Infants at high risk of cerebral palsy

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Chapter 1

Introduction

Worldwide, over 140 million babies are born each year.[1] Most of them are healthy and will develop typically, but some infants are at risk of neurodevelopmental disorders like cerebral palsy. This thesis is about the early identification of these 'at risk' infants and the prediction of their development, as such knowledge will assist in family counselling and in creating opportunities for early intervention.

NEUROMOTOR DEVELOPMENT

Human brain development is a fascinating, complex and long-lasting process. Neurodevelopment starts with the formation and the folding of the neural plate, which is derived from the ectoderm. The neural tube then differentiates into the forebrain, midbrain, hindbrain and spinal cord; the proliferation areas in the ventricular and subventricular zones create neurons and glia cells (Figure 1).[2,3] Millions of neurons subsequently migrate to their final destination by passive cell displacement and active cell migration, where the process of axon and dendrite sprouting can start or continue. The transient subplate has a vital role in cortical organization including navigation of axons and synaptogenesis. Neural organization is refined by apoptosis of neurons and the elimination of synapses and axons. Meanwhile, the glia cells start to differentiate into astrocytes, microglia and oligodendrocytes, the latter being crucial for myelination. Brain development continues after infancy: remodelling of cortical neuronal circuitries and myelination even lasts beyond adolescence (Figure 1).[2–5]

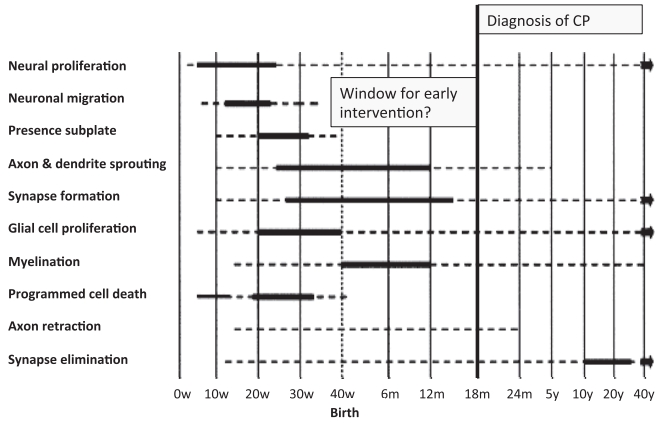

Figure 1. Timing of neurobiological processes in the telencephalon during human ontogeny based on the figure of de Graaf-Peters and Hadders-Algra 2006[3]. W = weeks PMA, M = postnatal months, Y = years. Reprinted with permission.

Normal motor development is characterized by variation, both in the execution and timing of motor behaviour.[6–8] The Neuronal Group Selection Theory (NGST) may serve as a framework to describe motor development by distinguishing a primary and a secondary phase of variability.[8,9] In the primary variability phase, the infant explores his abundant neuromotor repertoire, which is not tuned to external conditions. Next, in the secondary variability phase, the infant starts to adapt his motor behaviour to the specifics of the situation; this process of selection is based on active trial-and-error experiences. It takes until adolescence before all secondary motor repertoires reach their adult configuration.

CEREBRAL PALSY

Considering the complex and numerous processes that contribute to infant motor development, it is unfortunately not surprising that in some infants disturbances occur in the developing nervous system. Cerebral Palsy (CP) is one of the most common neurological disorders in childhood, with a Western European incidence above 2 per 1000 live births.[10–14] Nowadays, CP is defined as 'a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing infant or fetal brain'.[15] The definition further recognizes that CP is not merely a motor disorder as it can be accompanied by disturbances in several other domains.

More than 100 years ago CP was known as 'Little Disease', named after the orthopaedic surgeon William John Little (1810–1894) who was the first to describe neurological abnormalities and deformities in infants following perinatal asphyxia or mechanical injury during birth.[16] The term 'Cerebral Palsy' came from Sir William Osler (1849–1928), while Sigmund Freud (1865–1939) drew attention to the developmental pathways prior to birth and the associated conditions like cognitive impairments or epilepsy.[17]

The prevalence of CP increases with decreasing gestational age and birth weight.[18,19] In term born children, the following ten risk factors are known to be associated with CP: placental abnormalities, major and minor birth defects, low birth weight, meconium aspiration, emergency caesarean section, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia and neonatal infections.[20]

Brain imaging studies have demonstrated that an abnormal MRI (magnetic resonance imaging) is present in around 85% of children with CP.[19,21,22] The nature of the lesion depends on the timing of the interference in brain development. Periventricular white matter lesions are the most frequently observed brain lesions, which generally occur in the early third trimester of pregnancy.[21] The second most common are cortical and deep grey matter lesions, occurring in the late third trimester or the perinatal period. Brain maldevelopments occur in utero and may have a genetic cause. CP has a postnatal origin, e.g. meningoencephalitis, in around 10% of the children with CP.[19,23]

