka följrörelser. Vid 8 månaders korrigerad ålder utvärderades
förmågan att kunna gripa ett rörligt objekt. Denna förmåga är en tidigt ut-
vecklad aktivitet som är beroende av synen och ett uttryck för den exekutiva
visuomotoriska kapaciteten.

De mycket för tidigt födda spädbarnen i studien uppförde lägre nivåer av
mjuka följrörelser jämfört med de fullgångna kontrollbarnen. I gruppen
mycket för tidigt födda spädbarn uppförde pojkarna högre nivåer av mjuka
följrörelser jämfört med flickorna.

Den undergrupp av mycket för tidigt födda spädbarnen som inte hade
drabbats av svåra komplikationer i nyföddhetsperioden uppförde också
lägre nivåer av mjuka följrörelser jämfört med kontrollgruppen fullgångna barn. De mycket för tidigt födda barnen använde mer sackader för att följa,
och släpade efter lite mer med blicken i förhållande till objektet, men det
fanns ingen skillnad i förmåga att följa objektet med blicken hela vägen, då
man inbegrep huvudrörelser, sackader och mjuka följrörelser.

Båda grupperna utvecklades i nivåerna av mjuka följrörelser mellan 2 och
4 månaders korrigerad ålder, men de mycket för tidigt födda barnen uppvis-
sade en större spridning av dessa nivåer vid 4 månaders korrigerad ålder
jämfört med de fullgångna kontrollbarnen. De mycket för tidigt födda bar-
nens nivåer av mjuka följrörelser vid 4 månaders korrigerad ålder motsvara-
de nivåerna för de fullgångna kontrollbarnen vid 2 månaders ålder.
Ett antal perinatala riskfaktorer visade sig vara associerade till lägre nivåer av mjuka följrörelser, och denna effekt var mer uttalad hos barn med flera riskfaktorer.

Vid bedömningen av förmågan att gripa ett rörligt objekt vid 8 månaders korrigerad ålder uppvisade de mycket för tidigt födda spädbarnen signifikant mer bimanuell gripning och en krokidare bana för att fånga objektet jämfört med den fullgångna kontrollgruppen.

Sammanfattningsvis uppvisade den mycket för tidigt födda gruppen spädbarn en försenad visuomotorisk kapacitet vid 2, 4 och 8 månaders korrigerad ålder jämfört med en kontrollgrupp fullgångna spädbarn. En del av de mycket för tidigt födda barnen med perinatala riskfaktorer utvecklades inte avseende mjuka följrörelser mellan 2 och 4 månaders korrigerad ålder.

Katarina Strand Brodd, Institutionen för Kvinnors och Barns Hälsa, Uppsala universitet, SE-751 85 Uppsala

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Ni, som när jag haft stunder av -

* I’m so tired *(J. Lennon, The Beatles, The White Album; 1968)*

och

* I still haven’t found what I’m looking for. *(P D Hewson (Bono), U2, Joshua Tree; 1987)*

har präntat in mig att

* you’ve got to get yourself together, you’ve got stuck in a moment and now you can’t get out of it *(P D Hewson (Bono), U2, All that you can leave behind; 2000)*

och

* don’t give up, you still have us, don’t give up, I know you can make it good *(P. Gabriel, So; 1986)*.


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