Postural control during reaching in typical and atypical development
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 4: Early intervention and the development of postural adjustments during reaching in infants at risk of cerebral palsy: an in-depth analysis of a randomized controlled trial

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Submitted
ABSTRACT

Purpose: to investigate postural effects of the family-centered program COPCA (COPing with and CAring for infants with special needs) applied at 3-6 months corrected age in infants at high risk of Cerebral Palsy.

Methods: we analyzed postural adjustments during reaching in seated infants at 4, 6, and 18 months using surface EMG of arm, neck and trunk muscles. Infants randomly received COPCA \((n=21)\) or typical infant physical therapy (TIP; \(n=25\)). Using videotaped intervention sessions, we investigated correlations between time spent on specific physical therapeutic actions and direction-specificity, recruitment order, and anticipatory activation at 18 months.

Results: postural adjustments in both groups were similar, but development of direction-specificity and anticipatory activation in COPCA-infants mimicked typical development slightly better. These two parameters were also associated with COPCA-type physical therapeutic actions.

Conclusions: postural control was similar after both interventions. Trial-and-error experience seems to benefit early postural development.

Trial registration number: ISRCTN85728836.

Keywords

early intervention, pediatric physical therapy, electromyography, postural control, reaching, infants, cerebral palsy
INTRODUCTION

Recently, infants at high risk of cerebral palsy were found to gradually grow into a deficit of postural control between 6 and 18 months corrected age (CA). Since balance training may improve postural control in typically developing (TD) infants and in older children with CP and other neuromotor disorders, we aimed to study whether early intervention could influence the development of postural control in ‘at risk’ infants. The high-risk infants from the previous study were controls in a randomized controlled trial (RCT) on early intervention (the VIP-trial), that compared the effect of the novel family-centered program COPCA (COPing with and CAring for infants with special needs) to typical infant physical therapy (TIP, the control group) provided between 3 and 6 months CA. The next step is to compare postural parameters of the infants who had received COPCA to those who had received TIP. The COPCA-program has a family component, stressing family autonomy and a motor component based on the neuronal group selection theory (NGST).

NGST proposes two phases of development: primary and secondary variability. The former consists of exploration of all possibilities of the motor repertoire. In the latter phase, the child learns through trial-and-error to adapt the various motor strategies to specifics of the situation. NGST may also be used to explain development of postural control. According to the central pattern generator model, postural control is organized into two functional levels. The first or basic level consists of direction-specificity, which means for instance that when balance is threatened by a forward body sway, the muscles on the dorsal side are primarily activated. The second level consists of fine-tuning of direction-specific adjustments to the specifics of the situation, for example in the number of direction-specific muscles that are activated and the order in which they are activated.

Previously, direction-specificity was found to increase between 6 and 18 months in typically developing infants but not in high-risk infants. In addition, high-risk infants showed less anticipatory postural adjustments at 18 months than typically developing infants, and postural adjustments became slower at 18 months in high-risk infants but not in typically developing infants. These differences may reflect impaired selection of optimal motor strategies in infants at risk for CP, in other words impaired secondary variability. As the motor component of COPCA is based on increasing trial-and-error experience of the infants to improve adaptability, i.e., to
improve the ability to adapt motor behavior, we hypothesized that the differences we found between the high-risk and typically developing infants might be mitigated by COPCA. Therefore we computed the postural control parameters for the COPCA group of the VIP-trial and compared them to those of the TIP-group reported earlier.\textsuperscript{1}

As pediatric physical therapy is characterized by heterogeneity, we presumed that the contents of the two interventions would overlap. Hence, we anticipated that the difference in outcome of the two randomized groups would be minor at best. Indeed, at 18 months CA we only found a minor advantage of COPCA for cognitive development.\textsuperscript{14} In anticipation, we therefore had video-recorded physical therapy sessions, as quantification of the contents of physical therapy sessions would allow for process evaluation. This evaluation showed that COPCA characteristics, such as family involvement and coaching of family members, were associated with higher scores of functional mobility at 18 months, and the TIP characteristic ‘therapeutic handling’ with lower functional mobility scores.\textsuperscript{14} Therefore, we extended our postural control analysis with process evaluation by exploring associations between physical therapeutic actions and postural parameters.

