

# DEVELOPMENTAL DISREGARD IN UNILATERAL CEREBRAL PALSY

Behavioral & electrophysiological examinations  
of the underlying mechanisms

Ingar Marie Zielinski



Behavioural  
Science  
Institute

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**WHILE WE TRY TO TEACH  
CHILDREN ALL ABOUT LIFE,  
CHILDREN TEACH US  
WHAT LIFE IS ALL ABOUT.**

- Angela Schwindt

**Dedicated to all these special children  
that taught me what life is all about.**

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# **DEVELOPMENTAL DISREGARD IN UNILATERAL CEREBRAL PALSY**

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## **Proefschrift**

ter verkrijging van de graad van doctor  
aan de Radboud Universiteit Nijmegen  
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,  
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door

**Ingar Marie Zielinski**

geboren op 18 maart 1988  
te Haltern (Duitsland)

# **DEVELOPMENTAL DISREGARD IN UNILATERAL CEREBRAL PALSY**

**Behavioral & electrophysiological examinations  
of the underlying mechanisms**

## **Doctoral Thesis**

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from Radboud University Nijmegen  
on the authority of the Rector Magnificus prof. dr. J.H.J.M. van Krieken,  
according to the decision of the Council of Deans  
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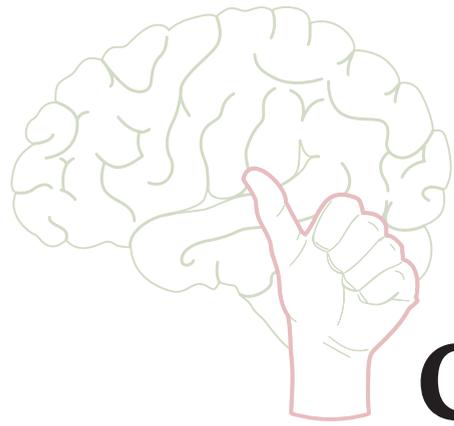
## Prologue

Being able to move is a fundamental aspect of life. Think about it for a moment: What would you be able to achieve during a typical daily routine if you were not able to move? The answer comes naturally: None of us would be able to independently live without the ability to move and navigate different parts of our body. Next to the fact that the ability to move our body enables us to achieve our daily routines, successful motor development is also known to be closely related to successful cognitive development (Diamond, 2000). We can argue that the ability to move also enables us to develop multiple cognitive abilities. The acquisition of motor competence is therefore considered to be one of the most important developmental milestones during early development. However, in some children this typical movement development is disrupted, with Cerebral Palsy (CP) as the most common cause of movement disability in childhood (Rosenbaum et al., 2007). These children experience difficulties related to the development of movement and posture (frequently expressed as spasticity), with about one third having predominant unilateral motor impairments, mostly effecting the upper limb. There are currently many different intervention programs aiming at improving the functionality of the affected side (AS) in these children with unilateral CP, with the ultimate goal to promote participation in life and society. These interventions frequently lead to a better capacity of the AS, but not always to an increased use of this side in daily life. This discrepancy between capacity and performance of the AS is referred to as developmental disregard. It can be considered as a significant limitation of daily functioning on top of the existing capacity limitations. This means that children with developmental disregard do not only experience limitations directly related to their reduced AS capacity, but furthermore do not seem to be able to use the remaining AS capacity to assist the other hand during their daily routine. Even though frequently observed in children with unilateral CP, the underlying mechanisms contributing to developmental disregard are not extensively studied and knowledge is currently limited.

The aim of the present thesis is to use a combination of behavioral and electrophysiological examinations to advance our knowledge of the underlying mechanisms of developmental disregard. The results will help to understand this phenomenon and facilitate the development of individualized intervention programmes that are focused on overcoming symptoms of disregarding the remaining capacity of the AS in children with unilateral CP.

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# CHAPTER \_\_\_\_\_ I

General Introduction



## 1.1 Cerebral palsy

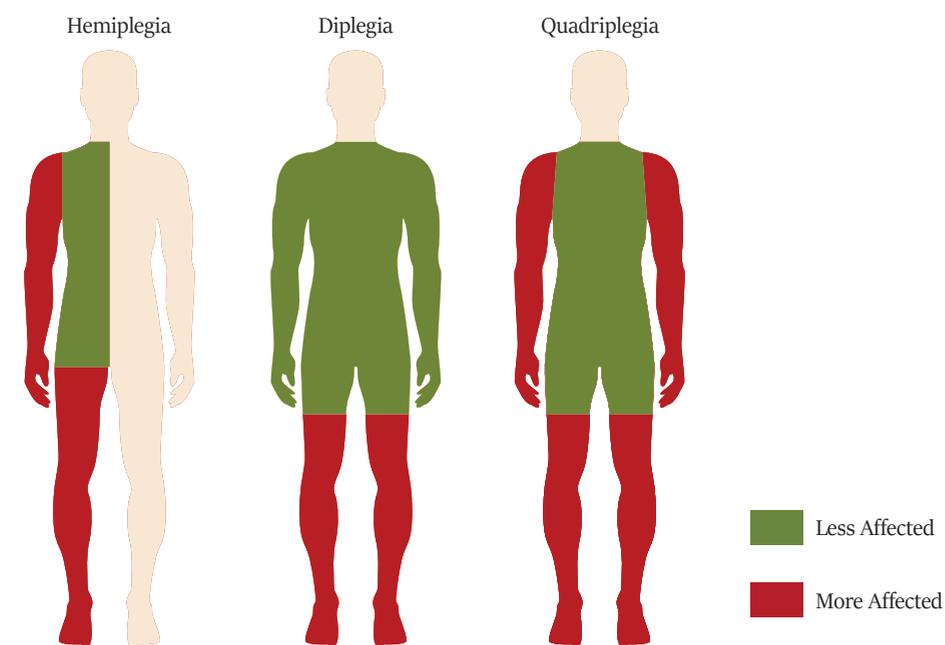
With an incidence of 1.5 – 3 per 1000 live births within western countries, cerebral palsy (CP) is considered the most common cause of movement disability in childhood (Odding, Roebroek, & Stam, 2006; Rosenbaum, 2003). It is defined as “(...) a group of permanent disorders of the development of movement and posture, causing activity limitations, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.” (Rosenbaum et al., 2007). In other words, CP is caused by non-progressive brain injury to parts of the brain involved in movement processes. It occurs before, during, or shortly after birth and predominantly affects the child’s motor functioning (having a motor impairment is obligatory for the diagnosis of CP). Even though non-progressive, it still is associated with lifelong motor impairments and disabilities (Rosenbaum et al., 2007). This is also related to the fact that motor disorders of children with CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior (Rosenbaum et al., 2007). Due to the variations in time of occurrence (before, during, or shortly after birth), localization of brain damage, and accompanying disturbances, children with CP form a very heterogeneous group (Rosenbaum et al., 2007).

### 1.1.1 Classification of Cerebral palsy

Due to the heterogeneity of the group, and to provide more insight in the differences between children with CP, various classification systems are in use. A first subdivision is frequently based on the predominant type of muscle tone or movement abnormality (Rosenbaum et al., 2007). Within this subdivision, the most common type of muscle tone abnormality is spasticity (72 – 91% of the cases), with much less children showing a dyskinetic (12 – 14% of the cases; further subdivided in athetoid vs dystonic), or ataxic (4 – 13% of the cases) movement disorder (Odding et al., 2006). Simply put, children with a spastic form of CP show an increased muscle tone, commonly related to primary damage of the motor cortex, children with a dyskinetic form display involuntary movements (athetoid: continuous; dystonic: triggered by attempts to move) commonly related to primary damage to the basal ganglia, and the ataxic form affects coordinated movement and is commonly related to primary damage to the cerebellum. Even though this subdivision is known to be important to better understand and treat the children’s disorder, it has to be acknowledged that children’s impairments may fall into different categories displaying mixed types of CP (e.g. spastic & dystonic).

A second subdivision focuses on the body parts that are predominantly affected. For this purpose, commonly three subdivisions are made: hemiplegia,

diplegia, and quadriplegia (Rosenbaum, 2003). Hemiplegia, or unilateral CP, is among the most common subtypes of CP, comprising 21–40% of the cases. These children show substantially greater motor deficits on one side of the body compared to the other side, with the upper extremity frequently being more affected compared to the lower extremity. Children with diplegia (13 – 25% of all cases) primarily display motor impairment of the legs, with usually some relatively limited involvement of the arms. In quadriplegia, also known as tetraplegia (20 – 43% of all cases), all four limbs are affected leading to a functional impairment of the whole body (Odding et al., 2006). For an overview of this subdivision of involved body parts please see **figure 1.1**.



**Figure 1.1. Representation of the subdivision of involved body parts in Cerebral palsy.** The typical body involvement for hemiplegia (or unilateral CP) is depicted on the left, diplegia in the middle, and quadriplegia (or tetraplegia) on the right. Red shows the body parts that are typically most affected. Green shows the body parts that are also affected, but typically less when compared to the red body parts. Adapted from "What is Cerebral Palsy" – CPL, n.d., Retrieved November 7, 2016, from <http://www.cpl.org.au/childrens-services/newly-diagnosed-/cp>.

Another frequently used classification is related to the severity of the motor impairments. In this respect, the Gross Motor Function Classification System (GMFCS) (Palisano et al., 1997) classifies walking and mobility on an ordinal

rating scale ranging from level 1 to 5. Children being classified as GMFCS level 1 are able to walk independently on most surfaces, whereas children in level 5 are entirely dependent on external help, even when using electric wheelchairs (Palisano et al., 1997). Furthermore, as fine-motor equivalent of the GMFCS, the Manual Ability Classification System (MACS) is used to classify the ability to handle objects in daily life. This scale is of special interest in children with unilateral CP, as most children with unilateral CP are able to walk (Eliasson et al., 2006). Similar to the GMFCS, the MACS is based on an ordinal rating scale ranging from level 1 to 5, with level 1 indicating that the child handles most objects easily and successfully and level 5 indicating that the child has a very limited ability to perform even simple actions (see **table 1.1.** for a detailed description of the different levels) (Eliasson et al., 2006).

