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Postural control and reaching throughout infancy

Boxum, Anke

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General discussion

In the Netherlands, nearly every day an infant is born who will develop cerebral palsy. The general introduction indicated that the infant at high risk of cerebral palsy is often referred to a paediatric physical therapist to address motor impairments and postural problems. This thesis had as general aim to increase knowledge on typical and atypical motor development and to provide clues for early intervention. More specific, this dissertation aimed to explore and increase understanding on the development of postural control and reaching in typically developing infants and infants at very high risk of cerebral palsy. The general discussion offers a brief reflection on the results of the thesis with clinical implications, followed by suggestions for future research and concluding remarks. However, the discussion starts with some methodological considerations.

METHODOLOGICAL CONSIDERATIONS

The design of LEARN2MOVE 0-2 (L2M 0-2) and POCOWALK allowed us to longitudinally study the development of postural control and reaching. In L2M 0-2, the extensive battery of neuromotor assessments provided the opportunity to also study postural control based on functional performance and compare the data to those of POCOWALK. Another strength of L2M 0-2 is the inclusion of infants at very high risk of cerebral palsy (CP), which resulted in sufficient sample sizes to study differences between infants who did and did not develop CP, since more than half of the infants developed CP. A limitation is that the L2M 0-2 program was initially designed to evaluate differences between two forms of early intervention, which may have influenced the results. However, the type of intervention (COPCA or traditional infant physiotherapy (TIP)) did not affect neurodevelopmental outcome¹ and preliminary data analyses indicated that postural control and reaching did not differ between both intervention groups. A second limitation is the diversity in CP within this relatively small sample size, it may limit the external validity. The setup of the postural assessments also yielded difficulties. To fairly compare postural adjustments, we studied infants sitting in an infant chair. However, for the youngest infants or infants who were severely affected it was not always possible to remain seated in the infant chair, whereas older infants who were able to walk did not always cooperate in the chair. In addition, the challenge of reaching in sitting position may be limited in infants who can sit independently for several months. This may have resulted in 'sloppy' postural strategies, i.e., they choose one of the multiple roads leading to Rome, while more demanding postural tasks at this age would have forced the child to select neatly tuned postural strategies.

REFLECTION

Postural control

Typical postural development

The development of postural control and motility are closely associated: adjustments of posture are virtually always necessary for goal directed-movements. In human motor development, the role of our genetic make-up, the environment and their interaction is highly complex. The observation that infants develop through the same milestones before they can walk – almost always in the same sequential order² – suggests that this process is under initial control of a genetically pre-defined process, guiding biological and physical development. When biological growth of brain and body is sufficient to perform a new skill, an infant can start to learn. Learning occurs in interaction with the child's environment and it changes behaviour due to experience. Variation in the age at which infants accomplish a new skill occurs among individuals, likely due to (culture-specific) differences in the environment.³

The various theories describing motor development differ in their opinion on the contribution of nature and nurture. Supporters of the Dynamic Systems Theory in general study development based on functional performance and therefore recognise a relatively large contribution of interaction with the environment.⁴⁻⁷ Advocates of the Neuronal Group Selection Theory (NGST) acknowledge besides nurture a substantial role for endogenous maturation of predetermined neuronal connections, hence study groups are often based on age.⁸⁻¹⁰ Regarding the development of muscular postural control, **chapters 2, 3 and 4** yielded results in favour of the NGST: in typically developing infants and infants at high risk of CP, our postural parameters did not change during the development of independent sitting or walking. Since the basic level of postural control – direction-specificity – is present (although not consistently) before infants learn a new skill, and the degree of direction-specificity does not change during this phase, it seems plausible that a genetically predefined process guiding biological development of the brain and central nervous system initially plays a large role in the development of direction-specificity. When a certain degree of direction-specificity is accomplished, the infant can start to learn the new skill. This suggestion fits to the study of van Balen et al. (2012), who showed that direction-specificity increases with increasing age.¹⁰ Also

Hedberg et al. (2004) pleaded for an innate origin of direction-specificity, as they demonstrated that during perturbations of a moveable platform, a certain degree of direction-specificity was already present at the age of 1 month.¹¹