**MATERIAL AND METHODS**

**Participants and intervention**

Infants admitted to the neonatal intensive care unit of the University Medical Center Groningen (UMCG) in 2003 to 2005 were eligible for inclusion if they presented with definitely abnormal general movements at 10 weeks CA, indicating a high risk of developmental disorders.\textsuperscript{15,16} Forty-six infants (20 boys, 26 girls) were enrolled at 3 months CA (gestational age at birth 25–40 weeks [median: 30 weeks]; birth weight 585-4750g [median: 1210 g]). The infants were randomized (see methods supplement S1) to receive either COPCA or TIP from 3 months to 6 months CA. The COPCA program was applied twice a week for one hour in the home situation. The frequency and location of TIP depended on the pediatrician’s advice – it was mostly provided at home. Three control infants did not receive physical therapy, at the pediatrician’s advice. After the randomized intervention period, 36 infants received physical therapy between the ages of 6 and 18 months (see supplement S1).
For the process evaluation, two intervention sessions per infant (one at 4 and one at 6 months CA) were recorded on video. Physical therapeutic actions during these sessions were quantified with the help of a standardized observation protocol.\textsuperscript{17}

**Outcomes and protocol**

Postural control was assessed with electromyography (EMG) at 4, 6 and 18 months CA. At 18 months the infants were neurologically assessed according to Hempel.\textsuperscript{18} Three infants were not assessed at 18 months due to logistical reasons. The infants’ parents gave informed consent and the ethics committee of the University Medical Center Groningen (UMCG; trial number NL39954.042.12) approved procedures.

The protocol and method were described in earlier work\textsuperscript{1,19} (see also supplement S1). In short, reaching movements were elicited from the infant seated in a supported sitting position (in an infant chair or on their parent’s lap). EMG was measured continuously with bipolar surface electrodes on the following right-sided muscles: deltoid (DE), pectoralis major (PM), biceps brachii (BB), triceps brachii (TB), neck flexor (NF, sternocleidomastoid), neck extensor (NE), rectus abdominis (RA), thoracal extensor (TE), and lumbar extensor. DE, PM, BB and TB are referred to as arm muscles; NF, NE, RA, TE, and LE as postural muscles. Sessions were recorded on video, which was time-coupled to the EMG recordings. Both the investigators who assessed the infants and recorded the EMGs, and those who analyzed the EMG data, were blinded to group allocation.

**Video and EMG analysis**

Using the video, we selected arm movements occurring in response to the toy.\textsuperscript{1} EMG analyses (artefact correction and detection of significant bursts of phasic muscle activity) were carried out with the PedEMG program (Developmental Neurology, UMCG, The Netherlands; see van Balen et al.\textsuperscript{19}). The EMG was scanned for activation of the arm muscles from 500 ms prior to visible movement in the video, and the start of the reach was defined as the onset time of the first arm muscle activity that was related to the reaching movement (i.e., the onset of the prime mover, the arm muscle initiating the reach). For the postural muscles, increased activity was included if found within a time window consisting of (a) 100 ms before activation of the prime mover.
(see Boxum et al.\textsuperscript{20}), and (b) the duration of the first 1000 ms of the reaching movement.

For each trial, we determined the following parameters (illustration in Figure 1): (1) Direction-specificity; a trial was direction-specific if the dorsal muscle was recruited prior to the antagonistic ventral muscle or without antagonistic activation. Direction-specificity at both neck and trunk level entailed direction-specific recruitment of both the trunk and neck muscles in the same trial; (2) Recruitment order (top-down, bottom-up, or otherwise). This could only be determined when at least two direction-specific muscles were recruited; (3) the presence or absence of anticipatory postural activity at the neck and/or trunk level (i.e., activation starting within 100 ms before the prime mover). Overall anticipatory activation was defined as anticipatory activation in at least one dorsal postural muscle, regardless of location (neck or trunk); (4) the recruitment latencies of postural muscles, defined as the time interval between the onset of the prime mover and the onset of activity in the postural muscle. For each infant at each age median latency values were calculated.