The predominant neurological symptoms are generally classified into three subtypes. The majority of children with CP have the spastic form, which can be unilaterally or bilaterally distributed. Other subtypes are dyskinetic CP, which can be further subdivided into dystonic or choreo-athetotic CP, or ataxic CP.[18] The Gross Motor Function Classification System (GMFCS) and the Manual Ability Classification System (MACS) are used to describe the severity of respectively gross motor and manual function in children with CP.[24,25] Communication performance can be classified with the recently developed Communication Function Classification System (CFCS).[26]

The above implies that the umbrella term CP describes a very heterogeneous group of children with respect to aetiology and type and severity of motor impairments and accompanying problems.[15]

Early diagnostics

The diagnosis of CP is preferably not assigned before children are at least 18 months of age, because of the numerous neurodevelopmental changes that occur within the first one and a half years of life (Figure 1).[3,27,28] The development of the young nervous system may either resolve early neurological abnormalities[29,30], or make them evolve into a clear neurological syndrome like CP; a phenomenon known as 'growing into a deficit'.[4,31,32] Consequently, this hampers the prediction of neurodevelopmental outcome in young infants.

However, there are several tools available to identify infants at high risk of CP and to assist in the prediction of further development. These include brain imaging techniques, neurophysiological tests, the neurological examination and neuromotor assessments.[4] The focus of this thesis is on the latter two instruments.

TRADITIONAL INFANT NEUROLOGICAL EXAMINATION

The infant neurological examination traditionally consists of several parts, including the assessment of so-called primitive reflexes, postural reactions, cranial nerves, deep tendon reflexes and muscle tone.[2] The neurological items below will be addressed in this thesis.

Asymmetrical tonic neck reflex

The asymmetrical tonic neck reflex (ATNR) can be examined by rotating the infant's head to one side; its presence results in extension of the limbs on the side towards which the face is turned and flexion of the limbs on the contralateral side. The ATNR phenomenon was first described by Rudolf Magnus (1873–1927) and Adriaan de Kleyn (1883–1949), who discovered that muscle tone in the limbs of decerebrated cats was influenced by their head position.[33]

The earliest 'fencing postures' can be observed in preterm born infants at 25 weeks gestational age.[34] In healthy newborns, the reflex can be present or absent.[35,36] The ATNR has a peak frequency around 2–4 months of age and typically disappears around 5 months of age.[35,36] Some spontaneous ATNR activity may be observed until 8 months of age as part of the infant's extensive motor repertoire.[35] A consistently present, obligatory ATNR may be a sign of neurological dysfunction.[36,37]

Although the ATNR is regarded as a primitive reflex that typically disappears during early development, electromyography studies reveal that some ATNR activity remains present throughout life.[38,39]

Moro response

In 1918, Ernst Moro presented his observation of an unusual movement in young infants when their pillow is hit on either side.[40–42] He suggested this movement to be analogous to the movements of young monkeys and bats, by which they instinctively cling to their mothers ('Umklammerungsreflex').[41,43] The response in young infants, i.e., abduction of the upper limbs and extension of the forearms and fingers, followed by flexion and adduction of the arms, was subsequently named after him.[41] Over the years, several methods to elicit the Moro response were put forward, including the application of cold water.[42] At present, the Moro is characteristically elicited by a drop of the infant's head, thereby signalling the vestibulum and neck propriocepsis.

Preterm born infants can demonstrate partial responses from 28–32 weeks gestational age onwards.[2] Typically, the Moro response is well established around term age.[35,36,41] The intensity of the response diminishes from 2–3 months of age

to eventually disappear around the end of the fourth month.[35,43] An asymmetric response could indicate the presence of a brachial plexus lesion or a clavicular fracture while a low threshold or a symmetrically absent response in early infancy is suggestive of disturbances of the central nervous system.[35,41]

Parachute reaction

Lowering the infant while in prone suspension evokes forward extension of the arms and dorsiflexion and opening of the hands. This parachute reaction of the upper extremities typically emerges between 4 and 11 months of age.[35,44,45] It is considered a vestibular response that can be reinforced by visual input.[35,46] The establishment of the optical placing reaction of the hands is associated with the appearance of the parachute reaction.[35]

Emergence of the parachute reaction typically precedes the development of independent walking, which has a protective function for the infant,[44,47] though the age at which this response and milestone appear is weakly correlated due to large variation in onset interval.[44,47,48]

Plantar grasp response

Most newborns have a positive plantar grasp response even if they are born preterm at 25 weeks gestational age.[34,36] The response, i.e. flexion of the toes in response to light pressure upon the ball of the infant's feet, may have a tonic character.[49] The plantar grasp response is regarded as a spinal reflex mediated by the L5-S2 spinal roots.[50,51] The grasp reflex could be considered an evolutionary relict, being essential to infant monkeys in arboreal areas.[51]