However, the postural control system has been a subject of research for many years from many different points of view. Generally, results from Centre of Pressure (COP) studies suggest that sway parameters do change when infants develop a new skill. For example Sundermier et al. (2000) studied reactive balance responses in children between 9 months and 10 years with the use of COP and EMG measures, and indicated that developmental level predicted balance improvement better than chronological age.¹² Also Harbourne et al. (2003) showed that infants increased their stability during the development of independent sitting expressed by nonlinear measures of COP data.⁶ With our results and the COP data combined it is likely that a certain degree of direction-specificity is a prerequisite to develop a new skill, after which the muscular strategies do not consistently change during developing this skill. Yet the achievement of the new skill is reflected in the 'net result' of postural control: infants achieve a more stable centre of pressure after learning a skill. It suggests that the muscular postural control system needs to reach a particular level of biological growth before the skill can develop, after which the infant can learn and practice how to keep the body stable in the newly developed skill. Results of **chapter 4** also corroborate this view: typically developing infants do not consistently change their muscular strategies during learning a new skill, in this case walking, but show each an individual muscular strategy. It may suggest that when the infants acquired a certain degree of direction-specificity, they can vary and explore the different postural strategies.

Atypical postural development

The prediction of neurodevelopmental outcome of infants with a brain lesion is difficult, since outcome varies widely.¹³⁻¹⁵ Predictions whether an infant with a brain lesion will learn to sit or walk independently are uncertain at early age. The inconclusiveness arises from resolving or evolving clinical signs suggesting the development of CP throughout infancy, due to the abundant processes and changes in the developing young nervous system.¹⁶ The 'growing into deficit' phenomenon describes the process that effects of brain injury may only manifest over time.^{17,18} It suggests that at a young age, certain brain functions are not present yet and that the deficit will only show up after the establishment of more advanced networks in the brain.

Van Balen et al. (2015) had indicated that infants at high risk of CP 'grow into' a postural deficit.¹⁹ The authors had compared muscular postural control of typically

developing infants to that of high risk infants, of which only 5 of the 23 developed CP. In our study in **chapter 5**, we compared muscular postural strategies of infants who developed CP with high risk infants who did not develop CP. Contrary to our hypothesis, both groups of infants did not differ in postural development between 5 and 21 months of age. However, compared to the rates of different parameters of typically developing infants, a similar picture as that of the van Balen study emerged.¹⁹ At a young age, rates in typically developing infants were comparable to those of our high risk infants, but at later age the high risk infants performed worse. The results suggest that the total group of infants at high risk of CP grows into a postural deficit, and that this deficit is not restricted to CP. Thus, the data of this thesis suggest that a similar postural deficit is present in high risk infants with complex minor neurological dysfunction (MND), as all but two of the children who did not develop CP had this type of MND.

Children with MND have neurological dysfunction in the absence of a clear neurological syndrome such as CP. In infancy, dysfunctions in MND occur within two or more of the following domains: fine motor function, gross motor function, posture and muscle tone, visuomotor function or reflexes.²⁰ After infancy, a simple and a complex form of MND are distinguished, in which the complex form is equivalent to the label MND in infancy (the simple form of MND being classified as normal-suboptimal). The prevalence of complex MND increases throughout childhood, it also shows us that the children 'grow into' their neurological deficit. Around 10 months the prevalence is 2%²¹; at 2 years complex MND occurs in 3%²² and between 6–9 years in 5–10% of the children.^{23,24} The increase in the prevalence throughout childhood presumably reflects the increasing complexity of neural circuitries, allowing for more sophisticated brain functions. Subtle dysfunctions like those in MND may only become apparent at later age when for example fine manipulative ability becomes more demanding for writing tasks.

Thus, results of **chapter 5** may suggest that toddlers with complex MND do not only grow into their neurological deficit at later age, but also develop dysfunctions in electromyographical measures of postural control during infancy like in CP. This fits to the idea that the aetiology of complex MND resembles that of CP.²⁵ Indeed, early risk factors associated with CP have also been related to the presence of complex MND, such as low fetal weight, preterm birth and intra-uterine growth retardation^{26,27} or maternal alcohol use during pregnancy.²⁸ Adversities that result in CP or complex MND occur mostly in the second half of gestation, at a time when

the fetus is able to survive outside the uterus. Developmental processes during the second half of gestation are especially active in the periventricular regions and the cerebellum, and include axon and dendrite sprouting, synapse formation, glial cell proliferation, myelination and programmed cell death.^{16–18} Any events during this phase may result in dysfunctions in the periventricular structures or cerebellum and their connections. It has been speculated that perinatal adversities resulting in complex MND cause for example fine manipulative and postural difficulties by dysfunction of certain complex pathways, that are also associated with behavioural and cognitive problems.²⁹ For instance the cortico-striato-thalamo-cortical pathway has been associated with motor functions such as finger movement tasks^{30,31}, and the cerebello-thalamo-cortical tract with motor learning, coordination and posture.^{30,32,33} Consequently, clinical signs of complex MND emerge when skills appeal to these pathways.