\textbf{Figure 1 (next page):} Examples of EMG recordings showing postural adjustments during reaching movements.
Pr, prime mover (the arm muscle initiating the reaching movement); NE, neck extensor; NF, neck flexor; TE, thoracal extensor; LE, lumbar extensor; RA, rectus abdominis.
Upper left panel: trial of an infant in the COPCA group at 4 months, with direction-specific postural activity in the neck but not in the trunk; there is anticipatory activation in the rectus abdominis.
Upper right panel: trial of an infant in the COPCA group at 18 months. Both neck and trunk muscles show direction-specific and anticipatory activation of the direction-specific dorsal muscles. Recruitment order of the dorsal postural muscles is top-down.
Lower left panel: trial of an infant in the TIP group at 6 months. TE and LE are recruited simultaneously and before RA (direction-specific at trunk level) but at neck level only the ventral muscle is active (NF; no direction-specificity at neck level). None of the postural muscles shows anticipatory activation.
Lower right panel: trial of an infant in the TIP group at 18 months. Activation in the trunk is direction-specific; activation in the neck is not. Recruitment order of the dorsal postural muscles is mixed (neither top-down nor bottom-up). There is no anticipatory activation; note the slow recruitment of the lumbar extensor.
**Figure 1:** Examples of EMG recordings showing postural adjustments during reaching movements. See Legends on previous page.
**Statistical analysis**

Statistical modelling was carried out using the Statistical Analytics Software (SAS) 9.3 (SAS Institute Inc., Cary, NC) and SPSS 20 (IBM Corp., Armonk, NY). For the dichotomous parameters a binomial generalized estimating equations (GEE) model with repeated measurements was fitted using predictor variables Age and Intervention. To take missing data into account, the parameters were modelled as ratios. For example, for each child at each age direction-specificity was modelled as the number of direction-specific trials divided by the total number of trials for which direction-specificity could be computed. Continuous variables (latencies) were modelled with a linear mixed model with repeated measurements. Odds ratios (OR; including 95% confidence intervals in square brackets) are reported for the statistical analyses; to aid interpretation of the results we also calculated the percentage of trials per infant for each outcome variable (e.g., the percentage of direction-specific trials), and report median values of these percentages. Finally, we used partial correlations to investigate associations between physical therapeutic actions (based on mean values of the therapeutic sessions at 4 and 6 months) and parameters of postural control at 6 and 18 months.

**RESULTS**

**Data available for analysis**

Figure 2 shows the flow chart of participant inclusion, assessment and outcomes. Missing data are due to (1) non-participation, for logistical reasons (three infants in the TIP group at 18 months), (2) technical issues with video or EMG recording, (3) lack of cooperation of the infants, resulting in an insufficient number of suitable trials, (4) the inability to reach (particularly at 4 months), and (5) difficulties in keeping the electrodes properly attached (especially at 18 months). Missing data were addressed separately for each outcome parameter, resulting in different $n$ (varying from 9 to 20 in the COPCA group and 7 to 20 in the TIP group) for each outcome parameter (see Figures).

Table 1 shows the group characteristics. The groups only differed for maternal education, which was significantly higher in the TIP group than in the COPCA group,
both in all infants (left side of the table) and the infants with postural outcomes available (right side). We also compared the infants with available data in the TIP group to those with missing data. Maternal education was lower for the TIP infants with missing data, which increased the difference in maternal education between the COPCA and TIP groups at this age. All further analyses were corrected for maternal education, and also for CP, as previous analyses had indicated that the associations between physical therapeutic actions and developmental outcome in children with CP differed from those in children without CP. The 18-months data of chair-sitting and lap-sitting were pooled.1

**Figure 2:** flow diagram of participants of the Early Intervention Project. COPCA = COPing with and CARing for infants with special needs; TIP = traditional infant physical therapy. Assessment age was corrected for premature birth. *n*-values reported for outcomes reflect the number of infants for whom direction-specificity at trunk level, the primary postural control parameter, could be computed.
Table 1: Group characteristics of the COPCA and TIP groups

<table>
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<tr>
<th>Demographics</th>
<th>COPCA (n=21)</th>
<th>TIP (n=25)</th>
<th>COPCA (n=19)</th>
<th>TIP (n=9)</th>
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<td>14 (56)</td>
<td>11 (58)</td>
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<td>23 (92)</td>
<td>17 (89)</td>
<td>8 (89)</td>
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<td></td>
</tr>
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<td>1143</td>
<td>1400</td>
<td>1265</td>
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<tr>
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<td>635-3460</td>
<td>585-4750</td>
<td>700-3460</td>
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<td>16 (84)</td>
<td>7 (78)</td>
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<td>3 (12)</td>
<td>3 (16)</td>
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<td>15 (79)</td>
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<td>14 (56)</td>
<td>17 (89)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>High</td>
<td>2 (10)</td>
<td>11 (44)</td>
<td>2 (11)</td>
<td>7 (78)</td>
</tr>
</tbody>
</table>

On the left side, characteristics of all infants included in the study are shown; on the right side the characteristics of the infants for whom direction-specificity in the trunk could be computed. a) Intraventricular hemorrhage (IVH), according to Volpe. b) Pearson Chi-square, \( p=0.019 \) for COPCA vs. TIP, all infants; \( p=0.001 \) for COPCA vs. TIP, infants with postural outcome data; and \( p=0.023 \) for TIP, infants with vs. without missing data.