The plantar grasp response is typically present in the first half of infancy and vanishes in the subsequent months or years.[35,42,52,53] Although the disappearance of the reflex typically occurs around the age when standing develops, the relationship between the two events is uncertain.[54,55] Actually, the reflex does not truly disappear but becomes inhibited by maturing higher brain mechanisms.[56,57] Therefore grasp reflexes may 'reappear' in cases of brain dysfunction like a frontal lobe lesion.[56–58]

Pull-to-sit manoeuvre

An infant can be gently pulled up from supine into sitting position by grasping the infant's wrists. Typically, the head follows in line by an active lift of the head and the arms are moderately flexed at the elbow. This reaction is already present in newborns.[36] A severe head lag, an asymmetric or a block-like performance

are considered to be abnormal.[36,59,60] The pull-to-sit manoeuvre is part of the Van Wiechenschema.[61] This Dutch screening instrument is used in well-baby clinics throughout the Netherlands and Belgium to identify infants at risk of developmental disorders; the pull-to-sit manoeuvre is tested from 1 till 15 months of age.

Vertical suspension test

For the vertical suspension test, the infant is lifted straight up with the examiner's hands placed under the child's axillae.[36,62] Slipping through, extension and stereotyped movements of the legs and fisting may be considered abnormal. Muscle-tone dysregulation or muscle weakness could contribute to these abnormal postural reactions. The vertical suspension test is also included in the Van Wiechenschema 1–15 months.[61]

Pupillary light reflex

Testing pupillary responses to light is part of the standard neurological examination at any age. Presence of the pupillary light reflex (PLR, i.e. constriction of the illuminated [direct response] and opposite pupil [consensual response]) has been documented from 31 weeks gestational age onwards, be it with a sluggish and variably response.[63,64] In typical development a consistent PLR is present after 35 weeks gestational age.[35,65] It has been theorized that the occurrence is related to the development and maturation of the Edinger-Westphal nucleus, the iris sphincter muscle and its connections or the myelinisation of visual pathways.[64–67] After 35 weeks of gestational age the PLR latency, i.e. the time between start of the light stimulus and pupillary constriction, decreases over the next few weeks.[68] In the same time period, visual evoked potential peak latencies also decrease.[67]

Knowledge on atypical development of the PLR in infancy is very limited. Theoretically speaking, an abnormal response may be brought about by damage or dysfunction of any of the structures involved in the classical neuronal pathway of the reflex, including the retina, the optic tract, the pretectal and Edinger-Westphal nuclei, the ciliary ganglion and the pupillary sphincter muscles of the iris.[64–67] In general, the most common causes of an absent or abnormal PLR (at any age) are damage of the optic or oculomotor nerve, severe brain stem dysfunction or depressant drugs.[69]

Patellar tendon reflex

The assessment of deep tendon reflexes is also a fundamental part of the standard neurological examination. The first tendon reflex was simultaneously described by Wilhelm Heinrich Erb (1840–1921) and Carl Otto Friedrich Westphal (1833–1890) in 1875.[70–72] It was the neurologist Erb who recognised the phenomenon as a true reflex and introduced the term patellar tendon reflex.[72] This reflex (also known as knee jerk) is elicited by a tap on the patellar ligament and the subsequent detection of stretch by the muscle spindles. The signal is conducted through afferent fibres to the motor units in the spinal cord causing the quadriceps muscle to contract. The afferent fibres also connect through an interneuron to the motor units of the antagonist muscle. An asymmetric response, areflexia, a persistent clonus (as an expression of hyperreflexia) or reflex irradiation generally denotes the presence of a neurological disorder.

Surface electromyography (EMG) studies revealed that reflex activity in infants differs from that in adults.[73,74] Healthy newborns demonstrate reciprocal responses, e.g., EMG activity at monosynaptic latencies in both tibialis anterior and soleus muscle in response to a tap to the Achilles tendon.[75] Infants may also demonstrate reflex irradiation, e.g., EMG activity in the tibialis anterior muscle when eliciting the knee jerk.[73] Reflex irradiation is a clinically observable phenomenon too: infants often exhibit crossed adductor responses when eliciting the knee jerk.[2] With increasing age, less reciprocal and irradiated responses are observed.[74,76] In children with CP, both reciprocal responses and reflex irradiation persist during development.[76–78]