More severe damage of the periventricular white matter may result in periventricular leukomalacia (PVL), usually originating between 24 and 34 weeks postmenstrual age in premature infants. One of the most severe lesions of the developing brain is cystic PVL (cPVL), in which focal necrotic lesions are found around the ventricles.^{34,35} Results of **chapter 5** indicated that compared to the other high risk infants, infants with cPVL showed dysfunctions at the second level of postural control – the fine-tuning of the basic level of direction-specificity to the situation – from early age onwards. It means that this group of infants do not ‘grow into’ a postural deficit, but express the deficit already at early age. Especially in cPVL, perinatal damage of the subplate and its connections is thought to contribute to the adverse neurological outcome.³⁵ The subplate is the transient structure beneath the cortical plate, and is specifically vulnerable for hypoxic-ischaemic injury.³⁶ It is thickest around 29 weeks postmenstrual age, and gradually disappears before 6 months post-term. Considering the importance of the subplate for neuronal differentiation, cortical organization and synaptogenesis^{18,35}, an extensive lesion at the time when development is highly active may already cause problems at early age. Our results also showed that in infants with cPVL the first and basic level of postural control – direction-specificity – increased throughout infancy and was significantly higher than that of the other infants after 21 months corrected age. Possibly, the extensive injury resulted in very few options for modulation at the second level, which shifted the focus and development of postural control to the first and basic level, that seems to be preserved in cPVL.

Reaching

Atypical reaching development

Whereas **chapter 5** showed that the postural development of high risk infants throughout infancy was similar for infants who did and did not develop CP, **chapter 6** indicated that infants with CP already have a worse quality of reaching from early age onwards, compared to other high risk infants without CP. Perhaps we could already observe the worse reaching quality at early age in the infants who later developed CP, because the networks in the brain that are needed for a reaching movement result in functional skills at earlier ages than those involved in postural control. That is, typically developing infants usually develop goal-directed motility and are able to reach and grasp objects around the age of 4 months. Between 4 and 6 months, the reaching movements become rapidly more smooth and fluent.^{37,38} On the contrary, postural skills become more demanding at later age. The early functionality of the networks for reaching would suggest that infants are able to learn and practice their reaching skills at early age, resulting already in difficulties for infants with CP. In infants who will develop CP, described from the perspective of the NGST, the early brain lesion probably caused damage to the primary neuronal networks, resulting in less possibilities to explore the different strategies for reaching. It is conceivable that adapting the reaching movement to the different environmental constraints is also more difficult for infants with CP, considering that this is based on afferent information, while CP is often associated with visual, sensational and cognitive disturbances.³⁹ Contrary to the neural networks that govern reaching movements, the networks guiding postural control result in functional skills at later age. A possible difference between CP and other high risk infants may therefore only become apparent at later age, beyond our age limit of 21 months.

However, the previous paragraph suggested that the total group of high-risk infants including infants with complex MND 'grows into' a postural deficit throughout infancy. It would be interesting to know whether the same holds true for the infants with complex MND regarding reaching development, in other words: to compare the two groups of VHR-infants with a typically developing group of infants.

Chapter 6 showed that the worse reaching quality in infants with CP was expressed by the use of more movement units (MU), a smaller transport MU, lower curvature indices and a longer reaching duration than in VHR-infants without CP. The former three parameters rely mostly on feedforward programming, whereas reaching duration is usually based on a mix between feedforward and feedback mechanisms.^{37,40} Feedforward planning requires the ability to simulate the forth-

coming action, in order to anticipate the end of the motor action.⁴¹ Problems with feedforward planning in CP have been recognized before. Mutsaerts et al. (2005) showed that adolescents with unilateral CP did not plan the latter part of a reaching movement when it consisted of two parts (grasping and rotating), contrary to control adolescents.⁴² Other studies also showed that a reaching movement with the less-affected arm of children with unilateral CP had worse reaching characteristics than a reaching movement of typically developing children.^{40,43} The involvement of the less-affected arm suggests that children with CP do not only have problems with the execution of the movement of the affected arm, but also with planning of movements in general. Disturbances in planning imply that infants and children with CP are dependent on on-line feedback of visual, vestibular or sensory systems for corrections. This makes the movements slower and less well programmed. The combination of problems with the execution of the movement and deficits in motor planning presumably result in the worse reaching characteristics that we found in infants with CP.