In the current thesis, we studied children with unilateral CP. These children are mostly spastic, usually display with GMFCS scores I or II, and frequently have MACS scores ranging from I to III (with most children being classified as level I or II) (Carnahan, Arner, & Hagglund, 2007).

**Table 1.1.** Summary of the criteria of the different GMFCS and MACS levels.

GMFCS	MACS
Level I	Level I
Walks without restrictions, limitations in more advanced gross motor skills.	Handles objects easily and successfully.
Level II	Level II
Walks without restrictions, limitations walking outdoors and in the community.	Handles most objects but with somewhat reduced quality and/or speed of achievement.
Level III	Level III
Walks with assistive mobility devices, limitations walking outdoors and in community.	Handles objects with difficulty; needs help to prepare and/or modify activities.
Level IV	Level IV
Self mobility with limitations, children are transported or use power mobility outdoors and in the community.	Handles a limited selection of easily managed objects in adapted situations.
Level V	Level V
Self mobility is severely limited, even with use of assistive technology.	Does not handle objects and has very limited ability to perform even simple actions.

**Abbreviations:** GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System

### 1.1.2 Treatment of upper limb functioning in unilateral CP

Therapies focusing on the upper limb functioning in children with unilateral CP (frequently referred to as “functional therapies”) have three principal components:

1. Training of the affected upper limb mainly in isolation (unimanual approach)
2. Training of both hands by training bimanual activities (bimanual approach)
3. Training of unimanual strategies with the less-affected upper limb for typical bimanual activities (compensation strategies)

The idea behind the unimanual treatment approach is to deliver the maximal training intensity to the AS to improve this hands capacity. Even though typical bimanual activities are not directly trained, an improved AS capacity is suggested to transfer to improvements in bimanual performance (Eliasson, Krumlinde-Sundholm, Shaw, & Wang, 2005). A commonly applied unimanual treatment approach for children with unilateral CP is the so called Constraint-induced movement therapy (CIMT) (Hoare, Wasiak, Imms, & Carey, 2007; Taub, 1980). It is based on the idea of re-learning the use of the upper limb through processes of operant conditioning following two fundamental principles: 1. constraint of the less-affected upper limb and 2. intensive and frequent training of activities with the affected upper limb. When introducing this treatment approach in pediatrics, concerns were raised about the feasibility of strict CIMT programs in children, because programs were not child-friendly, very intensive, and potentially invasive (Aarts, Jongerius, Geerdink, van Limbeek, & Geurts, 2010; Gordon, Charles, & Wolf, 2005). Therefore, child friendly and modified ( $\leq 3$  hours/day) versions of the CIMT program (mCIMT) were developed, which were reported to be effective and tolerated by children with uCP (Aarts et al., 2010; Brady & Garcia, 2009; Gordon et al., 2005; Taub et al., 2007).

Instead of only targeting the impaired unimanual capacity, bimanual training directly focuses on improving the coordination of both hands during typical daily activities (Sakzewski et al., 2011). This approach is based on the idea that children with unilateral CP experience bimanual impairments beyond their AS impairments (Gordon, Schneider, Chinnan, & Charles, 2007). Using an intensive bimanual training approach (frequently referred to as “Bimanual intensive Training”; BiT), the children’s bimanual performance is optimally targeted, however at the cost of a reduced intensity of training delivered to the AS.

Finally, children with a severely affected upper limb might benefit most from learning compensation strategies with their “good”, less-AS (Adler, Rauchenzauner, Staudt, & Berweck, 2014; Staudt, 2016). These compensation strategies of how to accomplish typical bimanual tasks by only using the less-AS hand can be highly effective in increasing the children’s participation during daily activities. This therapy approach does however discard the potential of the AS.



As all three approaches for treating upper limb functioning in children with unilateral CP have their own advantages and disadvantages, so called “hybrid” models have been introduced (Aarts, Jongerius, Geerdink, van Limbeek, & Geurts, 2011; Vaz, Mancini, Amaral, de Brito Brandao, de Franca Drummond, & da Fonseca, 2010). These models include components of each treatment approach, frequently applying them sequentially.

## 1.2 Developmental Disregard

The phenomenon of not using the affected upper limb to its full capacity has originally been described in adult stroke patients and been referred to as “learned non-use” (Taub et al., 1994). It has been explained as a learned suppression of movement due to repetitive failure when trying to move the AS. It is argued that this negative reinforcement resulting from the unsuccessful use of the affected upper limb is combined with positive reinforcement from the successful use of the less-affected upper limb. Via processes of operant conditioning, these reinforcement processes are argued to ultimately cause the observed non-use. In children with unilateral CP, similar behavioral symptoms of not using the affected upper limb capacity are often observed and therefore frequently compared to the phenomenon of learned non-use.

However, children with unilateral CP, as opposed to adult stroke patients, have acquired their brain injury (very) early in life, before, during, or shortly after birth. Thus, a substantial difference between these two patient groups is that adult stroke patients may lose the capacity to successfully perform specific motor activities due to their brain lesion, whereas children with unilateral CP potentially have never had the experience of successfully performing certain motor activities. In other words, these children have never learned to perform certain motor activities with their AS in the first place and thus have never “lost” this capacity. The pattern of non-use of the affected upper limb thus differs between both patient groups. Due to this developmental difference, the discrepancy between upper limb capacity and spontaneous daily life performance in children with unilateral CP has been referred to as “developmental disregard” instead of learned non-use (DeLuca, Echols, Law, & Ramey, 2006; Taub, Ramey, DeLuca, & Echols, 2004).

Developmental disregard can be defined as “...a failure to use the potential motor functions and capacities of the affected arm and hand for spontaneous use in daily life” (Houwink et al., 2011). This results in a preference for unimanual task performance, even though the capacity of the AS would allow or even predict the inclusion of this hand during common bimanual activities. While these children

may frequently be able to perform some tasks that are commonly characterized as being bimanual by using only one hand (using strategies such as using their teeth or stabilizing objects against the body), task completion time is prolonged (Van Zelst, Miller, Russo, Murchland, & Crotty, 2006). This does in turn frequently lead children to seek assistance of others, or even to avoid certain activities, reducing their independence during daily routines (Skold, Josephsson, & Eliasson, 2004).

Even though developmental disregard is frequently observed in children with unilateral CP (around 50% – 90% of all cases (Liu, Chen, Wang, & Shieh, 2016)), the underlying mechanisms of this phenomenon are not yet fully understood. Still, in the current literature, two general frameworks are referred to when attempting to explain the characteristic symptoms of developmental disregard: 1. the operant conditioning framework, comparing developmental disregard to learned non-use and 2. the information processing framework, stating that symptoms of developmental disregard might be best explained by disturbances to the development of cognitive mechanisms relevant for successful goal directed motor behavior. Even though being not mutually exclusive, the operant conditioning and information processing explanation would lead to considerable different approaches for developing training programs to overcome developmental disregard. While the operant conditioning framework would imply to focus on re-learning the use of the AS (unimanual approach, e.g. mCIMT), the information processing framework would imply to rather focus on involved cognitive deficits.

The aim of the current thesis is therefore to test hypotheses derived from both theoretical frameworks in a series of experiments to unveil underlying mechanisms of developmental disregard. For a schematic overview of the two frameworks and related theories, please see **figure 1.2**.

### 1.2.1 The operant conditioning framework: developmental disregard as a “learned” phenomenon

When trying to understand the underlying mechanisms of developmental disregard it has been suggested that the same negative and positive reinforcement mechanisms as in learned non-use underlie this phenomenon in children with unilateral CP (Crocker, MacKay-Lyons, & McDonnell, 1997; Taub et al., 2004). Even though not directly comparable to learned non-use observed in adult stroke patients (due to the developmental difference), this framework argues that developmental disregard is also caused by ineffective attempts of using the affected upper limb and concurrent successful use of the less-affected side (Taub et al., 2004). Therefore, developmental disregard was proposed to be viewed as a “... special case of learned non-use” (Taub et al., 2004), additionally incorporating the possible developmental delay processes.



In line with this theoretical framework of interpreting developmental disregard as a learned phenomenon, it has been suggested that so called mirror movements (MMs) might also be responsible for a learned suppression of movement of the affected upper limb (Hoare, Wasiak, Imms, & Carey, 2007; Kuhtz-Buschbeck, Sundholm, Eliasson, & Forssberg, 2000). MMs are defined as involuntary movements that accompany and mirror voluntary movements of the same muscles on the opposite side of the body (Kuhtz-Buschbeck et al., 2000). In other words, if one hand is moving voluntarily, the other hand performs the same action involuntarily. These MMs, even though being considered as a normal feature of motor behavior in young children, are frequently more pronounced and persistent in children with unilateral CP (Woods & Teuber, 1978). The notion that these “pathological” MMs strengthen the learned suppression of movement of the affected upper limb is based on the following reasoning:

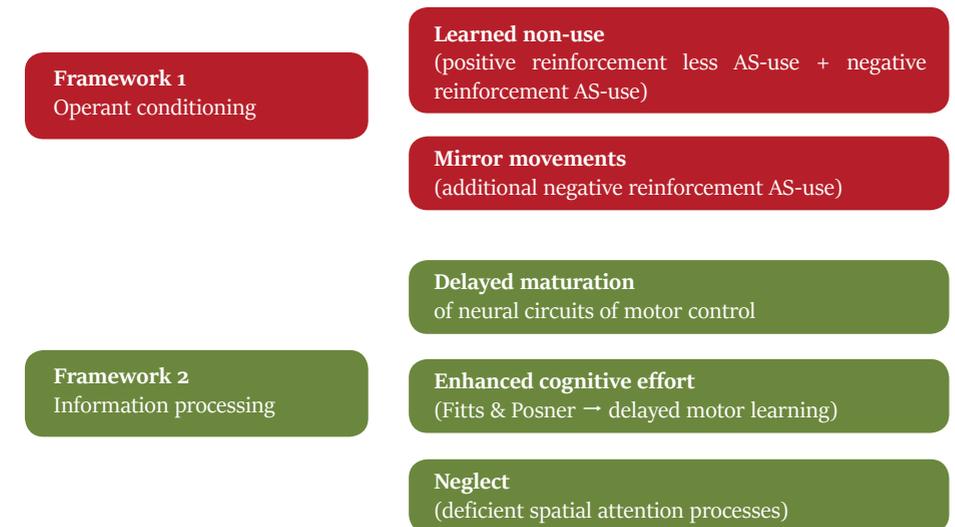
1. When actively moving the AS during bimanual asymmetric activities, MMs in the less-AS cause a reduction in independent control of this hand. Thus, the child learns that performing the same tasks unimanually is more successful, as this does not lead to “losing control” over the less-affected, “good” hand (Kuhtz-Buschbeck et al., 2000).
2. In the typical stabilizing function of the AS MMs during active movement of the less-AS result in difficulties to stabilise objects. The child subsequently learns that the AS does not appropriately assist the less-AS. This ultimately leads to preferred unimanual activities, not involving the AS for a stabilizing function (Klingels et al., 2015).