GENERAL MOVEMENTS ASSESSMENT

Next to performing a traditional neurological examination, assessing the quality of spontaneous movements is a useful and non-invasive tool to identify infants at risk of developmental disorders. Ultrasound studies have revealed that the earliest fetal movements can be observed from 7 weeks postmenstrual age (PMA) onwards, be it that these movements have a simple and stereotyped character.[79,80] General movements, i.e. endogenously generated complex and varied spontaneous movements in which all body parts participate, are present from about 9–10 weeks PMA.[79–81] They disappear around 4 months post term when goal-directed

motor behaviour emerges.[81–83] The form of typical GMs changes several times due to developmental transformations of the young nervous system.[84–86] Between 28 and 36–38 weeks PMA, the so-called preterm GMs consist of highly variable movements with clear involvement of the pelvis and trunk.[86,87] Thereafter, the GMs have a somewhat slower and more forceful character with less participation of the trunk; this 'writhing' GM phase lasts until 46–52 weeks PMA.[83,86,88] The last GM phase is characterized by the presence of a continuous stream of small and elegant movements occurring irregularly over the body. These fidgety movements gradually appear from 46 weeks PMA onwards and disappear at 56–60 weeks PMA: they bloom between 49 and 53 weeks PMA.[81,84,88]

Heinz Prechtl (1927–2014) was first to discover that the quality of GMs provides information on the integrity of the infant's brain.[85] At any GM phase, the quality of the infant's movements can be classified into four categories: normal-optimal (NO), normal-suboptimal (SO), mildly abnormal (MA) and definitely abnormal (DA).[82,87] Normal GMs are characterized by movement complexity and variation.[82,89,90] Infants typically try out the movement possibilities of each single joint: the numerous combinations within the participating body parts result in a complex performance.[82,86,89] Variation implies that the infant continuously explores all these combinations over time, with a large variety in speed and amplitude.[86,89] In abnormal GMs, complexity and variation are reduced. At the fidgety age, the absence of fidgety movements or an abnormal nature of the fidgety movements is also considered abnormal.[85,90] The presence of abnormal GMs is associated with perinatal risk factors including brain lesions and developmental disorders.[85,86,91–94] Nowadays, the GM assessment actually is the best clinical predictor for the development of CP.[95,96] Longitudinal assessments, e.g. assessments within each GM phase, predict development best.[86,91,97] Second best is a single assessment around 3 months post term, i.e. at the 'fidgety age'.[81,86,98]

EARLY INTERVENTION

Early identification of infants at risk of developmental disorders is particularly meaningful when effective early intervention programmes are available. Theoretically, intervention programmes may be most beneficial at an early age because of the many developmental changes that occur within the first year of life (Figure 1).[3,4] The high level of brain plasticity at this age is likely to offer possibilities for early intervention.[99–102] However, the effect of early intervention in infants at high risk for developmental disorders is still debated. Early intervention programmes for preterm infants seem to have a small positive effect on cognitive and motor outcomes in infancy; the rate of CP does not differ between infants who received early intervention or the standard follow-up.[103] The few studies

that followed the preterm born children beyond pre-school age are inconclusive or indicate no significant effect of early intervention on motor or cognitive outcome.[103]

Conclusions on the effect of early intervention are hampered by the variety of early intervention programmes and heterogeneity of study designs. Hitherto it is unclear which early intervention programme is most beneficial or which elements of intervention are effective in promoting better outcomes.

The lack of convincing evidence for a beneficial effect of existing physiotherapy programmes in high-risk infants inspired Tineke Dirks and Mijna Hadders-Algra to develop the early intervention programme COPCA (COPing with and CAring for infants with special needs – a family centred programme).[99,104,105] The effect of COPCA is evaluated in the VIP and LEARN2MOVE 0–2 years projects. These two Groningen early intervention projects will be introduced below. This is followed by an overview of the outcome measurements used in this thesis.

VIP project

The so-called VIP project (Dutch: Vroegtijdig Interventie Project) studied by means of an RCT and process evaluation the effect of the early intervention program COPCA in comparison to traditional infant physiotherapy (TIP). The major goals of COPCA are strengthening family autonomy and participation, and improving functional mobility. The underlying theoretical building blocks were the transactional model of development, emerging insights in the field of education and family care, and the Neuronal Group Selection Theory (NGST).[9,106–108] According to the transactional model, development is the result of a continuous interplay between infant behaviour, caregiver responses and environmental variables.[109] One of the key factors of the COPCA programme is therefore to optimise the caregiver-infant interaction. Within COPCA, the physiotherapist does not instruct the parents on how to handle their infant, but acts as a coach who respects the family's autonomy and lets the family define their priorities for intervention. By means of a continuous dialogue between caregivers and the physiotherapist (further referred to as 'COPCA coach'), families develop their own ways to cope with their infant with special needs.

The NGST considers development as a complex interaction between genetic make-up and experience.[7,9] In infants with a lesion of the brain, the repertoire of motor strategies is reduced, resulting in less movement variation and more stereotyped motor behaviour.[110] Furthermore, these children have difficulties in selecting the most appropriately adapted strategy out of their reduced repertoire (limited variability). COPCA aims to promote variation in motor behaviour and to stimulate active trial-and-error experiences by means of play. Facilitation of movements, a 'hands-on' technique, is avoided. During the

intervention sessions, it is the family (caregivers, siblings or grandparents) that stimulates the infant to show self-produced motor behaviour ('hands-off'). The family also determines the content of the session (e.g., activities such as playing, feeding, bathing or discussion of the difficulties the caregivers face in daily life). The COPCA coach observes and listens and may give suggestions or information on the importance of exploration, variation and trail-and-error in daily life activities.