**Evaluation at RCT-level**

**General**
In both groups, the postural parameters showed a large variation. Postural outcome of the COPCA group did not differ significantly from that of TIP group; this was true for postural parameters at any of the three assessments. However, there were age-dependent within-group differences in each individual group.
Direction-specificity

In the COPCA group, the percentage of reaches accompanied by direction-specific postural activity at trunk level increased between 6 and 18 months from 46% to 67% (median values; OR 1.92, CI [1.06-3.46]; Figure 3). The 18-months value (67%) was also significantly higher than the one at 4 months (50%; OR 1.70, CI [1.10-2.65]). There was no significant increase with age of direction-specificity at trunk level in the TIP group, which was 50–58% at all ages studied (median values; see Figure 3).

Direction-specificity at neck level was 33-42% in the COPCA group and 26-44% in the TIP group. In the COPCA group, 21-33% of trials were direction-specific at both neck and trunk level, which was similar to the TIP group (20-33%). In both groups, the rates did not change.

**Figure 3:** Percentage of direction-specific trials at 4, 6 and 18 months of age, in infants who received COPCA and infants who received TIP. **Left panel:** direction-specificity in the trunk muscles. **Middle panel:** direction-specificity in the neck muscles. **Right panel:** direction-specificity in both neck and trunk muscles simultaneously. * significant at p < 0.05. Odds ratios with 95% confidence intervals for direction-specificity in the trunk in the COPCA group were 1.92 [1.06-3.46] for 18m vs. 6m and 1.70 [1.10-2.65] for 18m vs. 4m. Low numbers are due to missing values in trials where the quality of one or more EMG signals was too poor to allow analysis.
**Muscle recruitment strategies**

In the COPCA group, bottom-up recruitment decreased between 4 and 18 months from 38% to 25% (median values; OR 0.50, CI [0.31-0.81]; see Figure 4). Although in both groups bottom-up recruitment seemed lower at 18 months (25% and 28% for COPCA and TIP, respectively) than at 6 months (33% and 38%), with low $n$ for this parameter we failed to demonstrate significant differences (COPCA OR 0.63, CI [38-1.05]; TIP: OR 0.57, CI [0.30-1.08]). As we reported earlier, top-down recruitment increased in the TIP group from 17% at 4 months to 31% at 18 months (OR 2.80, CI [1.63-4.83]). A similar increase was absent in the COPCA group (25% at 4 months; 36% at 18 months; OR 1.31; CI [0.67-2.53]).

![Figure 4](image-url)

**Figure 4:** Percentage of trials with top-down recruitment (left panel) and bottom-up recruitment (right panel) of infants who received COPCA and infants who received TIP, at 4, 6 and 18 months of age. *significant at $p < 0.05$; Odds ratios with 95% confidence intervals were OR 0.50 [0.31-0.81] for bottom-up recruitment, 18m vs. 4m in the COPCA group, and OR 2.80 [1.63-4.83] for top-down recruitment, 18m vs. 4m in the TIP group. Some numbers were low as analysis was restricted to direction-specific trials; in addition, see legends Figure 3.
Anticipatory activation and latencies

Figure 5A shows anticipatory activation in both groups. Infants in the TIP group had a lower rate of anticipatory activation in the trunk muscles at 18 months than at 6 months (20% vs. 33%; OR 0.36, CI [0.18-0.74]). In addition, the TIP group also showed less anticipatory activation in the neck muscles at 18 months compared to 6 months (24% vs. 33%, OR 0.48, CI [0.27-0.84]), resulting in an overall lower anticipatory activation rate at 18 months compared to 6 months (41% vs. 71%, OR 0.33 [0.17-0.65]). Similarly, in infants who received COPCA, there was less anticipatory activation in the trunk muscles at 18 months (25%) than at 4 months (40%; OR 0.44, CI 0.26-0.77)), but unlike TIP infants, the COPCA group did not show a decrease with age in the overall anticipatory activation rate (60%, 46% and 60% at 4, 6 and 18 months, respectively).