CLINICAL IMPLICATIONS

Clinicians will evaluate studies on the development of typical and atypical postural control especially in terms of early intervention: what do the results mean in terms of intervention strategies? The majority of the studies on postural control in cerebral palsy, like the studies in this thesis, are however observational or descriptive. They provide information on the underlying mechanisms of postural dysfunction. The next step is to translate this knowledge into an effective early intervention program and test whether it is effective.

Systematic reviews showed that currently, effects of intervention on motor outcome are inconsistent. The inconsistency is the result of the use of various early intervention programs, heterogeneous groups of patients, diverse types of outcome measures and studies of low quality.⁴⁴⁻⁴⁶ Literature specifically assessing the effect of early intervention on postural control and reaching in cerebral palsy in infancy is limited. Preliminary analyses in **chapters 5 and 6** indicated that the type of intervention from the L2M 0-2 study did not affect reaching quality or our parameters of postural control. The absence of a difference between the interventions in our study group does not mean that intervention did not have an effect at all. Both groups received a form of paediatric physical therapy, and we observed an improvement of postural strategies with increasing age, in which early intervention could have played a role. Other studies suggest that intervention can have a positive effect on postural control. The question is, which intervention is most valuable?

In typically developing infants it was shown that balance training in sitting or standing accelerated the selection of appropriate direction-specific muscles or the fine-tuning at the second level of postural control.^{47,48} In preschool age and school age children with CP, effects of NDT intervention, treadmill training, orthoses, hippotherapy and other physical therapeutic interventions show in general neutral to positive effects on various postural control outcome measures.^{49–52} Muscular postural strategies also improve in children with CP by balance training from a platform,⁵³ horseback riding therapy⁵⁴ or a tilted seating position.⁵⁵ Two studies evaluated the effect of COPCA in a previous RCT on early intervention in infancy. COPCA seemed to have subtle beneficial effects on the development of postural strategies at 6 months⁵⁶ and 18 months.⁵⁷ The studies suggest that postural training is effective in improving balance and muscular postural strategies. Unfortunately, there is no univocal answer to the question what type of intervention is most beneficial, since many types of intervention have positive effects. Possibly, the type of intervention is not the most important factor for improvements in postural control, but maybe an important factor is that postural training is provided, in any form whatsoever.

Besides the effects of many different forms of training, it is challenging to draw conclusions on the effects of early intervention in the group of infants at risk of CP, considering the heterogeneity in brain lesions and clinical development. The age at injury, size and site of the lesion, uni- or bilateral injury, sex of the fetus or infant and the environment all influence developmental outcome.^{17,18} In light of this heterogeneity, perhaps not all infants at high risk of CP would benefit from the same type of early intervention. This idea relates to **chapter 4** in which we showed that typically developing infants all learn to walk, but every infant uses his own muscular strategy. Also Woollacott et al. (2005) indicated that children with CP improved in postural performance after training, but each child in his own way.⁵³ Another study suggested that the type of sitting position that promoted muscular postural strategies of children with unilateral CP differed from the position that benefitted children with bilateral CP.⁵⁵ Hence, tailor-made intervention seems the ideal option. Conceivably, infants with different brain lesions, infants who are uni- or bilaterally affected and infants with more or less severe symptoms benefit from different training strategies. For example, in children with unilateral brain lesions, constrained induced movement therapy (CIMT)⁵⁸ can be used to stimulate the preservation of the ipsilateral descending cortico-spinal motor projections from the not-affected hemisphere. In this way, the contralateral hemisphere can (partially) take over motor commands of the affected side.⁵⁹ The intervention should presumably be applied as soon as possible, to profit most from the plasticity of the developing brain.¹⁷ Infants with a severe lesion like cPVL or severe symptoms possibly

benefit more from adaptive seating systems or external support at early age, since they show clear dysfunctions in postural strategies from early age onwards, like we showed in **chapter 5**. Hence trunk support provides the opportunity to participate in daily life activities. In contrast, infants with a less severe lesion may benefit more from early postural training, since we implied that their muscular postural strategies are delayed in development.