During the VIP project, Dutch TIP was mostly based on the principles of neurodevelopmental treatment (NDT).[111,112] Bertha and Karel Bobath developed the NDT approach more than 70 years ago. Then, the primary aims of the treatment were inhibition of spasticity and facilitation of normal posture and movement patterns by means of various handling techniques.[113] Over time, the original effort to influence muscle tone shifted towards a more functional approach.[111] The goal of NDT baby treatment is to teach the infant typical, efficient movements rather than atypical, stereotyped movements.[114] The therapist's hands facilitate, guide, and control the infant through movements to provide the infant with typical sensorimotor experiences (hands-on). As caregivers are recognised as the most important team members, the therapist teaches them treatment activities.

In the VIP project, 46 infants at risk for developmental disorders had been randomly assigned to either COPCA (n = 21) or TIP (n = 25).[115] Inclusion in the VIP project was based on the presence of definitely abnormal GMs around 10 weeks corrected age (CA).[82] All infants had been submitted to the Neonatal Intensive Care Unit of the Beatrix Children's Hospital of the University Medical Center Groningen between March 2003 and May 2005. Infants with severe congenital anomalies and infants whose caregivers had insufficient understanding of the Dutch language had been excluded. The randomised intervention was applied between 3 and 6 months CA. The COPCA intervention was provided twice a week for one hour in the home situation. The frequency, duration and location of TIP varied (median value once a week, mean duration 30 minutes).[115] After the age of 6 months CA, physical therapy was continued when the infant's paediatrician considered it necessary.[116] Infant development was assessed at 3, 4, 5, 6 and 18 months CA.[115,116] To evaluate the actual content of the intervention, video recordings of intervention sessions were made at 4 and 6 months CA. The relative time spent on physiotherapeutic actions (e.g. physiotherapeutic facilitation techniques [such as handling], spontaneous motor behaviour, coaching, communication actions, family involvement and educational actions) was classified according to the protocol of Blauw-Hospers et al (2010).[117] To gain more insight into the application of the intervention principles in daily life activities, video recordings of bathing and playing were performed at 3, 6 and 18 months CA.

At the RCT level, developmental outcome of both groups was similar at 6 and 18 months CA.[115,116] Ten children had CP, five in each group. Analysis of the developmental changes between 6 and 18 months revealed one difference:

children in the TIP group showed a significant deterioration of their Mental Developmental Index score between 6 and 18 months, whereas the children in the COPCA group did not. This 'relative' deterioration (the children did improve in their total score, but less than their full term born peers) was influenced by the level of maternal education and the type of intervention.[115]

Process evaluation revealed that associations between physiotherapeutic actions and developmental outcome differed for children who did and those who did not develop CP.[115,116] In children without CP, facilitation was associated with a lower functional mobility, and the time spent on 'instructing the caregiver by means of assigning' showed a negative correlation with movement fluency at 18 months CA. Within the group of children who did develop CP, some COPCA characteristics were associated with improved developmental outcome at 18 months CA: 1) the time spent on caregiver coaching had a positive correlation with the variability of the child's motor behaviour, 2) the time spent on challenging the infant to self-produced motor behaviour, continued by the infant with little variation, showed a positive correlation with the quality of the child's motor behaviour, and 3) family involvement and educational actions, postural support at the verge of the infant's abilities and challenging the infant to self-produced motor behaviour, continued by the infant with large variation, had a positive association with the child's functional mobility. Two TIP-related actions had a negative association with outcome at 18 months CA: the time spent on sensory experiences showed a negative correlation with the quality of the child's motor behaviour, and passive motor experiences were negatively associated with a neurological optimality score.

Studies on the longer-term effects of early intervention programs are scarce. Follow-up studies are needed since some dysfunctions may only emerge when the brain develops new functions. In the VIP project, 18 months CA was relatively early to diagnose CP. In addition, learning or behavioural problems could not be determined at that age.

LEARN2MOVE 0-2 years project

The above-mentioned results of the VIP project, in particular the outcome of the sub-analysis in infants with CP, gave rise to the start of the LEARN2MOVE 0–2 years project (L2M 0–2). This randomised controlled trial aims to study the effect of COPCA in infants at high risk for CP (Chapter 9).[118] Compared to the VIP project, the L2M 0–2 project included infants with a higher a priori risk for CP and the study design comprised a longer intervention period and an improved implementation of the COPCA program.

L2M 0–2 is part of the Dutch national LEARN2MOVE program, which aims to evaluate the effect and working mechanisms of intervention in children and adolescents with CP. The research program consists of four different age cohorts (0–2, 2–3, 7–12 and 16–24 years), coordinated from medical centres in Groningen, Utrecht, Amsterdam and Rotterdam, respectively.[118–121]

Developmental assessments

Various methods are available to study infant development and neurodevelopmental outcome, of which the following are used in this thesis.