To summarize, the framework of operant conditioning suggests that developmental disregard in children with unilateral CP develops as a consequence of negative feedback when using the AS (1. reduced capacity of the AS and 2. interference with mirror movements) and simultaneous positive reinforcement when successfully performing tasks with (only) the less-AS. This is in turn suggested to negatively influencing typical movement development, causing a potential developmental delay. Based on this framework, children with developmental disregard would benefit mostly from therapies aimed at reducing MMs and re-conditioning the use of the affected upper limb. The latter is directly targeted in the earlier introduced mCIMT approaches (Hoare, Wasiak, Imms, & Carey, 2007; Taub, 1980).

### 1.2.2 The information processing framework: developmental disregard as a phenomenon of a deficient and/or delayed development of cognitive processes involved in movement control

A second theoretical framework that has been used to explain developmental disregard focuses on the cognitive processes that contribute to the phenomenon

of developmental disregard (Deluca et al., 2006; Houwink et al., 2011). This framework is based on the assumption that symptoms of developmental disregard might be best explained by disturbances in information processing mechanisms relevant for successful goal directed motor behavior. Related to this framework three hypothesis have been made.

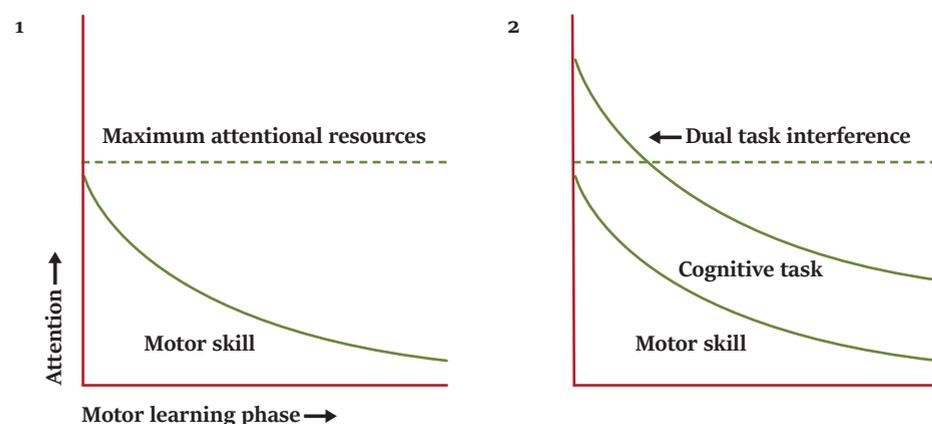


**Figure 1.2. Schematic overview of the two frameworks explaining developmental disregard.** Depicted are the two frameworks that are aiming to explain the observed symptoms of non-use in children with unilateral CP and developmental disregard. Both frameworks (operant conditioning: red; information processing: green) are related to different hypothesis that are depicted on the right side of the figure and matched in colour.

#### 1.2.2.1 Developmental disregard and the delayed or deficient development of neuronal circuits of motor control

At a neurophysiological level, developmental disregard has been proposed to be the result of an impaired development and refinement of neural circuits typically involved in motor control (Deluca et al., 2006). This hypothesis of underlying aberrant neural connectivity in areas responsible for volitional movement might be explained by a lack of movement input of the affected upper-limb during sensitive developmental periods (Deluca et al., 2006). This is, as the neural substrate underlying volitional upper-limb movement is known to develop when actively moving the limb (Martin, 2005; Sanes & Donoghue, 2000). A reduced use of the upper-limb, especially during sensitive developmental periods of

early development might thus result in a lack of establishment, refinement, and coordination of the neural circuits for controlling entire classes of motor behavior. This was suggested to possibly underlying the symptoms of non-use symptoms of developmental disregard. Following this line of reasoning, developmental disregard is explained by a delayed or deficient development of neural circuits involved in voluntary movement. Based on this assumption, early intervention programs could be considered as most effective. By actively stimulating movement of the affected upper-limb during specific corticospinal axon refinement periods, developmental disregard could be “treated” by preventing such a delayed or deficient development.



**Figure 1.3.** Depiction of the theoretical motor learning model by Fitts and Posner. 1) In the early phase of motor learning almost all attentional resources are needed to perform the motor task. The amount of attentional resources decreases within the motor learning phase, as the motor skill becomes more automated. 2) When a motor skill is not yet sufficiently automated (so that no attentional resources remain available) dual task interference occurs when concurrently performing a cognitive task. Adapted from “A neurocognitive perspective on developmental disregard in children with hemiplegic cerebral palsy.”, by A. Houwink, 2011, *Res Dev Disabil*, 32(6), 2158. Copyright [2011] by Elsevier Ltd.

### 1.2.2.2 Developmental disregard and enhanced cognitive effort

Another hypothesis focussing on involved cognitive processes in developmental disregard is based on a widely accepted model of motor learning by Fitts and Posner (1967; Houwink et al., 2011). The central statement of their model is that improvement in motor skills runs parallel with a decrease in demands on attentional resources when performing the motor task (see **figure 1.3.1**). Following this model, a motor skill that is not yet automated, claims a great

deal of attentional, or cognitive resources. If at the same time a cognitive task needs to be performed (i.e. listening, talking), a so called dual task interference occurs, leading to a failure in completing one of the two tasks, as the maximum attentional resources are already exceeded (see **figure 1.3.2**).

Building on this model of motor learning, the neurocognitive perspective to explain developmental disregard suggests that certain motor skills of the affected upper limb are not (yet) automated in children with developmental disregard (Houwink et al., 2011). Consequently, during typical daily activities involving cognitive resources (e.g. playing, listening, walking) continuous dual task interferences occur when attempting to include the AS during typical bimanual activities. As attentional resources are depleted when attempting to perform these tasks together, children ultimately fail to use their AS, leading to a non-use of this hand. Following this line of reasoning, it has been suggested that developmental disregard might be best explained by an enhanced cognitive effort related to movements of the affected upper limb. This approach is in line with the hypothesis that developmental disregard might be related to a general developmental delay. Based on this neurocognitive perspective, children with developmental disregard would mostly benefit from therapies aiming at learning and automating bimanual motor skills (e.g. BiT).

### 1.2.2.3 Developmental disregard and motor neglect

A different line of reasoning compares developmental disregard to the neuropsychological disorder of post-stroke motor neglect (Sutcliffe, Logan, & Fehlings, 2009). As in children with developmental disregard, stroke patients with motor neglect seem to forget to use their AS during spontaneous daily activities, independent of the preserved strength and coordination (Gurd, Kischka, & Marshall, 2010; Saevarsson, 2013). As these symptoms are very similar to the symptoms observed in learned non-use, motor neglect is indeed also often confused with this behavioral phenomenon, exemplifying the similarities between the related symptoms (Saevarsson, 2013). However, unlike learned non-use, motor neglect is thought to be the direct result of brain injury to cortical areas involved in spatial attention processes resulting in a deficit of body awareness (Chatterjee, 2002; Saevarsson, 2013). It has been argued that developmental disregard in children with unilateral CP might as well be directly related to cortical lesions responsible for spatial attention processes that are important for voluntary motor behavior (Sutcliffe et al., 2009). Consequently, attention is never automatically directed to the affected upper limb, leading to the observed neglect of the existing motor capacities. If developmental disregard is indeed related to deficient spatial attention processes, therapies aiming at reducing developmental disregard should be based on training these children to attend voluntarily to their contralesional space.



### 1.2.3 Assessment of developmental disregard

To assess the difference between what a child can do with his/her AS and what a child actually does during daily activities (i.e. to assess developmental disregard) it was suggested to combine the outcomes of a capacity based test with the outcomes of a performance based test (Klingels et al., 2010). The underlying assumption for this method is that children with developmental disregard would receive a lower score on the hand performance assessment than what would be expected based on their capacity assessment. This method was repeatedly applied when studying the phenomenon of developmental disregard (Klingels et al., 2015; Sutcliffe et al., 2009). However, the difference scores of comparing varying assessment outcomes have never been validated. This makes it difficult to decide how big the difference between the hand capacity and performance outcome should be, to be considered as developmental disregard.