Overall, it may be concluded that early intervention promotes postural control in high-risk infants. In light of the NGST we assume that developmental potential is determined by the genetic make-up, but the environment is crucial in reaching this potential. From the above it appears that many types of intervention can be valuable. Nevertheless, I think that making use of trial and error and challenging the infant in different positions with variation in support can be useful. The incorporation of these aspects into daily living situations may improve functional outcome.⁶⁰ In addition, elements of CIMT can be favourable for infants with unilateral brain lesions. I would recommend to start therapy as early as possible^{17,59}, make it fun for the infant, incorporate as many training situations in daily life as possible⁶⁰, but do not hesitate to make use of external support in infants with severe symptoms, (**chapter 5**) since in my opinion functional performance and participation in daily life should be the most important goal of therapy.

FUTURE PERSPECTIVES

As I suggested that different groups of high risk infants would possibly benefit from different types of intervention, I would advocate to further assess postural and reaching development throughout infancy in subgroups of high risk infants. I propose to compare postural control and reaching characteristics of infants with unilateral brain lesions to that of infants with bilateral brain lesions, and again subdivide the groups into severe and less severe lesions. To achieve sufficient power, larger sample sizes are needed. Fortunately for the infants, neonatal health care is still improving, resulting in a lower number of infants with severe brain lesions like cPVL. A multi-centre study would be an optimal solution to accomplish larger sample sizes. Ideally – from a theoretical perspective – a subgroup of high risk infants should be included who do not receive early intervention, to be able to longitudinally assess the effect of early intervention. However, since I give credence to the value of intervention, it would not be ethical to withhold infants early intervention.

The influence of specific postural training – for example for independent sitting – can be studied by measuring postural control before and after a period of specific training, compared to a group of infants who receive standard interven-

tion. It would be interesting to also study individual changes in postural strategies, corresponding to the results of **chapter 4**. For the infants with a unilateral brain lesion, I would suggest to study the effects of CIMT on postural control. Baby-CIMT may have a positive influence on hand function⁶¹, but possible effects on postural control are unknown.

Results of **chapter 6** may suggest that infants with CP have difficulties with the planning of motor actions. Crajé et al. (2010) showed that 3–6 year old children with unilateral CP improve in motor planning after 8 weeks of training, consisting of 6 weeks CIMT and 2 weeks bimanual training. They speculated that variation in training motor tasks may positively affect the development of planning.⁶² In older children with CP, the use of motor imagery seems promising.⁶³ It includes the mental performance of movements instead of actually executing the movement. Motor imagery has shown positive effects in adults with stroke⁶⁴, and is based on the concept that the planning of movements is a higher-order brain function which can affect the execution of the movement.⁴¹ I suggest to implement a trial in infants to see whether motor imagery using a variety of reaching tasks can be used to improve reaching in young typically developing and high-risk infants, for instance with the use of videos.

Chapter 5 showed that infants with MND, like infants with CP, ‘grew into’ a postural deficit. Previous research indicated that the prevalence of MND decreased after puberty, suggesting that these children can also ‘grow out’ of a deficit.⁶⁵ It would therefore be interesting to study further development of postural control in older children with MND. Also, I would like to compare reaching kinematics of our VHR-infants developing CP and our VHR-infants developing MND to a typically developing group. In this way we are able to assess whether reaching quality of infants with MND differs from typical development at early age, or whether they also ‘grow into’ a deficit in reaching characteristics.

Future research on the underlying mechanisms of postural dysfunction can perhaps make use of diffusion tensor imaging (DTI). With this technique, neural tracts and networks can be visually represented in a 2- or 3D-model. It has been shown that white matter characteristics of DTI-images are related to postural control in patients with traumatic brain injury.⁶⁶ DTI can possibly be used to study the networks for postural control in typically developing and high risk infants, and can hopefully provide clues on the development and plasticity of these networks, which would be very useful knowledge for early intervention.

CONCLUDING REMARKS

Findings of this dissertation suggest that: 1) at group level, muscular postural control strategies improve with age rather than with functional performance; 2) when learning a new skill, infants reorganize their postural control system using individual approaches; 3) infants at high risk of CP 'grow into' a postural deficit with increasing age, with a similar development for infants with and without CP; 4) infants with severe brain lesions such as cystic periventricular leukomalacia show dysfunctions in postural control from early age onwards; 5) high risk infants developing CP show worse reaching kinematic quality than other high risk infants from early age onwards. These results may indicate that early intervention addressing postural dysfunction warrants an individual approach for infants with different brain lesions and severity of symptoms. The results on individual postural development and recommendations on tailor-made intervention of this thesis perfectly fit to the quote by Gerald Edelman: "Every single brain is absolutely individual, both in its development and in the way it encounters the world."

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