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Postural control and reaching throughout infancy

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General introduction

“Every single brain is absolutely individual, both in its development and in the way it encounters the world”, is what Gerald Edelman wrote, cell biologist and physician. In his books on the biological theory of consciousness, he presents the theory of Neuronal Group Selection (NGST). Using the framework of the NGST to describe human motor development, this thesis sheds light on the development of postural control in typically developing infants and infants at very high risk of cerebral palsy.

MOTOR DEVELOPMENT

The NGST is one of many theories describing motor development. In the theories, the contribution of nature and nurture to motor development remains an ongoing debate. Outdated neuromaturational theories assume that the normal sequences of motor development are the consequence of genetically determined structural changes in the central nervous system.¹⁻³ On the contrary, the Dynamic Systems Theory emphasizes the importance of interaction with the environment and considers motor development as a non-linear process. Motor behaviour is considered to be the product of multiple interacting sub-systems within the body with different tasks and environments. Spontaneous self-organization of the sub-systems produces the most efficient motor strategy for specific tasks.⁴⁻⁶ The NGST meets both theories halfway by emphasizing a complex interaction between nature and nurture: the theory acknowledges the genetically determined organization of variable networks in the central nervous system, while also endorsing the effect of interaction with the environment.

Gerald Edelman argued that the formation of the cortical and subcortical structures into networks is determined by genetic factors, in which development and growth determine the formation of individual synaptic connections between neurons and determine their organization in functional neuronal groups. This process induces a tremendous amount of variation in neural circuitries between individuals. The functional plasticity of the neuronal groups and the abundant neuronal connections facilitate the organization of complex and adaptable ‘networks’ of neuronal groups. Within these primary networks, neurons are stronger connected to each other than to neurons in other networks. After forming the initial primary networks, development continues by the process of selection. Selection of specific neuronal groups for specific behaviour is modulated by afferent signals providing information on the success of behaviour, thereby changing the strength of synaptic connections between neurons and neuronal groups. The process of selection results in the formation of secondary networks with altered connectivity, in which

specific neuronal groups will be selected for different situations. Edelman draws similarities with Charles Darwin's Theory of Natural Selection, accordingly he refers to his theory as *Neural Darwinism*.⁷⁻⁹

When human motor development is described according to the framework of the NGST,^{10,11} two phases of variability can be distinguished.^{10,11} In the phase of primary variability, young infants first explore the many possibilities of the central nervous system. This phase is characterized by abundant variation in motor activities: a large repertoire of motor actions. The output of the self-produced motor behaviour gives rise to afferent information, which will in turn provide information on selection of the best motor strategy for a specific situation: the phase of secondary variability. The selection process of the motor strategy is based on the selection of specific neuronal groups.¹¹

An early brain lesion may cause damage to the different primary neuronal networks, leading to less possibilities for exploring motor actions of the central nervous system. Clinically it will result in less variation: a poor repertoire of motor actions. As motor impairments due to brain lesions are often associated with other impairments such as visual problems, the selection process in the secondary variability is often also hampered. The development of secondary neuronal networks is therefore presumably delayed and the secondary networks will remain limited in infants with brain lesions.¹⁰

CEREBRAL PALSY

Cerebral palsy (CP) is caused by a lesion to the developing brain and is one of the most common developmental motor disorders in children, with an incidence around 2 on 1000 live births.^{12,13} According to the definition of Bax et al. (2005), Cerebral palsy is "a heterogeneous group of motor disorders. CP describes a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behaviour, and/or by a seizure disorder."¹⁴

As the definition proposes, CP can be caused by different lesions to the brain during pregnancy, delivery or the first months of postnatal life. For instance parenchymal infarctions or haemorrhages can result in CP. Also periventricular leukomalacia is a well-known cause of CP, it occurs most often in premature infants. Actually, cystic periventricular leukomalacia (cPVL) is one of the most severe lesions to the developing brain, in which cyst formation is the result of focal periventricular

necrosis. Around the cysts, generally a more diffuse damage of the cerebral white matter is present, including the cortical subplate.¹⁵ The variety in brain lesions causing CP lead to different and heterogeneous appearances of CP. Spastic CP is the most common type, in which a hypertonic muscle tone is most prominent. Ataxic CP is mainly characterized by problems in balance and loss of normal muscle coordination and dyskinetic CP by a fluctuating muscle tone and involuntary stereotyped movements. In addition, CP can be classified according to the distribution of the limbs involved: the symptoms can be uni- or bilateral.¹⁶ Also severity of CP varies: children with Gross Motor Function Classification System (GMFCS) level I are least affected and are able to walk independently, while children with GMFCS level V are not able to move around independently, or use electric wheelchairs with extensive adaptations.¹⁷