Assessments in infancy

The primary outcome measurement of both the VIP and L2M 0–2 project is the Infant Motor Profile (IMP). The IMP is a video-based assessment to evaluate motor behaviour and consists of 80 items, such as variability of arm movements and sitting ability.[122] These items can be divided into five domains, of which the first two are derived from the NGST: variation (i.e. the size of the motor repertoire, 25 items), variability (i.e. the ability to select adaptive motor strategies, 15 items), symmetry (10 items), fluency (7 items) and performance (23 items). Both an IMP total score and five domain scores can be calculated. The interobserver reliability, construct validity and concurrent validity of the IMP are good.[123,124]

The Touwen Infant Neurological Examination (TINE) was used to specify the infant's neurological condition in terms of the absence or presence of clear neurological syndromes, such as CP, or minor neurological dysfunction (MND). The TINE describes the following five domains: reaching and grasping, gross motor function, brain stem function, visuomotor function and sensorimotor function (i.e., reflexes and muscle tone).[35] Age-specific cut-off scores for dysfunction are available for all domains. The neurological condition is considered normal when none of the domains meet the criteria for dysfunction. The presence of one or two dysfunctional domains indicates a normal-suboptimal neurological development. Neurological condition is classified as MND in the presence of more than two domains of dysfunction, but in the absence of a clear neurological condition. The TINE is regarded a reliable instrument.[125,126]

The Hempel neurological examination is designed to assess MND in children aged 1.5–4 years of age and was therefore used in some of the infants aged 18 and 21 months corrected age. The Hempel distinguishes five domains, which are slightly different from the TINE: fine motor function, gross motor function, posture and muscle tone, reflexes, and visuomotor function.[127,128] Like the TINE, the Hempel assessment specifies neurological condition according

to the presence of dysfunctional domains–in the case of the absence of a clear neurological syndrome like CP. From preschool age onwards, two forms of MND can be distinguished, namely simple and complex MND. At preschool age simple MND denotes the presence of one deviant domain (except for reflexes) and can be considered a normal but non-optimal neurological condition. Complex MND is the clinically relevant form of MND and indicates the presence of more than one domain of dysfunction. The inter-rater reliability of the Hempel examination is satisfactory.[128]

In children with CP, the GMFCS was applied, which classifies children's gross motor abilities from level I (most able) to level V (most limited).[24] The GMFCS is a reliable and valid classification system that uses age-specific bands.[24] Although there is a specific age band for children below two years of age, reclassification at an older age is recommended.[129]

The Alberta Infant Motor Scales (AIMS) is a frequently used tool to identify infants with a delay in gross motor development.[130] The 58 test items evaluate gross motor function in prone (21 items), supine (9 items), sitting (12 items) and standing position (16 items). Percentile scores based on the total AIMS score are available for infants up to 18 months of age. The AIMS has a good reliability and validity but experiences a ceiling effect in older infants.[125,131]

The Bayley Scales of Infant Development (BSID-II) were administered to define global motor and mental development.[132,133] The BSID-II is a widely used instrument to evaluate development in children up to 3.5 years of age. The infant's performance results in a raw score that can be converted into an age-specific psychomotor and mental developmental index score (PDI and MDI, respectively). The BSID-II is a reliable and valid instrument with Dutch norm scores.[133] Recently, a third version of the BSID, i.e. the BSID-III, has been developed. Dutch norm scores for the BSID-III became available only after the start of the L2M 0–2 study.

In early childhood, functional capability and performance can be evaluated with the Pediatric Evaluation of Disability Inventory (PEDI).[134] The PEDI is a standardised parental interview that includes 197 functional skill items and 20 items on the need for caregiver assistance within the domains self care, mobility, and social function. For this thesis, only scores in the mobility domain are used. The PEDI is designed for children 0.5 to 7.5 years of age and also the adapted Dutch version has proven to be reliable and valid.[135,136]

Assessments at school age

To evaluate functional outcome at school age, we used the Vineland Adaptive Behavior Scales (VABS), the Developmental Coordination Disorder Questionnaire (DCD-Q), and the Child Behaviour Checklist (CBCL). The VABS is a scoring list on the functional status in communication, daily living skills, socialisation, and

motor skills in children until 18 years of age.[137,138] These four domains enclose eleven subdomains, such as receptive communication, community skills and fine motor skills. Scores can be calculated for each domain and subdomain; the raw scores can be translated into matching developmental ages. The VABS is assessed by means of a structured parental interview and is a reliable and valid instrument in children with developmental disorders and in typically developing children.[139,140]