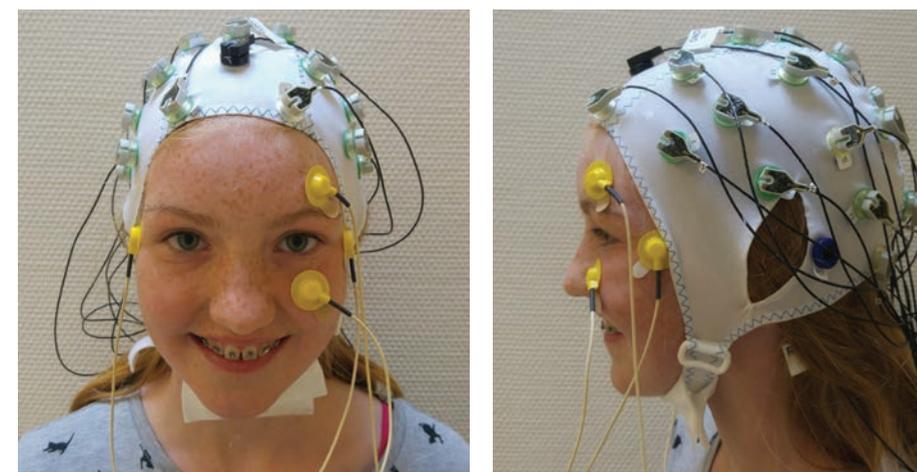
The most reported assessment tool to diagnose developmental disregard in children with unilateral CP is the validated “Video-Observation Aarts and Aarts module: Determine Developmental Disregard” (VOAA-DDD-R) (Houwink, Geerdink, Steenbergen, Geurts, & Aarts, 2013). Using this video based observation tool, the upper limb activity on two different typical bimanual tasks is compared within individuals to investigate the spontaneous use of the affected upper limb during bimanual tasks. One of these two tasks (decorating a muffin) is hardly stimulating the use of the AS. This means that this typical bimanual task could be performed with one hand only, even though bimanual use would be beneficial. The choice to use the AS during this task is therefore used as a (spontaneous) bimanual performance measure. The second task (stringing beads) is developed to provoke the use of the AS. It is hardly possible to perform this bimanual task with one hand only. If the hand capacity of the child is sufficient, it is thus expected that this hand is included during this second task (instead of for example using other strategies such as stabilizing objects against the body). The inclusion of the AS during this task is therefore used as a hand capacity measure. To determine developmental disregard, the difference of the AS use between both tasks is of interest. The developmental disregard score is thus calculated by the difference in duration of AS use between the two tasks (capacity vs. performance). This assessment procedure was revised (VOAA-DDD-R) and validated in 2013 (Houwink et al., 2013).

Recently, a new observation-based evaluation to investigate developmental disregard has been introduced. This “Observatory Test of Capacity, Performance, and Developmental Disregard” (OTCPDD) was developed to detect the performance of the affected upper limb use during daily routines (Liu et al., 2016). The authors criticize the lack of common tasks of daily routines used for the VOAA-DDD-R, as they argue that the selected tasks do not reflect the child’s actual upper limb use in daily routines.

### 1.3 Using EEG to study cognitive aspects of voluntary movement

The electroencephalogram, or EEG, is the recording of the electrical activity of the brain (Luck, 2005). The main advantage, compared to many other neuroimaging techniques, is its high temporal resolution. This characteristic makes it possible to capture rapidly succeeding cognitive operations preceding planned movements. The EEG is therefore frequently applied to study covert cognitive processes that accompany overt actions (e.g. voluntary movement). Furthermore, EEG recordings are non-invasive (as opposed to some other imaging techniques). This makes it especially appealing to be applied within the pediatric population. This is also, as EEG recordings can be applied without fixating the participants head and children can perform the task in a natural sitting position. A final advantage of using EEG as a technique within the pediatric population is the possibility of using mobile labs. Measurements can therefore be obtained in environments that are familiar to the child (e.g. school, hospital, or even at home).

To register the electrical activity of the brain, electrodes are placed on the scalp of a participant (international standardized arrangement: the 10–20 system; see **figure 1.4.**).

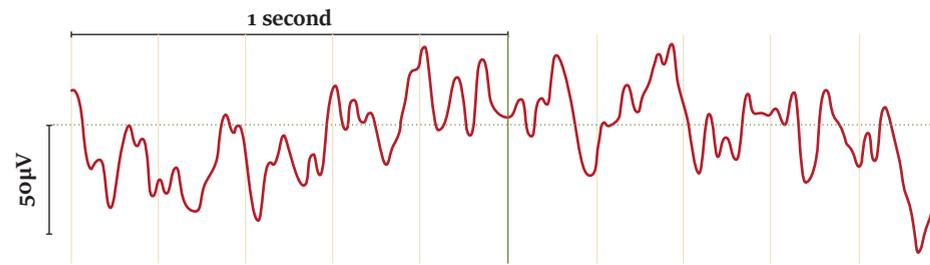


**Figure 1.4. Representation of EEG electrode placement.** Measurement of EEG with 32 electrodes arranged according to the standard 10–20 system. Yellow electrodes show additional Electrooculography (EOG) electrodes to register eye movements.

The recorded EEG activity is the result of joint neuronal activity (fluctuations resulting from ionic currents within the neuron) and is generated by large populations of (mainly pyramidal) neurons. This activity is registered



as the voltage differences between two electrodes (when the summed currents of the neurons reach the electrodes on the scalp, the electrons on the metal of the electrodes are pushed or pulled) and plotted over time. As the amplitude of this voltage differences is very small (typically  $10\ \mu\text{V}$  to  $100\ \mu\text{V}$  in humans), the measured signal is strongly amplified. **Figure 1.5.** shows an example of a two second EEG recording.



**Figure 1.5. Representation of EEG signal.** A two second EEG recording from one electrode (filtered between 0.5 and 30 Hz).

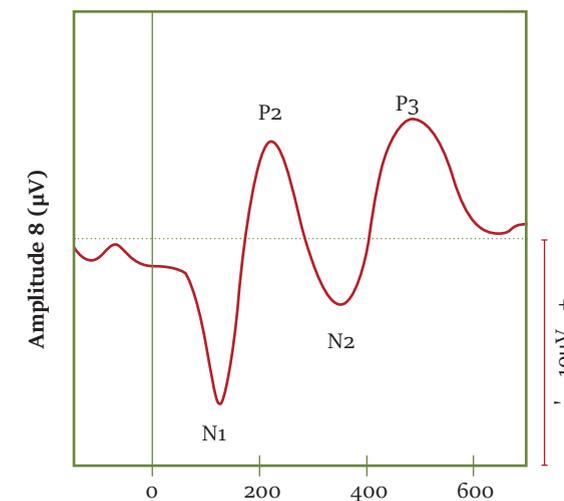
### 1.3.1 Event-Related Potentials to study cognitive mechanisms related to voluntary movement

One way of using EEG data to study different cognitive processes related to voluntary movement is by using an Event-Related Potential (ERP) procedure. The recording of ERPs can be seen as the most straightforward way of measuring the response of the brain to a given event (e.g. the presentation of a visual stimulus). An ERP can be defined as a voltage polarity fluctuation in the EEG that is time-locked to the onset of this event (Luck, 2005). The magnitude of this ERP is very low (e.g.  $10\ \mu\text{V}$ ) compared to the background EEG (around  $50\ \mu\text{V}$ ). This makes it difficult to identify an ERP of a single event (e.g. one stimulus presentation). To solve this problem, ERP designs usually rely on an averaging procedure based on the following steps: 1. the event is repeated for several times, 2. the EEG signal is segmented based on the exact time point of the event, and 3. averaged ERPs are calculated by averaging the segments across all trials (Luck, 2005).

The resulting ERP consist of multiple, consecutive positive and negative peaks: the ERP components (see **figure 1.6.**). ERP components can be characterized by differences in polarity (positive or negative), amplitude (strength of the component in microvolt), latency (the onset and duration of the effect in milliseconds), and topography (where on the scalp in this component displayed). Differences that arise in any of these characteristics can be used to make inferences about the cognitive processes involved in the processing of the stimulus. The naming of these components is based on the polarity (P for

positive and N for negative) and the order (P1, N1, P2, N2, P3) or latency (in ms) of the different peaks (e.g. P300).

One possible way to study cognitive processes related to voluntary movement is to present stimuli (e.g. a visual signal, or target) to induce a goal directed motor responses (e.g. a voluntary hand movement). The ERP elicited by this visual stimulus represents the cognitive mechanisms involved in the processing of the stimulus presentation (e.g. response preparation) and can be compared between different conditions or groups. The most commonly identified ERP components within cognitive tasks are the N1, P2, N2, and P3 components (Jonkman, 2006; Luck, 2005). Whereas the N1 component has been associated with orienting and early spatial attention processes and the P2 component is known to be modulated by the complexity of the stimuli (Luck, 2005), the later latency N2 and P3 components are known to reflect processes associated with cognitive and attentional control (Key, Dove, & Maguire, 2005). This knowledge about the related processes can in turn be used to interpret differences (e.g. between groups or conditions) in amplitude or latency of the components.



**Figure 1.6. Schematic of Event-Related Potentials.** Event-Related Potential as a result of time-domain averaging. The x-axis represents the time (milliseconds) and the y-axis the voltage (microvolt). The stimulus is presented at time point 0.

### 1.3.2 Frequency analysis to study cognitive mechanisms related to voluntary movement

Another possibility to use EEG data to study cognitive processes related to voluntary movement is by applying spectral power or frequency analysis.

As opposed to ERP analysis, spectral power analyses focuses on the relative contribution of a specific frequency to the recorded EEG signal. For this purpose, the EEG signal can be subdivided into different bandwidths (delta: ~0.5 – 3.5Hz, theta: ~3.5 – 7Hz, alpha (& mu): ~7 – 13.5Hz, beta: ~13.5 – 30Hz, & gamma: > ~30Hz). Comparable to the knowledge about related underlying cognitive processes of different ERP components, every bandwidth can be related to different (ab)normal brain processes (Luck, 2005). Within movement studies, the mu frequency is of specific interest. It is a rhythm between 7 to 13.5 Hz, measured over the sensorimotor cortex (Klimesch, Sauseng, & Hanslmayr, 2007). It is known to be most prominent when the body is physically at rest and has therefore originally been interpreted as a cortical “idling” state (Pfurtscheller, Stancak, & Neuper, 1996). However, recent theories suggest that the presence of synchronous mu activity reflects top-down, inhibitory control processes, to inhibit irrelevant information and be prepared to perform new relevant tasks (Klimesch et al., 2007). The mu-rebound, or the return to a synchronous mu frequency of the sensorimotor areas after movement, is therefore of special interest when studying top-down cognitive control mechanism involved in voluntary movement production.

## 1.4 The content and outline of this dissertation

The focus of this dissertation is on the different factors that are hypothesized as likely contributors to developmental disregard in children with unilateral CP. This was done via a combination of behavioral and electrophysiological examinations.