The clinical diagnosis of CP requires serial examinations, as clinical signs can evolve or resolve when the nervous system matures.¹⁸ The diagnosis is often made in the first two years of life, but when symptoms are mild, the diagnosis can be delayed.¹⁹ In terms of motor development, infants who are later diagnosed with CP are delayed in the development of milestones, and show a reduced variation in movements in different positions.

POSTURAL CONTROL

Assessment of postural control

As the definition of CP indicates, a major motor problem in CP is postural dysfunction. Every motor activity requires proper postural control; the body needs to maintain its balance and keep the centre of mass within the support surface.²⁰ Postural control is essential for virtually all daily life activities, yet most of the time we are not aware of using the postural control system, until it is challenged or damaged. Postural control is a highly complex task, in which almost all parts of the central nervous system are involved.^{21,22} The complexity ensures a long-lasting development, at least until adolescence. It can be assessed in different ways.

Some researchers focus on the assessment of postural sway: the body is never able to stand perfectly still, it continuously 'sways' due to everlasting corrections in posture by the central nervous system. The sway might indicate that the central nervous system searches for the limits of the stability.²³ By studying postural sway, centre of pressure (COP) parameters are often used. The COP indicates the point of application of the vector of the ground reaction force, in which

the vector of the ground reaction force represents the sum of all forces between the supporting surface and the body. When analysing COP behaviour, multiple parameters can be used, including postural sway area and amplitude, COP velocity and COP travel path. The parameters yield in particular information on the size of postural sway, and little on neural control mechanisms.

Research on postural sway provides information on the net result of the postural control system, but does not include information on the muscular strategies of the central nervous system to achieve the stability. Bernstein (1935) realized that the central nervous system had to cope with many degrees of freedom in upright stance, induced by a body consisting of multiple joints and muscles. He suggested that the nervous system solved this problem by creating motor synergies. Motor synergies provide supraspinal control centres with the possibility of activating a predefined set of muscles, instead of controlling every singular muscle contraction.²⁴ In 1994, Forssberg and Hirschfeld divided the neural control of postural synergies into two functional levels, the first level was labelled as direction-specificity. It means that when the body sways in a forward direction, the dorsal muscles are activated prior to the ventral muscles in order to maintain balance. When the body sways backward, ventral muscles are activated primarily. At the second level, these directionally appropriate adjustments are adapted to the specifics of the situation.²⁵ The muscular activity can be assessed by means of surface electromyography (EMG). In EMG-studies, mainly two types of paradigms are used. In the first paradigm the participants rely on feedback mechanisms (reactive neural control) when experiencing external perturbations from e.g., a moving platform. On the other hand, feedforward mechanisms (active neural control) can be assessed. In this case participants rely on anticipatory postural control, for example tested during reaching movements.

Typical postural development

Evidence shows that postural sway decreases with increasing age and experience, in supine,²⁶ sitting²⁷ and upright stance.^{28,29} Regarding muscular postural control, the principles of the NGST can be applied to its development. In early infancy, the postural activity is highly variable, and not adapted to the situation: the phase of primary variability.³⁰ Secondary variability emerges when the second level of postural control starts to become functional.