The DCD-Q was used to assess motor performance at school age. This brief parental questionnaire contains items on control during movements, fine and gross motor skills and general coordination.[141] The DCD-Q is designed to identify motor problems that may indicate the presence of Developmental Coordination Disorder (DCD). Additional assessments are needed to diagnose DCD according to the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, fifth edition).[142] The Dutch translation of the DCD-Q is a reliable and valid tool in children between four and 14.5 years of age.[143]

The CBCL is frequently applied in both research and clinic settings to describe the child's behaviour. The parental questionnaire contains 113 items on a three-point Likert scale. The items can be categorised into syndrome scales regarding internalizing behaviour (i.e. anxious/depressed, withdrawn/depressed, and somatic complaints), externalizing behaviour (i.e. rule-breaking behaviour and aggressive behaviour) or other problems (i.e., social problems, attention problems, and thought problems). Internalizing, externalizing and a total problem scale score can be calculated, as well as scores on six DSM oriented scales: affective problems, anxiety problems, attention deficit/hyperactive problems, conduct problems, oppositional defiant problems and somatic problems. Scores indicate normal, borderline or clinically abnormal behavior. The CBCL has specific versions for children aged 1.5 to 5 years and for children aged 6–18 years. The Dutch translation of the CBCL is reliable and valid.[144–146]

Figure 2 provides an overview of the timing of the neurological, neuromotor and developmental assessments used in this thesis.

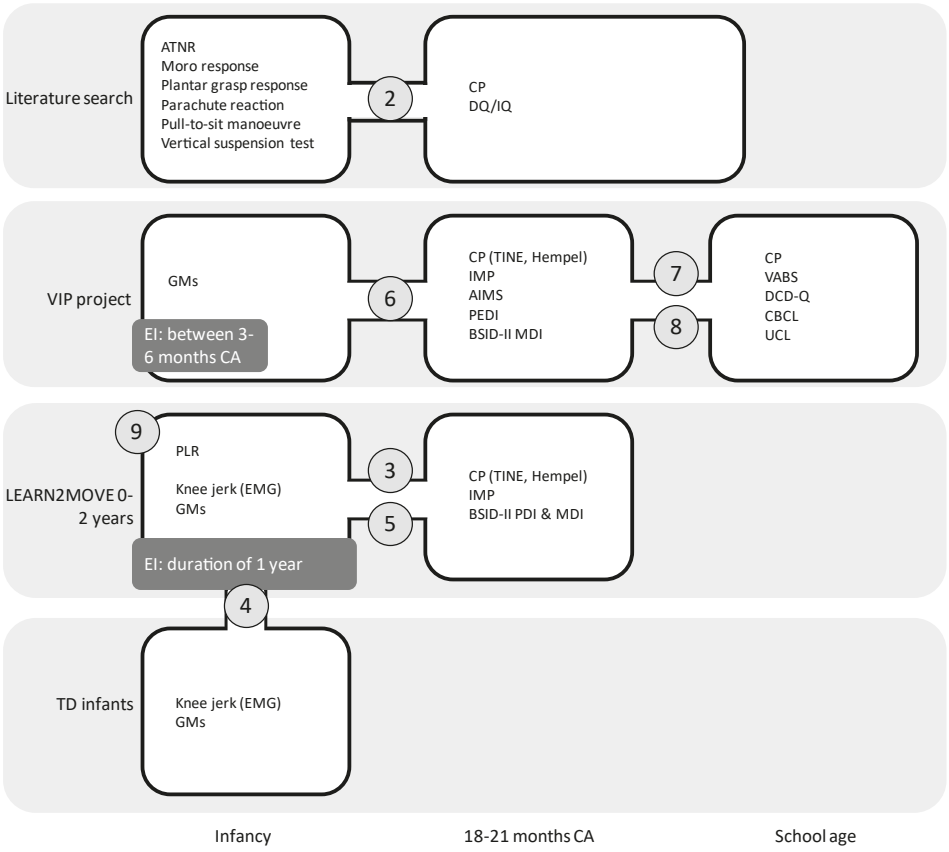

Figure 2. Overview of the assessments used in this thesis, categorised per age period and type of project. The numbers display the corresponding chapters.

AIM AND OUTLINE OF THE THESIS

This thesis focuses on neuromotor behaviour in infants at risk of CP and on the effect of the early intervention programme COPCA. Our primary aim is to enhance the identification of infants most at risk of CP and to improve prediction of neurodevelopment using traditional neurological items (part I) and the GM assessment (part II). As early identification creates opportunities for early intervention, our secondary aim is to investigate the effect of COPCA in infants identified as being 'at risk' (part III).