Latencies to postural muscle recruitment varied considerably in both groups, at all ages and in all muscles (Figure 5B). Within-group analyses revealed the following significant changes with age. In the COPCA group, NE recruitment was 70 ms slower at 6 months than at 4 months (95% confidence interval: [1-138 ms]). In infants who received TIP, LE recruitment was 94 [17-171] ms slower at 18 months than at 6 months and RA recruitment was 122 [38-206] ms slower at 18 months than at 4 months.

Associations between physical therapeutic actions and postural control parameters

The process evaluation, in which the time spent on specific physical therapeutic actions was correlated with the postural outcome parameters, revealed that two therapeutic actions were correlated with postural outcome at 18 months. First, the time the physical therapist spent interfering with the infant’s actions was negatively associated with direction-specificity at trunk level at 18 months (r= -0.642; p<0.001). Second, the time during which the infant was allowed to produce spontaneous motor behavior without interference, a typical COPCA action, was associated with higher overall anticipatory activation at 18 months (r=0.644; p=0.003).
Chapter 4

Figure 5: Anticipatory activation and recruitment latencies of postural muscles of infants who received COPCA and infants who received TIP, at 4, 6 and 18 months of age. A: Percentage of trials with anticipatory activation in the trunk muscles (left panel), neck muscles (middle panel) and trunk or neck muscles (overall anticipatory activation; right panel). * significant at $p < 0.05$; see text for details. B: Recruitment latencies of postural muscles. Bold horizontal bars are medians; vertical bars represent ranges. * significant at $p < 0.05$; Odds ratios with 95% confidence intervals: COPCA, NE 6m vs. 4m: 70 [1-138] ms; TIP, LE 18m vs. 6m: 94 [17-171] ms; TIP, RA 18m vs. 4m: 122 [38-206] ms. Some numbers were low as analysis was restricted to direction-specific trials; in addition, see legends Figure 3.
DISCUSSION

Implications of the results

Between-group analyses indicated that postural outcomes of the COPCA and TIP groups were similar. Within-group analyses revealed some differences: 1) infants who had received COPCA showed an increase in direction-specificity with increasing age; a similar age-dependent increase was absent in infants who had received TIP; 2) infants of the TIP group showed a slower recruitment of the trunk muscles with increasing age; a similar slower recruitment was absent in the COPCA group; 3) associated with the previous finding: a more pronounced decrease of anticipatory activation with increasing age in the TIP group than in the COPCA group. Interestingly the process evaluation indicated that a physical therapeutic action characteristic for TIP was associated with worse postural performance (less direction-specificity at trunk level) and that one physical therapeutic action characteristic for COPCA was associated with better performance (anticipatory activation) – the same postural parameters in which the within-group analyses revealed group differences.

Our findings suggest that infants who received COPCA developed slightly more like typically developing infants: typically developing infants show a marked increase of direction-specificity in the trunk at 18 months and a stable rate of anticipatory activation with increasing age. Nevertheless, the postural outcomes of the two high-risk groups were more similar to each other than to those of typically developing infants, confirming that development of postural control in infants at high risk of CP differs from that of typically developing infants. In the light of NGST, these differences could be seen as an impaired ability to select motor strategies that are adapted to the specifics of the situation, as previously suggested. This is supported by our current finding that more time spent during therapy with spontaneous motor activity, in other words, more trial-and-error experience that helps selecting optimal strategies, is related to more anticipatory postural adjustments at 18 months. The importance of trial-and-error has also been demonstrated in older children with CP learning a new motor task: the amount of errors made during practice is related to the amount of learning. Similarly, in our data, more time spent interfering with the child’s actions – which deprives the child of the opportunity of learning from his/her mistakes – was related to lower direction-specificity in the trunk at 18 months. However, this relationship may also mean that
infants with limited postural control may have elicited more interference, or ‘assistance’ from the physical therapist – a statistical association does not automatically imply a causal relationship.