### 1.4.1 Prefix: Novel tools and procedures to study aspects of developmental disregard

To be able to study different underlying mechanisms possibly contributing to developmental disregard, two new research methods were developed. In **chapter 2**, a new tool to quantitatively assess MMs in children with unilateral CP is presented. This tool was developed to test the hypothesis that children with developmental disregard do indeed show prolonged MMs, possibly explaining the non-use of the affected upper limb. In **chapter 3**, an Event-Related Potential (ERP) protocol is reported. This protocol was developed to study cognitive aspects involved in upper limb control in children with movement disabilities. It will be applied to study potential differences in cognitive processing between children with and without developmental disregard when actively moving their hands.

### 1.4.2 Part 1: The operant conditioning framework: developmental disregard as a “learned” phenomenon

The operant conditioning framework to explain developmental disregard suggests that this phenomenon develops due to negative (unsuccessful use of AS) and simultaneous positive (successful use of the less-AS) reinforcement processes, negatively influencing typical movement development. Following this theory, non-use of the AS can be explained by a learned suppression of movement and related developmental delay processes.

**Chapter 4** presents the results of a study comparing the effects of a therapy program between two groups of pediatric patients: children with unilateral CP and children with obstetric brachial plexus palsy (OBPP). As opposed to children with unilateral CP, children with an OBPP do not have any central nervous system injury. However, actual unimanual capacity impairments are comparable between both patient groups. It was hypothesized that if developmental disregard can be fully explained by a learned suppression of movement related to the reduced unimanual capacity and related developmental delay processes, then symptoms of developmental disregard would be comparable between groups. Thus, improvement on spontaneous bimanual performance following a therapy aiming at overcoming developmental disregard should be similar between both groups.

Next to the direct impact of the reduced unimanual capacity frequently leading to unsuccessful use of AS, learned non-use in unilateral CP has also been suggested to be caused by the ineffective use of the AS related to involuntary mirroring of one hand when the other hand is actively moving (i.e. MMs). In **chapter 5** the hypothesis that children with developmental disregard show enhanced MMs was tested. To this aim, the novel tool presented in **chapter 2** was used.

### 1.4.3 Part 2: The information processing framework: developmental disregard as a phenomenon of a deficient and/or delayed development of cognitive processes involved in movement control

Next to the framework of operant conditioning comparing developmental disregard to learned non-use, Electro-encephalography (EEG) measurements were applied to directly examine information processing mechanisms potentially underlying the observed symptoms of developmental disregard.

**Chapter 6** reports results reflecting on the EEG mu-rebound after voluntary hand movements in children with unilateral CP and developmental disregard. This was done to study a possible deficient or delayed neural circuitry development involved in motor control. The typical mu-rebound after voluntary movement was studied during a repetitive unimanual squeezing task. The



amount of mu was compared between resting and squeezing periods, separately for children with and without developmental disregard.

**Chapter 7** describes the study results on the research question if children with developmental disregard need an enhanced amount of cognitive effort when moving their affected upper limb during bimanual tasks compared to children with unilateral CP but without developmental disregard. This was performed by studying Event-Related Potentials (ERPs) preceding task-related motor responses during an unimanual (capacity) and a bimanual (performance) task. To do this, the protocol introduced in **chapter 3** was used.

As a follow-up on **chapter 7**, **chapter 8** describes study results focusing on the question if higher order motor executive functions (EFs) are also diminished in children with developmental disregard as compared to children with unilateral CP but without developmental disregard. It was hypothesized that this would be the case, if developmental disregard is related to a delay of motor development. This is as EFs are known to be especially prone to be affected by a delayed development. This was again investigated by using a version of the protocol introduced in **chapter 3**.

#### 1.4.4 General discussion

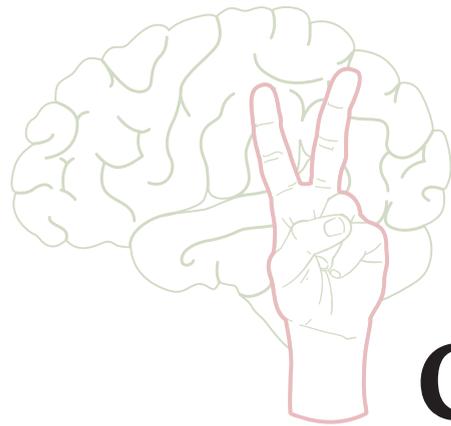
**Chapter 9** is the general discussion of the current dissertation including a detailed summary of our findings. It addresses the main finding of the thesis and discusses some important possible implications of the reported results. Furthermore, future steps are proposed to follow up on the discussed findings.



# PREFIX

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**NOVEL TOOLS AND  
PROCEDURES**  
to study aspects of  
Developmental Disregard



# CHAPTER II

## A New Quantitative and Objective Assessment for Mirror Movements in Unilateral Cerebral Palsy: Introduction of the Windmill-task

### Abstract

In children with unilateral cerebral palsy (CP) mirror movements (MMs) are frequently observed. They are typically assessed with the observation-based Woods and Teuber scale (W&T). However, due to its subjective nature and variable administration, interpretation of data across studies is problematic. We introduce the Windmill-task, a new objective assessment to quantify the presence of MMs. The concurrent validity of the Windmill-task is assessed and sensitivity and specificity for MM detection is compared between both assessments. To assess the concurrent validity, Windmill-data from a prospective cohort of 23 children with unilateral CP (mean age=10y5m, SD=2y7m) are compared to W&T-data using Spearman-rank ( $\rho$ ) correlations for two conditions (AS-moving vs. less-AS-moving). Sensitivity and specificity are compared by presenting the mean percentage of children being assessed inconsistently across both assessments. Results showed that outcomes of both assessments correlate significantly (AS-moving:  $\rho = .520$ ;  $p = .005$ ; less-AS-moving:  $\rho = .488$ ;  $p = .009$ ). However, many children displayed MMs on the Windmill-task, but not on the W&T (sensitivity: AS-moving: 27.5%; less-AS-moving: 40.6%). Only two children displayed MMs on the W&T, but not on the Windmill-task (specificity: AS-moving: 2.9%; less-AS-moving: 1.4%). These results indicate that the Windmill-task is a valid tool to assess MMs in children with unilateral CP and has additional advantages especially related to the sensitivity of detecting MMs.

### This chapter is based on:

Zielinski, I.M., Steenbergen, B., Schmidt, A., Klingels, K., Simon-Martinez, C., De Water, P., & Brian, H. (under review). A new quantitative and objective assessment for mirror movements in unilateral cerebral palsy: introduction of the Windmill-task. *Arch Phys Med Rehabil* (under review).



## 2.1 INTRODUCTION

Mirror movements (MMs) are involuntary movements that accompany and mirror voluntary movements of homologous muscles on the opposite side of the body (Woods & Teuber, 1978). They commonly occur during typical development and mostly appear during hand movements (Cox, Cincotta, & Espay, 2012). In typical development MMs gradually disappear during the first decade of life (Connolly & Stratton, 1968). However, in children with unilateral cerebral palsy (uCP), MMs are frequently more pronounced and persistent (Carr, 1996; Koerte et al., 2010; Woods & Teuber, 1978). Studies on these “pathological” MMs have predominantly focussed on the underlying mechanisms (Carr, 1996; Staudt et al., 2004; Woods & Teuber, 1978) and their impact on upper-limb function (Adler, Berweck, Lidzba, Becher, & Staudt, 2015; Holmstrom et al., 2010; Islam, Gordon, Skold, Forssberg, & Eliasson, 2011; Klingels et al., 2015; Kuhtz-Buschbeck, Sundholm, Eliasson, & Forssberg, 2000).

Two general mechanisms for MMs are typically described. First, the motor cortex of the less-affected hemisphere also controls the affected side (AS) by an uncrossed corticospinal tract to the ipsilateral side of the spinal cord. This ipsilateral projection might depend on preserved ipsilateral projections to the AS or a branching of crossed corticospinal fibres (Carr, Harrison, Evans, & Stephens, 1993; Cox et al., 2012). These ‘re-wiring’ profiles are suggested to cause MMs in both, but especially the AS (Friel, Williams, Serradj, Chakrabarty, & Martin, 2014; Jaspers, Byblow, Feys, & Wenderoth, 2015; Norton, Thompson, Chan, Wilman, & Stein, 2008; Staudt et al., 2004). Second, there is widespread and bilateral cortical activation that occurs when actively moving the AS, caused by sensorimotor impairments of this hand and thus increased effort required to move. This lack of ‘inter-hemispheric inhibition’ is proposed to cause MMs in the less-AS (Jaspers et al., 2015; Klingels et al., 2015; Staudt et al., 2004). MMs occurring in only the less-AS are therefore thought to be related to sensorimotor impairments of the AS, while MMs in the AS have been proposed to indicate one motor cortex controlling both hands. Accordingly, MMs detected in the AS may act as a “... low-risk clinical biomarker to probe corticospinal tract wiring” (Jaspers et al., 2015), compared to more invasive and time-consuming neuroimaging methods (e.g. TMS, fMRI). If accurate, this would have a significant impact on clinical practice, allowing development of individualized therapy programmes based on the child’s ‘re-wiring’ profile<sup>16</sup>. However, to date, studies using various assessments for MM detection report conflicting results, challenging its usefulness to probe cortical ‘re-wiring’ (Holmstrom et al., 2010; Staudt et al., 2012; Verstynen et al., 2007).

With respect to the impact of MMs on upper-limb function, results generally point to an association between pronounced MMs and impaired upper-

limb function (Adler et al., 2015; Klingels et al., 2015; Kuhtz-Buschbeck et al., 2000), especially in bimanual tasks. However, findings are also not ubiquitous. Some studies report correlations between impaired bimanual performance and MMs in both the affected and less-AS (Adler et al., 2015; Kuhtz-Buschbeck et al., 2000), while others report an association only for MMs appearing in the less-AS (Klingels et al., 2015; Zielinski et al., 2016). Other studies report little association between MMs and bimanual performance (Holmstrom et al., 2010; Islam et al., 2011), while some studies even indicate that MMs might assist movements of the AS (Klingels et al., 2015; Zielinski et al., 2016). These contradicting results might be explained by the different methods to assess MMs. To advance our understanding of the mechanism of MMs and their impact on upper-limb function in uCP, it is essential to apply a standardized, objective, valid, and reliable clinical assessment (Jaspers et al., 2015; Klingels et al., 2015).