Part I: Traditional neurological examination in infants at risk for CP

Chapter 2 consists of a systematic review on the prognostic significance of neurological signs in high-risk infants. The review provides an overview of predictive values of the ATNR, Moro, plantar grasp, and parachute response, pull-to-sit manoeuvre and vertical suspension test in infancy. *Chapter 3* describes our observation of slow pupillary light responses in high-risk infants. We explored whether slow responses were associated with both the presence of specific brain lesions and developmental outcome at 21 months corrected age. In *chapter 4*, we examined – by means of surface electromyography–the differences in knee jerk responses between healthy infants and infants at high risk of CP around 3 months of age. In *chapter 5*, we longitudinally studied knee jerk responses in high-risk infants and explored whether this development was related to the presence of cystic periventricular leukomalacia or diagnosis of CP.

Part II: General movement assessment in infants at risk of CP

In this part, we examined whether specific movement characteristics may improve the predictive power of definitely abnormal GMs for developmental outcome – including CP – at 18 months corrected age (*Chapter 6*) and at school age (*Chapter 7*).

Part III: Early intervention in infants at risk of CP

In *Chapter 8* we present our follow-up data of the VIP project: we investigated whether daily functioning at school age of children who had received COPCA differed from that of infants who had received TIP as early intervention. *Chapter 9* describes our research protocol and hypothesis for the LEARN2MOVE 0–2 years study.

Chapter 10 provides a general discussion of our findings including the clinical implications and future perspectives. The content of this thesis is summarized in *Chapter 11*.

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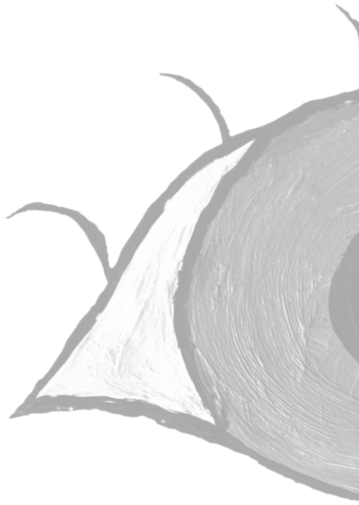

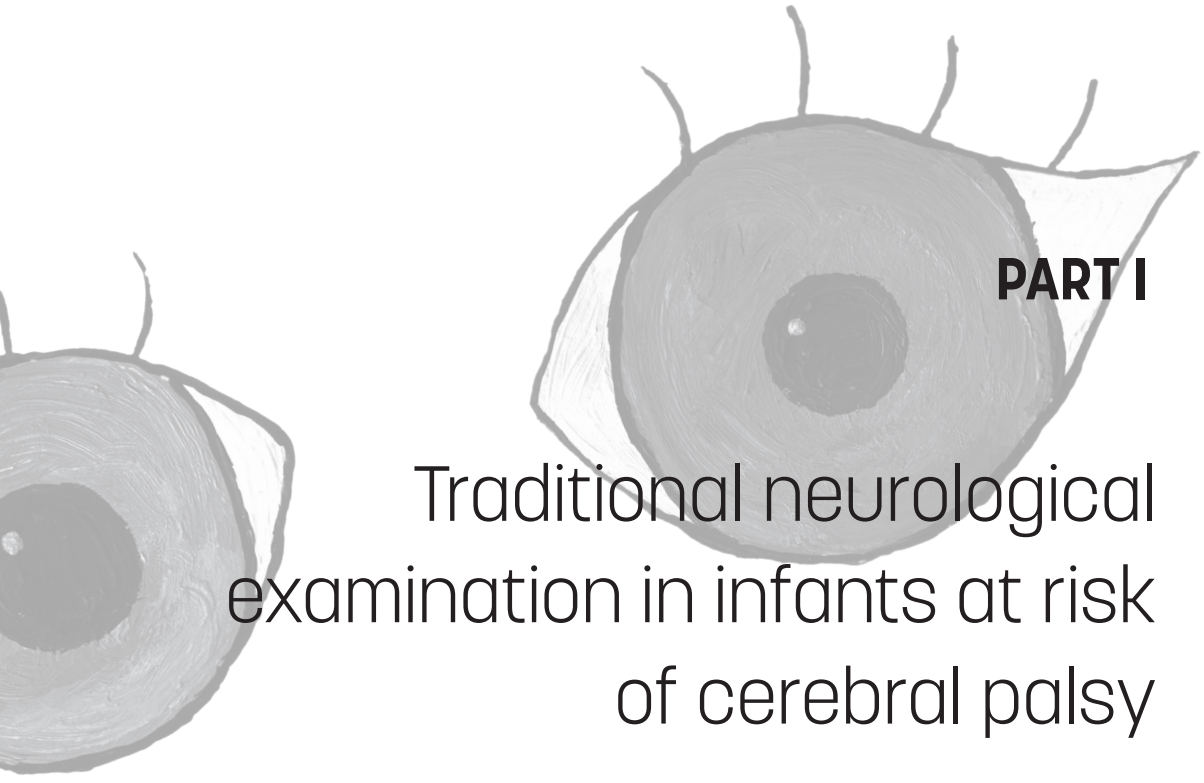

PART I

Traditional neurological examination in infants at risk of cerebral palsy