To our knowledge, the only other study that compared detailed parameters of postural control between infants with different types of physical therapy is the study of Harbourne et al.,23 which compared the effects of a child-focused perceptual-motor program and a family-centered home program on center-of-pressure (COP) parameters in infants learning to sit. The authors reported that COP-parameters of the perceptual-motor group were closer to those of typically developing infants than those of the home-program group, although both groups improved their sitting skills after the intervention. This may seem contradictory to our findings. However, a closer look reveals that, in fact, the home program of Harbourne et al.23 resembled TIP more than COPCA (for example in repositioning the child when it made ‘sitting errors’), while the perceptual-motor program resembled COPCA, as it focused on problem solving via trial-and-error. In addition, the studies differed in outcome parameters (COP vs. EMG) and in the age at which intervention was applied (one year vs. 3-6 months). Taking the differences between the studies into account, both studies suggest that trial-and-error experience during early phases of development may have a beneficial effect on postural control of infants at risk of developmental motor disorders.

Methodological considerations

The strengths of this study include the longitudinal RCT-design, blinded data analysis, and the setup reflecting activities in daily life. In addition, the prospective process evaluation enabled us to link specific details of physical therapy to postural control that were not visible at RCT level.

However, the study also has several limitations. First, there may be beneficial effects on other postural parameters such as EMG amplitude-modulation,6,24,25 and center-of-pressure dynamics,25 which were not included in the study.

Second, one might argue that a sample of two physical therapy sessions may not adequately represent the contents of the entire physical therapy program provided. However, heterogeneity is particularly present between therapists and/or between children, and less so between sessions of the same infant-therapist combination. Indeed, the therapy session at 4 months of each infant was very similar.
in content to that of the same infant at 6 months implying that they are representative for the physical therapy provided.

Another limitation is that postural control at 18 months may have been influenced by (1) physical therapy between 6 and 18 months, which was more frequently provided in TIP than in COPCA, (2) between-group differences in frequency and duration of therapy, and (3) larger heterogeneity of the contents of TIP compared to COPCA. The latter two limitations did not apply to the process evaluation, which was specifically designed beforehand to circumvent this anticipated difficulty and revealed differences in outcome that were in favor of the COPCA approach. Therefore, it is possible that an RCT with more uniform groups and maximally different therapy between groups will find differences in outcome between the randomized groups.

Finally, the study suffered from missing data, particularly at 18 months. This may have resulted in a selection bias apart from the group characteristics we corrected for in the models (maternal education and CP). However, analysis of the missing data did not reveal any patterns pointing to a potential bias or systematic cause of ‘missing-ness’ other than the ones mentioned in the results section. Therefore, although we cannot exclude the possibility of accidental selection bias, we presume that the available data give a reasonably good representation of each group. Second, the resulting small group sizes reduced the study’s power. However, we did find within-group differences, and we previously found significant between-group differences with an even smaller group of typically developing infants, suggesting that if a major effect of intervention had been present, we would have been able to demonstrate it. Third, we had only a small number of infants in our data who later developed CP, and these infants (except one) developed only the milder forms of CP, i.e., GMFCS levels I-III, implying limited generalizability.

**Concluding remarks**

We conclude that COPCA and TIP result in similar postural muscle recruitment patterns during reaching in a sitting position. Compared to typically developing infants, infants at high risk of CP suffer from postural impairments that may affect their activities and participation. Nevertheless, the study indicated that intervention may have some effect on postural development, as (1) postural development after COPCA but not TIP displayed some resemblance to that of typically developing
infants, and (2) intervention with spontaneous motor behavior with trial-and-error and without interference of the therapist is associated with improved postural development.

Acknowledgements
We kindly acknowledge the contribution in statistical analysis of Prof. dr. Edwin van den Heuvel, and the contribution in data collection and data analysis of Tom van Leussen, Ines Krabben, Janneke Viergever, Victorine B. de Graaf-Peters, PhD, Cornill H. Blauw-Hospers, PhD, Hanneke Bakker, MSc, Leo A. van Eykern, Jeroen van der Eb, PhD, and Michiel Schrier. The study was supported by Stichting Fonds de Gavere, the Johanna KinderFonds, the Cornelia Stichting, Stichting de Drie Lichten and the Post-graduate School BCN Groningen. There was no involvement of the funders in study design, data collection, data analysis, manuscript preparation and/or publication decisions.

Conflict of interest
The authors have stated that they had no interests that might be perceived as posing a conflict or bias.
REFERENCES


METHODS SUPPLEMENT

Design Overview

Infants at high risk for CP were given either COPCA or TIP between 3 and 6 months corrected age (CA). Postural control parameters were assessed with electromyography (EMG) during reaching in sitting infants at 4, 6 and 18 months CA.