Already at the age of one month, infants are able to produce (reactive) direction-specific adjustments in 85% of the testing trials in the dorsal muscles, when placed in sitting position on a moving platform. The presence of the first

level of postural control at this age suggests an innate origin.³¹ Direction-specificity in sitting during external perturbations remains around 70–85% until the age of 4–5 months and is consistently present from 7–8 months onwards.^{32–34} In standing position, direction-specificity on a moving platform is not consistently present in infants in the pull-to-stand phase with³⁵ and without support.³⁶ However, infants who are able to stand independently all show consistent direction-specificity during external perturbations.^{35,37,38} Active – and internally triggered – postural control shows a slightly different development, mostly studied during reaching in sitting or supine position. At the age of 4–6 months, when goal-directed reaching movements emerge, infants show variable direction-specificity of dorsal muscles in about 40–50% of the reaching movements.^{39,40} Throughout infancy, the percentage increases to 60–80% at 18 months⁴⁰ and reaches 100% at the age of two years.⁴¹ However, no literature is available addressing the question whether the development of direction-specificity during reaching is related to age or to developmental stage such as learning to sit or walk independently.

In the phase of secondary variability, the second level of postural control becomes functional.²⁵ Every situation requires a different postural strategy and muscle activity. For instance, a reaching movement in sitting position demands other postural activities than a reaching movement in standing position. The fine-tuning of the direction-specific adjustments is adapted to the difficulty of the postural task. The development of adaptation to the situation starts for example with the selection of the complete pattern – the pattern in which all the direction-specific muscles are activated in concert. During external perturbations in sitting, the complete pattern is present in 5–20% of the perturbations at 1 month of age, disappears around 3 months and emerges again after 3–4 months. It increases to about 30–50% at 6 months, 75–100% at 9–10 months of age and after the age of 2,5–3 years the preference for the complete pattern disappears again.^{31,34,42} In standing, the dominance of the complete pattern is present from 2 years onwards, at least until the age of 10 years.^{35,37,43} During internally triggered postural adjustments while reaching in sitting position, the complete pattern is present in about 50% of the reaching movements at 6 months.³⁹ It becomes the preferred pattern until 18 months,⁴⁰ but the preference for this pattern disappears again after 18–24 months.^{41,42} The difference in timing of presence of the complete pattern in different positions and during differently triggered (external or internal) perturbations show that fine-tuning of postural control depends on the situation and difficulty of the postural task. Other ways of adaptation to the situation are changing the order of recruitment of the postural muscles, antagonistic activity, activating the postural muscle prior to the movement (anticipatory activity) and the most subtle way of adaptation is the

modulation of the muscle contraction.^{23,25} As postural control is a highly complex neural task, adult levels of the second level of postural control will only be reached after adolescence.⁴¹

Atypical postural development

Considering the complexity of postural control, it is not surprising that the postural control system is vulnerable for brain injury, resulting in problems in children with CP. Postural sway data indicates that infants at risk of CP and children with CP show a worse postural stability compared to typically developing infants and children.⁴⁴⁻⁴⁶ Regarding muscular postural control, children with CP are in general able to produce direction-specific adjustments at school-age, but show difficulties with the second level of postural control. The degree of dysfunction is related to the severity of CP.⁴⁷ In the study of van der Heide et al. (2004), children with CP used a stereotyped top-down recruitment order during reaching in sitting position, while typically developing (TD) children showed variation and at the youngest ages a slight preference for bottom-up recruitment. Children with CP also presented with problems in modulating the degree of muscle contraction to sitting position and reaching velocity.⁴⁷

As the diagnosis of CP cannot be made in the first year of life, research into the development of these problems is mainly restricted to infants at high risk of CP (HR-infants). Van Balen et al. (2015) showed that in early infancy, HR-infants have similar postural strategies as TD-infants, but display a delayed development of direction-specificity at 18 months. HR-infants also had lower rates of anticipatory activity, used less often the complete pattern and had longer latencies to recruitment of postural muscles at 18 months, but did not differ from TD-infants early in infancy.⁴⁸ However, in this study only five of the 23 HR-infants developed CP. Another study described the development of seven infants who were all diagnosed with CP at 18 months. The five infants with unilateral spastic CP showed direction-specificity and similar features of the second level of postural control as TD-infants from 15 months onwards, with the exception that they were not able to modulate postural muscle contraction. One infant with bilateral CP had a similar postural development as the infants with unilateral spastic CP but the development was slower. The other infant was diagnosed with bilateral CP and athetosis, she presented with a lack of direction-specificity and a disorganized second level of control.⁴⁹