The universal standard for clinically evaluating MMs is a qualitative observational method based on the Woods and Teuber scale (W&T) (Woods & Teuber, 1978). It is based on visual evaluation of MMs of one hand during voluntary movements of the other hand (Woods & Teuber, 1978). Owing to its easy application and clinical utility, the W&T is widely used in studies on uCP, offering the potential opportunity for comparison of data (Adler et al., 2015; Holmstrom et al., 2010; Klingels et al., 2015). However, its subjective scoring procedure and lack of published guidelines for administration hinders comparison of data. In fact, there is a broad variation in administration and inconsistent use of manual tasks across studies (Holmstrom et al., 2010; Klingels et al., 2015; Woods & Teuber, 1978). The latter is especially problematic, as the severity of MMs is known to be dependent on the type and complexity of movements (Koerte et al., 2010; Woods & Teuber, 1978).

The observational nature of the W&T may impact on the accuracy of detecting MMs, and thereby test validity. Likewise, test sensitivity may be suboptimal, thus increasing the likelihood of not detecting MMs that are actually present. This might be due to the extent of mirroring activity (too subtle for visual detection), or the orientation of the hand under observation (e.g. persistent wrist flexion of the AS). In addition, test specificity may be compromised, in this case increasing the chance of observing MMs that are not truly mirroring the intended movement of the active hand. Finally, as the close matching of both hand movements in time is not feasible using the W&T, MMs cannot be distinguished from other extraneous movements. These cumulative shortcomings might explain the conflicting results related to the use of MMs to probe cortical re-wiring (Holmstrom et al., 2010; Staudt et al., 2012; Verstynen et al., 2007) as well as to the impact of MMs on upper-limb functioning (Adler et al., 2015; Holmstrom et al., 2010; Islam et al., 2011; Klingels et al., 2015; Kuhtz-Buschbeck et al., 2000).



To overcome the shortcomings of the W&T, simultaneous EMG recordings of homologous muscles during single hand movements have been applied in earlier studies (Carr, 1996; Kuhnke et al., 2008; Staudt et al., 2004). However, it can be argued that these recordings rather reflect mirror recruitment (muscle activity), than actual MMs. Furthermore, the clinical utility remains questionable. To objectively assess actual MMs while being clinically applicable, simultaneous grip-force measurements of both hands during single-hand movements might offer a solution (Carr, 1996; Kuhnke et al., 2008; Staudt et al., 2004).

Here we introduce a new, easy to use, objective, standardised, and quantitative assessment for MMs known as the Windmill-task, using grip-force data of both hands during single hand squeeze movements. Quantitative data from the Windmill-task are compared to observation-based data from the W&T on a group level to examine concurrent validity and estimate differences in sensitivity and specificity for MM detection at an individual level. It is hypothesized the Windmill-task is a valid tool to assess MMs, and furthermore exhibits higher sensitivity and specificity compared to individual data of the W&T.

## 2.2 METHODS

### 2.2.1 Participants

Children with uCP (age:6-15y) were recruited from Monash Children's Hospital, Melbourne, Australia from 11-2015 to 04-2016 as a convenience sample from a cohort of children previously recruited for a larger study (ACTRN12614000631606). Inclusion criteria for this prospective cohort were diagnosis of uCP with a Manual Ability Classification System (MACS) (Eliasson et al., 2006) level I-III. The study was approved by Monash Health Human Research Ethics Committee (HREC:12167B). Informed consent was obtained prior to enrolment in the study.

### 2.2.2 Observational-based assessment of MMs: W&T

Hand movements were videotaped during three unimanual tasks: 1) fist opening and clenching (W&Tfist), 2) finger opposition (fingers sequentially touch the thumb; W&Topposition), and 3) finger tapping (fingers sequentially tap on the table; W&Ttapping) (Klingels et al., 2015; Kuhtz-Buschbeck et al., 2000). Each task was repeated five times for each hand with the less-AS first (MMs in AS), followed by the AS (MM in less-AS).

The occurrence of MMs was evaluated for each task separately based on a four-point-scale, from 0 (no clear imitative movement) to 4 (movement equal to that expected for intended hand) (Woods & Teuber, 1978), yielding a total score between 0 and 12 (W&Ttotal) for each condition separately (affected-hand-

moving vs. less-AS-moving). Videos were scored by an experienced occupational therapist blinded to the Windmill-task data.

### 2.2.3 Quantitative assessment of MMs: Windmill-task

The Windmill-task is a custom-made, repetitive squeezing task developed to quantitatively detect MMs by simultaneously measuring the continuous grip-force of both hands via two grip-force transducers (equipped with micro load cells: 0-20kg; weight: 45g, circumference:10cm) between thumb and index- plus middle-finger (pinch-grip). When the child was not able to apply this pinch-grip, additional fingers were allowed to stabilize the grip (adapted-grip). Grip-forces were recorded with a peak of 200N, with an accuracy of 0,2N, and a sampling rate of 50Hz. The analog signal was amplified using an INA125p amplifier and converted into a digital signal using Arduino Board Nano®. A customized written script (Psychopy© v1.83) was used to calibrate the device, set task parameters, run the experiment, and record the data.

Prior to the MM assessment, the maximal voluntary contraction (MVC) of the pinch-grip (or adapted-grip) was assessed for each hand separately. One grip-force transducer was placed in the child's hand and the child was asked to press as hard as possible. This was repeated three times, first with the less-AS followed by the AS. The average of the three squeezes was used as the MVC per hand.

For the MM assessment, children were instructed to hold the transducers in both hands with their forearms or elbows supported on the table. The grip of the less-AS was always matched to the grip of the AS (pinch-grip vs. adapted-grip). One transducer was connected to a miniature windmill (**figure 2.1**). The motor of the windmill started rotating once the connected transducer was pressed beyond a threshold (20% of MVC). To speed up rotation, the child's grip needed to return to a lower threshold by loosening the grip (17.5% of MVC) and again reach the upper threshold within 1000ms, so that a repetitive squeezing pattern was induced ( $\geq 1$ Hz frequency). Children were instructed to repetitively squeeze the connected transducer with the active hand ('rotate the windmill as fast as possible') and simply lift and hold the second transducer with the passive hand.

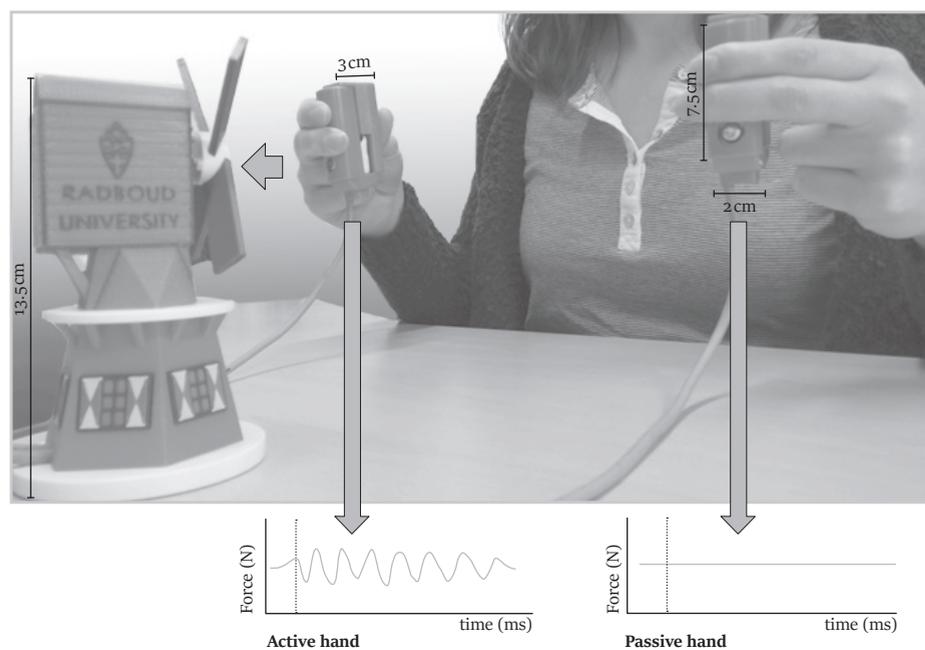
Children performed 10 unimanual squeezing trials with each hand (10sec; 5sec rest between trials). A pre-recorded voice indicated the start and stop for rotating the windmill. The less-AS was tested first. The visual feedback from the rotating windmill guided the children through the task, but instructions contained no information about MMs.

#### 2.2.3.1 Data processing

The trial started 500ms after the 'start' signal and lasted 10 seconds to control for the slight delay following the auditory 'start' and 'stop' signals. To quantify



MMs the force pattern of both hands during each squeezing session (10×10sec) was cross-correlated (Nelson-Wong, Howarth, Winter, & Callaghan, 2009). Both grip-force signals were correlated by iteratively shifting one signal forwards in time against the other signal. A correlation-coefficient (Pearson's  $r$ ) was calculated for each phase shift (steps of 20ms), resulting in a time series of  $r$  values. This time series represented a correlation function at each increment of the phase shift between the two signals. The maximum correlation-coefficient of this function was used as index of similarity between the signals. This value can be directly related to a time-lag value showing the match in timing between the two signals. A negative time-lag indicates the passive-hand-movement lagging behind the active-hand-movement. A positive time-lag indicates the active-hand-movement lagging behind the passive-hand-movement. Further, mean grip-force of the passive hand during each squeezing session was calculated. To ensure a sufficient signal to noise ratio, only peaks exceeding the maximum noise values (0.4N) were considered as mirror activity, and used.