Setting and Participants

Infants admitted to the neonatal intensive care unit of the University Medical Center Groningen (UMCG) in 2003 to 2005 were eligible for inclusion if they presented with definitely abnormal general movements at 10 weeks CA, indicating a high risk of developmental disorders. Fifty-six infants (20 boys, 26 girls) were included in the study at 3 months CA, with gestational age at birth ranging from 25-40 weeks (median: 30 weeks) and birth weight from 585-4750 grams (median: 1210 g). Sample size was based on the primary outcome, the Infant Motor Profile total score, which is described in Blauw-Hospers et al. 2011. Earlier power analysis for a similar study on postural adjustments in typically developing infants revealed that with group sizes of 10-12 participants, a difference in direction-specificity of 25% could be detected with 80% power ($\alpha=0.05$, mean and SD based on De Graaf-Peters et al.).

Randomization and Interventions

The infants were randomized through block randomization (full-term infants, blocks of N=2; preterm infants, blocks of n=12) to receive either COPCA or TIP from 3 months to 6 months CA. The randomization sequence was kept by one person only and was unknown to the investigators involved in data collection and analysis. This person contacted the allocated caregiver after inclusion of a participant. The COPCA program was applied twice a week for one hour in the home situation. The frequency and location of TIP depended on the pediatrician’s advice – it was mostly provided at home. Three control infants did not receive physiotherapy. After the randomized intervention period, 38 infants received physiotherapy between the ages of 6 and 18 months. In the COPCA group, 16 infants continued with physiotherapy (13 with COPCA [median number of sessions 2] and three with TIP as no COPCA coach was
available [median number of sessions 10]), four infants stopped receiving physiotherapy, and data were missing for one infant. In the TIP group, 22 infants continued with physiotherapy (all TIP; median number of sessions 14), two infants did not receive physiotherapy between the ages of 6 and 18 months, and data were missing for one infant.

For the process evaluation, two intervention sessions per infant, chosen at random within the given time constraints (one at 4 and one at 6 months CA) were recorded on video. Physiotherapeutic actions during these sessions were quantified with the help of a standardized observation protocol. The observation protocol classified physical therapy actions into 8 main categories: (A) Family involvement and educational actions; (B) Communication; (C) Facilitation techniques; (D) Sensory experience; (E) Passive motor experience; (F) Self-produced motor behavior, no interference from physical therapist or caregiver; (G) Challenge to self-produce motor behavior where the infant is allowed to continue activity; and (H) Challenge to self-produce motor behavior that flows over into handling. Some of these categories were subdivided into several variables in order to cover >95% of the physical therapy contents, resulting in 25 physical therapy actions. For instance, the main category ‘Family involvement and educational actions’ had five variables, four of which reflected TIP activity (‘caregiver interferes with infants’ activities’, ‘physical therapist interferes with infants’ activities’, ‘physical therapist guides the infant’, and ‘physical therapist gives caregiver training’), and one of which was specific for COPCA (‘physical therapist coaches the caregiver’). Eight physical therapy actions were typical COPCA actions, 14 actions were typical TIP actions, and three were part of both programs and therefore a priori less discriminatory (see Dirks et al. 2011 and 2016).

**Outcomes and Follow-up**

Postural control was assessed with electromyography (EMG) at 4, 6 and 18 months CA. At each age, the infants’ developmental status was assessed. These assessments included the Alberta Infant Motor Scale (AIMS) and a standardized neurological examination according to Touwen (at 18 months according to Hempel). The diagnosis of CP was based on the neurological examination at the age of 18 months. In children with CP gross motor function was classified with the Gross Motor Function Classification System (GMFCS). Two infants were not assessed at 18 months due to
The infants’ parents gave informed consent and procedures were approved by the ethics committee of the University Medical Center Groningen (UMCG; trial number NL39954.042.12). The trial was registered at the ISRCTN registry with trial registration number ISRCTN85728836.

Protocol

The protocol and method were described in van Balen et al 2012 and 2015. The infants were tested in a supported sitting position. The infants sat either in an infant chair with back support and a horizontal bar as additional frontal support, or on their parent’s lap, with their legs in a semi-flexed position. The lap position was only applied if necessary for the infant’s cooperation, which was the case for one infant at 4 months and three infants at 18 months of the TIP group and two infants at 18 months of the COPCA group. Care was taken that the sitting position on the parent’s lap closely resembled that in the infant chair.

Reaching was elicited by presenting small toys in the midline at an arm’s length distance. We aimed at recording at least ten reaching movements with the right arm, but when the infant became fussy or tired, the session was shortened.