Literature on postural control in infants and children with severe CP is scarce. Infants or children with severe CP often use adaptive seating systems with

support of the trunk, pelvis, head and/or legs to engage in daily life activities,^{50,51} but it is unknown to what extent the children regulate their own postural control. Follow-up at 4 years of the infant lacking direction-specificity revealed that she was not able to sit independently.⁴⁹ Another 4-year-old child with CP from a different study also lacked direction-specificity during perturbation experiments and was not able to sit independently.⁵² These two case reports of children with CP functioning at GMFCS level V suggest that the absence of the basic level of postural control precludes the development of independent sitting. Also children with GMFCS level IV require trunk support during sitting,¹⁷ and postural control data of 8 children with CP with GMFCS level IV indicated a variable and inconsistent presence of direction-specific muscle activity at neck or leg level.^{47,53} The latter data complement the suggestion of a relation between direction-specificity and independent sitting.

The above indicates that the development of the postural problems in early infancy in CP (instead of in high-risk infants) remains mostly unknown. Also the effect of different types of brain lesions on postural development is lacking.

REACHING

Typical development of reaching

Most of the studies on internally triggered postural adjustments were conducted during reaching in sitting position, as successful reaching is highly dependent on postural control. It requires involvement of the whole body. This is for example demonstrated by research showing that infants who are not able to sit improve in reaching quality when extra pelvic support is provided⁵⁴ and research showing that more direction-specificity in sitting position was associated with a higher percentage of reaching movements resulting in successfully grasping or touching the object.³⁹ Reaching is an important milestone, e.g. it offers the possibility to explore the environment, it is involved in many daily life activities like eating and drinking and it is essential for interaction with other infants or adults.^{55,56} Important neural circuits, including primary motor and somatosensory cortices and frontal and parietal areas are involved in reaching movements. Learning to reach is challenging, not only in view of the neural complexity, but also considering the biomechanical complexity.

Newborn infants are not able to reach and grasp objects. Soon after birth, they start to follow objects or persons with their eyes. As soon as interest in the environment emerges, the infant starts to move the arms in response to an attrac-

tive object more often than might be expected by chance.⁵⁷ These are so-called pre-reaching movements.⁵⁸ Around the age of 4 months, infants accomplish to grasp the presented object, although the reaching movement is not yet smooth and fluent.⁵⁹ Reaching movements are variable in speed, duration, trajectory and amplitude.^{5,60} During the next few months, they become rapidly more smooth and fluent.^{59,61} Initially, infants use both hands for reaching and grasping movements. Around the age of 6–8 months it changes to a preference for unilateral reaching, although the preference for uni- or bilateral reaching remains dependent on the position of the infant and the size and shape of the object.^{62,63}

Kinematically, reaching movements can be described using the number of corrections in the movement trajectory: movement units (MUs). One MU consists of one acceleration and one deceleration in the velocity profile of the reaching movement.^{61,64} In adults the reaching movements usually involve one MU; it indicates that reaching movements are programmed in advance. Infants who just mastered the ability to reach towards an object around the age of 4–5 months, produce reaching movements with several MUs.^{61,64} It suggests that infants at this age mainly rely on feedback mechanisms and continuously adapt the trajectory of the reaching movement. The number of MUs decreases rapidly until the age of 6 months.^{59,61,65} After this age, development of reaching continues to improve until adolescence.^{59,66,67} Also in other reaching parameters the major part of the improvement is seen between 4 and 6 months.^{59,61,65} Parameters that rely on feedforward control are for example the relative size of the transport MU – the first MU that covers most of the transport of the hand – and the curvature index describing the straightness of the movement. Reaching parameters that rely on a mix of feedforward and feedback mechanisms are reaching duration, average speed and length of the movement.⁶⁸

Atypical reaching development

Van der Heide et al. (2005) showed that at school-age, children with CP have a worse kinematic reaching quality of the dominant arm compared to TD-children, expressed as longer reaching durations, lower average speed and less often reaching movements consisting of one MU. The transport MU appeared to be smaller in children with bilateral CP compared to TD-children, but the transport MUs of children with unilateral CP were similar to those of TD-children. Performance on kinematic parameters was associated with severity of CP: infants with severe CP scored worse than infants with mild or moderate CP. The detailed kinematic reaching parameters were also associated with scores on the Pediatric Evaluation of Disability Inventory