**Figure 2.1. Schematic of the Windmill-task.** Participant performing the Windmill-task with the right-hand actively squeezing. The participant is holding the grip-force transducers in each hand, with the right transducer being connected to the windmill. Both transducers are connected to a computer, digitizing and storing the data recorded of both hands' time-locked grip-force (N). This figure represents a squeezing pattern with the passive hand showing no MMs.

In a second step, the average of the maximum correlation-coefficient (CCCmax) of valid trials (>5 squeezes with active hand reaching at least 10% of the MVC) was calculated. Hence, CCCmax is indicative of the intensity of MMs, with  $r=0$  reflecting no mirroring of the passive hand during active-hand-movement, and  $r=1$  reflecting that the passive hand is performing the exact same movement as the active hand. Whenever CCCmax was greater than or equal to 0.30, children were classified as having MMs, as correlations smaller than 0.30 are known to be negligible (Mukaka, 2012). CCCmax calculations were performed for both conditions separately (AS-moving vs. less-AS-moving).

#### 2.2.4 Data analysis

Shapiro-Wilk tests indicated that of the four variables (1.CCCmax AS-moving, 2.CCCmax less-AS-moving, 3.W&Ttotal AS-moving, and 4.W&Ttotal Less-AS-moving) one variable (W&Ttotal less-AS-actively-movement) was not normally distributed. Additionally, the number of participants was small ( $N<30$ ), therefore non-parametric tests were used to compare outcome measures of both assessments.

To assess the concurrent validity of the Windmill-task, MM scores on the Windmill-task (CCCmax) were correlated to the total scores on the W&T (W&Ttotal) for both conditions separately (AS-moving vs. Less-AS-moving) using non-parametric one-tailed Spearman-rank ( $\rho$ ) correlations. Correlation coefficients greater than 0.70 were considered as high, 0.50 to 0.70 as moderate, 0.50 to 0.30 as low and less than 0.30 as negligible (no MMs) (Mukaka, 2012).

To estimate the sensitivity of the W&T data as compared to the Windmill-data, the percentage of children showing MMs on the Windmill-task ( $\text{CCCmax} \geq .30$ ), but no MMs on the W&T ( $\text{score} \leq 1$ ) were calculated. This was performed for each W&T subscale (W&Tfist, W&Topposition, W&Ttapping) separately and in a second step, these percentages were averaged across subscales.

To estimate the specificity, the percentage of children showing MMs on the W&T subscales ( $\text{scores} \geq 2$ ) (Klingels et al., 2015), but no MMs on the Windmill-task ( $\text{CCCmax} \leq .30$ ) was calculated. Again, this was performed for each subscale and averaged afterwards.

## 2.3 RESULTS

### 2.3.1 Participants

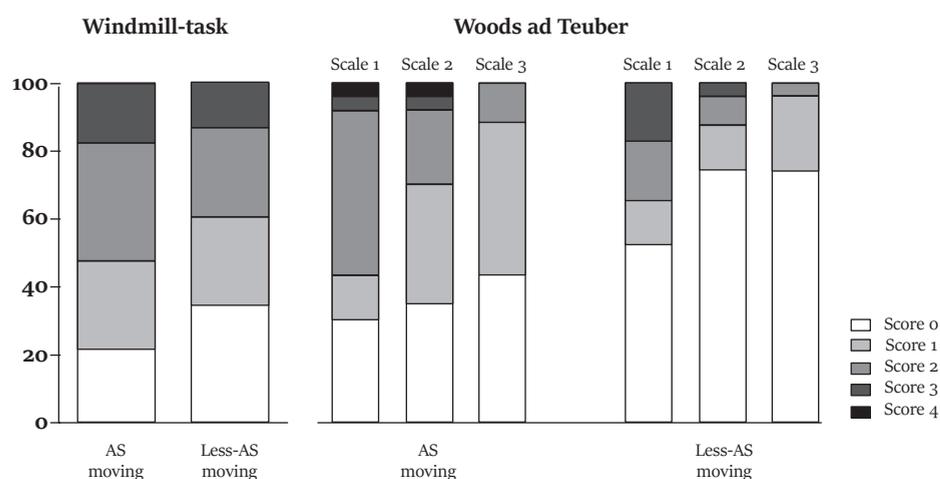
Twenty-three children with uCP participated (13 girls; 16 right-AS; mean age=10y,5m; SD=2y7m; range:6y,4m–14y,12m; MACS I:N=5; MACS II:N=18).



Mean time since last Botulinum-toxin-A injection was 1y7m (range:2m-6y8m). Two children had previous upper-limb surgery (>2 years before assessment).

### 2.3.2 Mirror Movements

The median value of MMs assessed by the W&T (W&Ttotal) is 3 for the AS-moving and 2 for the less-AS-moving condition. For the Windmill-task (CCCmax) the median values are 0.509 for the AS-moving and 0.441 for the less-AS-moving condition. A distribution of MMs for both assessments and both conditions is provided in figure 2.2.



**Figure 2.2. Distribution of MM scores.** Distribution of the MM scores across all participants for both assessments (Windmill-task vs. W&T; separated by subscales) and both conditions (AS-moving vs. Less-AS-moving). Division of scores of the Windmill-task (CCCmax) is based on a generally accepted division of correlation coefficients: Score 0: .00-.30, Score 1: .31-.50, Score 2: .51-.70, Score 3: .71-.90, Score 4: .90-1.00. The subscales of the Woods and Teuber are: Scale 1 for fist opening and clenching, Scale 2 for finger opposition, and Scale 3 for finger tapping. AS, affected side.

Using the Windmill-task, the cross-correlation data of all children that showed MMs (CCCmax >0.30) when moving their less-AS had a negative (N=13, median=-10) or zero time-lag (N=2), indicating that the AS-movements are either lagging behind the less-AS-movements or happening simultaneously. When actively moving the AS, 4 children that showed MMs (CCCmax >0.30) had a positive time-lag (median=16), indicating that in these 4 children the “active” AS-movements are actually lagging behind the less-AS movements.

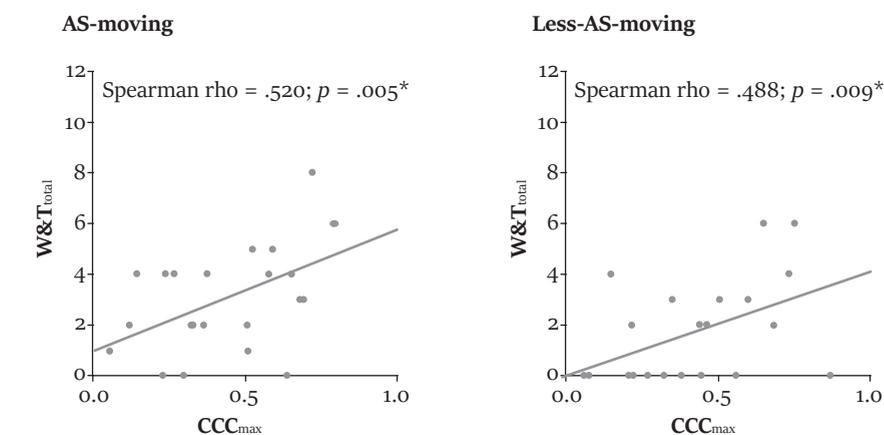
### 2.3.3 Concurrent validity

Evaluation of concurrent validity demonstrated significant correlations between CCCmax and W&Ttotal for both conditions (AS-moving vs. Less-AS-moving). Correlation for the “AS-moving” condition were moderate (rho=.520; p=.005) and low for the “less-AS-moving” condition (rho=.488; p=.009; figure 2.3).

### 2.3.4 Sensitivity & Specificity

Results for sensitivity demonstrated that for every subscale of the W&T, some children displayed MMs on the Windmill-task (CCCmax >.30) which were not evident from the W&T subscales (score≤1). In the AS-moving condition, 27.5% of children demonstrated this pattern (W&Tfist:17.4%, W&Topposition:30.4%, W&Ttapping:34.8%) and 40.6% of the cases in the less-AS-moving condition (W&Tfist:21.7%, W&Topposition:52.2%, W&Ttapping:47.8%).

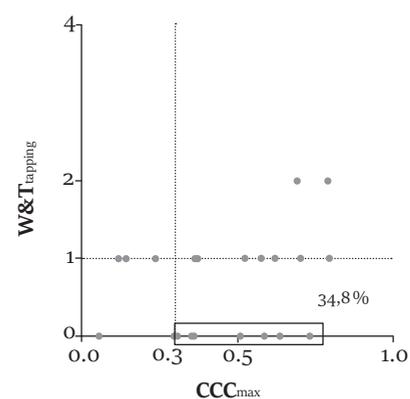
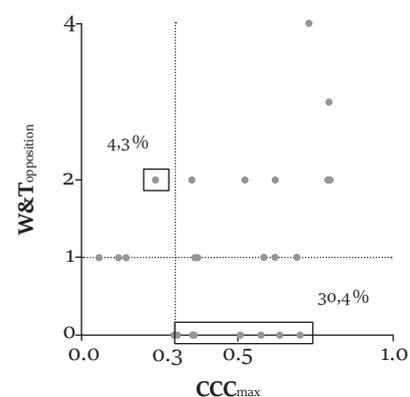
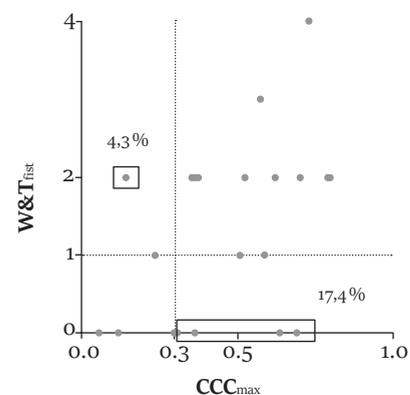
Results for specificity demonstrated two children with clear MMs on at least one of the W&T subscales (>1), but no MMs on the Windmill-task (CCCmax≤.30). This leads to an average of 2.9% showing this pattern in the “AS-moving” (W&Tfist:4.3%, W&Topposition:4.3%, W&Ttapping:0%) and 1.4% in the “less-AS-moving” condition (only W&Ttapping:4.3%). Figure 2.4. depicts the individual scores for every subscale of the W&T in direct comparison to the individual CCCmax while highlighting children that were assessed inconsistently across both assessments.