EMG was measured continuously with bipolar surface electrodes on the following right-sided muscles: deltoid (DE), pectoralis major (PM), biceps brachii (BB), triceps brachii (TB), neck flexor (NF, sternocleidomastoid), neck extensor (NE), rectus abdominis (RA), thoracal extensor (TE), and lumbar extensor. DE, PM, BB and TB are referred to as arm muscles; NF, NE, RA, TE, and LE as postural muscles. Sessions were recorded on video, which was time-coupled to the EMG recordings. Both the investigators who assessed the infants and recorded the EMGs, and those who analyzed the EMG data, were blinded to group allocation. Group allocation was only added to the dataset after video and EMG data analysis was complete.

Video and EMG analysis

Using the video, we selected arm movements occurring in response to the toy, excluding trials with inappropriate sitting position, attentional state, or reaching movements not involving the right arm. EMG analyses (artefact correction and detection of significant bursts of phasic muscle activity) were carried out with the PedEMG program (Developmental Neurology, UMCG, The Netherlands; see van
The EMG was scanned for activation of the arm muscles from 500 ms prior to visible movement in the video, and the start of the reach was defined as the onset time of the first arm muscle activity that was related to the reaching movement (i.e., the onset of the prime mover, the arm muscle initiating the reach). For the postural muscles, increased activity was included if found within a time window consisting of (a) 100 ms before activation of the prime mover, (see Boxum et al. 2014)\(^4\) and (b) the duration of the first 1000 ms of the reaching movement.

For each trial, we determined the following parameters (see Figure 1): (1) Direction-specificity; a trial was direction-specific if the dorsal muscle was recruited prior to the antagonistic ventral muscle or without antagonistic activation. Thus, a trial was direction-specific at trunk level if TE and LE were recruited before RA, or if either TE or LE was recruited without RA-recruitment. Direction-specificity at both neck and trunk level entailed direction-specific recruitment of both the trunk and neck muscles in the same trial; (2) Recruitment order (top-down, bottom-up, or otherwise). This could only be determined when at least two direction-specific muscles showed significant phasic activity. If two muscles were activated within an interval of 20 ms, recruitment was considered simultaneous. Recruitment of three dorsal muscles with TE earlier than NE and LE was defined as mixed order recruitment; (3) The presence or absence of anticipatory postural activity at the neck and/or trunk level (i.e., activation starting within 100 ms before the prime mover). Overall anticipatory activation was defined as anticipatory activation in at least one dorsal postural muscle, regardless of location (neck or trunk); (4) The recruitment latencies of postural muscles, defined as the time interval between the onset of the prime mover and the onset of activity in the postural muscle. For each infant at each age median latency values were calculated;

**Statistical analysis**

Statistical modelling was carried out using the Statistical Analytics Software (SAS) 9.3 (SAS Institute Inc., Cary, NC) and SPSS 20 (IBM Corp., Armonk, NY). For the dichotomous parameters (the presence or absence of direction-specificity, the complete pattern, top-down and bottom-up recruitment and anticipatory activation), a binomial generalized estimating equations (GEE) model with repeated measurements was fitted using predictor variables Age and Intervention. To take missing data into account, the parameters were modelled as ratios, i.e., the number
of trials with the parameter value ‘true’, divided by the total number of trials. For example, for each child at each age direction-specificity was modelled as the number of direction-specific trials divided by the total number of trials for which direction-specificity could be computed. Continuous variables (the median latencies) were modelled with a linear mixed model with repeated measurements. Finally, partial correlations were used to investigate associations between physiotherapeutic actions and parameters of postural control at 6 and 18 months. Odds ratios (OR; including 95% confidence intervals in square brackets) are reported for the statistical analyses; to aid interpretation of the results we also calculated the percentage of trials per infant for each outcome variable (e.g., the percentage of direction-specific trials, the percentage of trials with top-down recruitment, and so on), and report median values of these percentages.

**Group characteristics and missing data**

Taking the missing data into account, we constructed the table of group characteristics not only with the number of infants originally included in the study, but also with the availability of direction-specificity at 18 months (Table 1). Preliminary data analysis indicated that EMG activity of the 18-month-old lap-sitting infants (n=3 in each group) did not differ from that of their chair-sitting peers (n=6 for TIP and n=18 for COPCA). Therefore, the 18-months data of chair-sitting and lap-sitting were pooled.
REFERENCES (METHODS SUPPLEMENT)