(PEDI), indicating that better kinematic reaching quality was associated with better functional performance in daily life.⁶⁹ Also other studies revealed that children with CP show a worse kinematic reaching quality than TD-children.^{70,71}

Research into the development of these problems is again restricted to infants at risk, as neurological outcome is difficult to predict at early age. Heterogeneous groups of preterm infants have been studied. Compared to full-term infants not at risk, the kinematics of reaching in low-risk preterm infants show signs of slightly advanced development at 4 months CA – probably due to more extrauterine experience.⁷² At 6 and 8 months CA, low-risk preterm infants use less efficient reaching strategies compared to term-aged peers.^{73,74} However, high-risk preterms, i.e., infants with an Apgar score <3 after 5 minutes or with respiratory problems, do not have an advantage in kinematic characteristics of reaching compared to full-term infants at any age, presumably because the negative effects of preterm birth overshadow the advantages of additional extrauterine experience. At 6 months, high-risk preterms show less optimal reaching movements compared to full-term and low-risk infants, as expressed by a combined measure of peak velocity and number of MUs.⁷² The study of Fallang et al. (2005) showed that this worse kinematic reaching quality at 6 months was related to the development of complex minor neurological dysfunction and fine manipulative disability at the age of 6 years.⁷⁵ It suggests that already at early age, the subtle measure of kinematic reaching quality is associated with neurological outcome. However, in these studies, infants who later developed CP or infants with a very high risk of CP were excluded. Therefore the development of the kinematic reaching problems in CP remains largely unknown.

EARLY INTERVENTION

Promoting postural control is incredibly important, considering its involvement in virtually every daily life activity. Therefore, postural problems, but also other motor impairments, are frequently addressed in early intervention programs. Early intervention is likely to be most beneficial early in infancy, in light of the considerable plasticity of the brain in early life. Neuroplasticity refers to the ability of the central nervous system to mature, structurally and functionally change and adapt to experiences or injury throughout the life of an individual. Considering the many developmental changes and the formation and adaptation of the neuronal networks based on experiences at a young age, neuroplasticity seems to be more extensive early in life, creating opportunities for early intervention in infants with brain lesions.^{10,18,76–78} The efficacy of different early intervention programs on neuro-

logical and motor outcome however, is largely unknown. Studies evaluating different forms of early intervention programs are often of low quality, with small sample sizes, and they vary widely in intervention approaches, length of intervention and outcome measures.^{79–82} The indistinct effect of different early intervention programs was the inspiration for the development of an early intervention program based on the principles of the NGST: COPing with and CARing for infants with special needs (COPCA).⁸³ The effects and working mechanisms of COPCA were compared to traditional infant physiotherapy (TIP) in the Netherlands in a randomized controlled trial: LEARN 2 MOVE 0–2 years (L2M 0–2).⁸⁴ To understand working mechanisms of an intervention program and evaluate whether intervention has an effect on postural development, it is essential to know typical and atypical developmental patterns of postural control. Thus, within L2M 0–2, data were collected on reaching and postural control throughout infancy.

STUDY GROUPS OF THE THESIS

LEARN 2 MOVE 0–2 years

LEARN 2 MOVE is a Dutch national research program evaluating the effects and working mechanisms of age-specific intervention programs for infants, children and adolescents with CP.⁸⁵ The national program is divided into four age cohorts, with the youngest cohort being L2M 0–2 years.⁸⁴ As the diagnosis CP can only reliably be made after 18 months, L2M 0–2 deals with infants at high risk of CP.

In L2M 0–2 years, the effects of two types of early intervention are assessed in infants at very high risk of CP. The infants were included before the corrected age of 9 months, based on a severe brain lesion around birth, or neurological dysfunction suggestive for the development of CP. The infants received 1 year of intervention: either traditional infant physiotherapy (TIP) or COPCA.⁸⁴ TIP is in the Netherlands mainly based on the principles of neurodevelopmental treatment (NDT). Traditionally, Karel and Berta Bobath – the founders of NDT – aimed at inhibiting spasticity and abnormal reflexes by using handling techniques to facilitate normal movement patterns and muscle tone.⁸⁶ As neuroscience and paediatric physiotherapy developed and the Bobaths gained more experience through the years, NDT evolved into a living concept: the treatment principles changed according to additional under-

standing of the central nervous system and its associated disorders. The goal is nowadays to enhance daily function of the individual by teaching the infant typical movement patterns. Direct handling techniques are used to provide the infant with sensorimotor experiences of typical movements. The physical therapist teaches the parents treatment techniques to incorporate the intervention into daily life.^{87,88}

COPCA is a family centred program with two components. The first component is the family: COPCA focusses on family autonomy, responsibility and parenting specific for the family. A coach observes and helps the family to challenge the infant in different daily life activities, within the family's own perspective on raising a child. The second neurodevelopmental component is based on the principles of the NGST. COPCA is aimed at functional mobility of the individual, and accepts atypical motor patterns if they do not hamper but promote participation in daily life activities. COPCA acknowledges the importance of variation in motor development, and intends to promote the exploration of means to enlarge the reduced motor repertoire. In addition, the child is challenged to explore and select within his available motor strategies. Facilitation techniques are avoided, the infant learns and develops by means of trial-and-error experiences during self-produced motor behaviour.⁸³

The postural control and kinematic data of reaching in this thesis were collected as additional explorative data on the working mechanisms of intervention in the 43 infants at very high risk of CP participating in L2M 0–2.

POCOWALK

During the course of postural control and kinematic data collection and analysis in L2M 0–2, a gap in knowledge of postural control data of typically developing infants became evident. The ultimate goal of human postural control is aimed at standing and walking on a narrow support base. Yet, no study had addressed the relationship between muscular postural control and the development of independent walking. To this end, the POCOWALK study was designed. Twenty-eight typically developing infants were included when they were at the verge of being able to walk independently. Longitudinal postural control and kinematic data in sitting position while reaching were collected at 3 points in time: 1) when the infant could pull to stand but was not able to walk independently; 2) within one week after the infant had mastered to take his first steps; 3) one month after the second session.

AIM AND OUTLINE OF THE THESIS

This thesis focuses on postural control and reaching in typically developing infants and infants at very high risk of CP. The aim is to explore and increase understanding on the development of postural control and reaching in typically developing and high-risk infants, which may in turn provide knowledge and clues for early intervention. Insight in developmental trajectories of postural control during the development of milestones and in infants with different types of brain lesions or severity of symptoms may for example guide early intervention towards early postural training or the early provision of external support.

Chapter 2 comprises a study investigating whether muscular postural parameters change when typically developing infants and infants at very high risk of CP develop the ability to sit independently. Since case-reports from the literature suggested that direction-specificity could be a prerequisite for the development of independent sitting, we hypothesize that postural parameters would improve when learning to sit independently.

Chapter 3 evaluates differences in postural control of the high-risk infants of L2M 0–2 and typically developing infants before and after the infants develop the ability to walk independently. We hypothesize that if the postural parameters are related to independent walking, postural control will improve after learning to walk independently.

Chapter 4 deals with a more detailed look into the development of postural muscle activity in typically developing infants during the emergence of learning to walk – the POCOWALK study. We hypothesize that developing the ability to walk independently requires a reorganization in postural control. We assess whether infants who just mastered to take their first steps differ in postural control from infants who are not able to walk and those who have more walking experience.

Chapter 5 consists of a study evaluating the longitudinal development of postural control in VHR-infants throughout infancy. The effects of the diagnosis of CP and presence of cystic periventricular leukomalacia on development of postural control are explored. Corresponding to prior research, we expect that infants developing CP would ‘grow into a postural deficit’ with increasing age. However, we also predict that infants with cystic periventricular leukomalacia – one of the most severe brain lesions – will show postural problems from early age onwards.

Chapter 6 describes the longitudinal development of kinematic reaching quality in VHR-infants throughout infancy. Again, the effects of presence of cystic periventricular leukomalacia and diagnosis of CP are taken into account. Corresponding to chapter 5, we hypothesize that infants with CP 'grow into a deficit', while infants with cystic periventricular leukomalacia show difficulties with reaching from early age onwards.

Chapter 7 provides a general discussion on the results and contents of this thesis and provides clinical implications and prospects for future research.

Chapter 8 gives a summary on the content of the thesis.

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