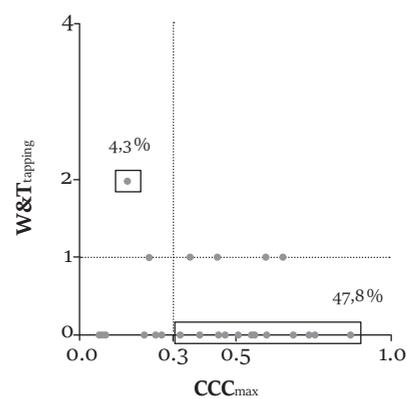
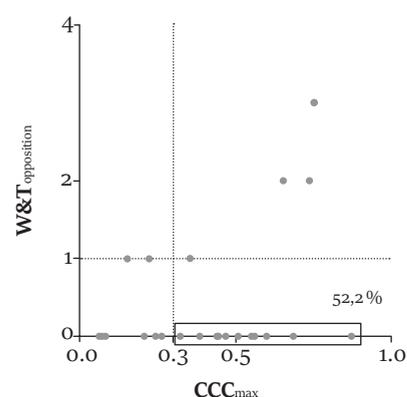
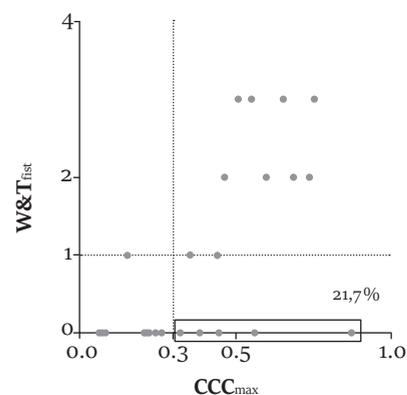
**Figure 2.3. Correlations between outcome measures of both MM assessments.** Depicted are Spearman-rank correlations (rho) between CCCmax and W&Ttotal values for both conditions separately (AS-moving vs. Less-AS-moving), with \* representing significance (p<0.05). AS, affected side.



## AS-moving



## Less-AS-moving



**Figure 2.4. Individual data comparison between outcome measures of both MM assessments.**

Depicted are the individual data points per participant comparing the outcomes of the Windmill-task (CCC<sub>max</sub>) to the outcomes of the separate subscales from the W&T (W&T<sub>fist</sub>, W&T<sub>opposition</sub>, W&T<sub>tapping</sub>) for both conditions separately (AS-moving vs. Less-AS-moving). Dashed lines indicate the cut-off score for MMs for both assessment tools (W&T=1; Windmill-task=0.3). Framed data points indicate children that were assessed inconsistently across both assessments based on the cut-off score for mirror movements of both assessment tools. Corresponding percentages of the children being assessed inconsistently are presented. AS, affected side.



## 2.4 DISCUSSION

We introduced a new method to quantify MMs and compared its data to the commonly used W&T data (Woods & Teuber, 1978). Outcomes provide support to the Windmill-task as a valid, objective, standardised, and quantitative assessment of MMs in children with uCP. Specifically, comparison to the W&T demonstrated that both measures detect involuntary and simultaneous movements of the mirroring hand, confirming the concurrent validity of the Windmill-task. Correlations, however, were found to be moderate to low. The comparison of sensitivity and specificity of the W&T to the Windmill-task revealed a likely explanation for these findings. With respect to specificity, only two children displayed MMs on the W&T, but not on the Windmill-task, indicating only a minor advantage of the Windmill-task regarding test specificity. However, results were different for sensitivity. When actively moving the AS, 27.5% of the children displayed MMs in the less-AS using the Windmill-task, but none of them on the W&T. For assessment of MMs in the AS, this percentage increased to 40%. These combined findings indicate that visual observation with the W&T might lead to an underestimation of mirror activity, and thus a reduced sensitivity in detecting MMs. The use of simultaneous grip-force recordings using the Windmill-task seems to enhance sensitivity for detecting MMs in children with uCP.

The objective nature, standardized administration procedure, and improved sensitivity of the Windmill-task supports its use in the future. Previous studies on the impact of MMs on upper-limb functions or the underlying mechanisms causing MMs are not uniform. This is most likely due to the varying methods to assess MMs and the subjective nature of the W&T. Understanding the impact of MMs on upper-limb function has the potential to improve therapy recommendations based on the individual's MM profile (Staudt, 2016). With respect to the underlying mechanisms, it still needs to be established if MMs appearing in the AS are indicative of one motor cortex controlling both hands (Friel et al., 2014; Jaspers et al., 2015; Norton et al., 2008; Staudt et al., 2004).

If neuroimaging outcomes (e.g. TMS, fMRI) are found to be consistent with outcomes from the Windmill-task this would allow clinicians to quickly and easily assess the ‘re-wiring’ profile of children and allow treatment programs to be individualized based on this profile (Kuhnke et al., 2008). Currently, no clinical outcome measure has been found to reliably detect the presence of ipsilateral projections in children with uCP. A further potential advantage of the more sensitive Windmill-task data lies in the opportunity of detecting subtle changes in MMs following different therapy programmes.

The clinical utility of an assessment is an important feature and might favour the use of the W&T. However, its lack of sensitivity demonstrated in this study shows that despite its ease of administration, up to 40% of children with uCP were classified as not having MMs based on the W&T, even though these were actually present. If MMs appearing in the AS are indeed indicative of preserved ipsilateral cortical projections (Friel et al., 2014; Jaspers et al., 2015; Norton et al., 2008; Staudt et al., 2004), then our preliminary data suggests that 40% of the children would have been classified with the incorrect ‘re-wiring’ profile using the W&T. Furthermore, the Windmill-task also present some potential advantages for clinical application. The turning of the windmill provides direct feedback so that the task of repetitively moving the hand becomes meaningful and motivating. This design, along with a short, easy and highly standardised assessment procedure supports the clinical utility of the Windmill-task.

Aside from improved sensitivity to detect MMs, the Windmill-task captures the individual strength and timing of these movements. This information can potentially provide evidence for the strategic use of MMs, as it has earlier been reported (Zielinski et al., 2016). The information of the timing of the mirroring signal might also help to identify different underlying mechanisms of MMs (interhemispheric inhibition vs. ipsilateral corticospinal projections). How to use this time-lag information for greater understanding of MMs requires further investigation.

#### 2.4.1 Study limitations

This study is limited by the small number of participants and lack of inclusion of children at MACS level III. Furthermore, reliability of the Windmill-task requires investigation, especially via test-retest reliability calculation. Finally, reference scores need to be developed by assessing MMs in typically developing children, to inform on how strong MMs need to be to be considered as “pathological” and up to which age a certain amount of MMs can be considered as physiological.

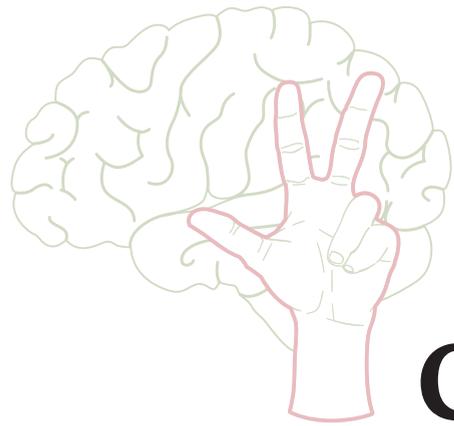
#### 2.4.2 Conclusions

To conclude, this study demonstrates that the Windmill-task is a valid, standardized, objective, and motivating assessment tool to assess MMs in children with uCP as well as quantifying the timing and intensity of these movements. Outcomes demonstrated enhanced sensitivity and specificity when compared to the observational-based W&T.

### 2.5 ACKNOWLEDGEMENTS

We want to thank all the children and their families who took part in this study. We also want to kindly acknowledge Mark van de Hei from the technical support group of the Radboud University Nijmegen for his valuable and professional assistance in developing the Windmill-task. This work is part of a doctoral dissertation that was supported by grants from (in alphabetical order): Hersenstichting Nederland, Johanna KinderFonds, Stichting Rotterdams Kinderrevalidatie Fonds Adriaanstichting, Phelps Stichting voor Spastici, and Revalidatiefonds. The authors have stated that they had no interests which might be perceived as posing a conflict or bias.





# CHAPTER

# III

## Event-Related Potentials During Target-response Tasks to Study Cognitive Processes of Upper Limb Use in Children with Unilateral Cerebral Palsy

### Abstract

Unilateral Cerebral Palsy (CP) is a neurodevelopmental disorder that is a very common cause of disability in childhood. It is characterized by unilateral motor impairments that are frequently dominated in the upper-limb. In addition to a reduced movement capacity of the affected upper limb, several children with unilateral CP show a reduced awareness of the remaining movement capacity of that limb. This phenomenon of disregarding the preserved capacity of the affected upper limb is regularly referred to as developmental disregard. Different theories have been postulated to explain developmental disregard, each suggesting slightly different guidelines for therapy. Still, cognitive processes that might additionally contribute to developmental disregard in children with unilateral CP have never been directly studied. The current protocol was developed to study cognitive aspects involved in upper limb control in children with unilateral CP with and without developmental disregard. This was done by recording Event-Related Potentials (ERPs) extracted from the ongoing EEG during target-response tasks asking for a hand-movement response. ERPs consist of several components, each of them associated with a well-defined cognitive process (e.g., the N1 with early attention processes, the N2 with cognitive control and the P3 with cognitive load and mental effort). Due to its excellent temporal resolution, the ERP technique enables to study several covert cognitive processes preceding overt motor responses and thus allows insight into the cognitive processes that might contribute to the phenomenon of developmental disregard. Using this protocol adds a new level of explanation to existing behavioral studies and opens new avenues to the broader implementation of research on cognitive aspects of developmental movement restrictions in children.

### This chapter is based on:

Zielinski, I.M., Steenbergen, B., Baas, C.M., Aarts, P., & Jongsma, M.L.A. (2016). Event-related Potentials During Target-response Tasks to Study Cognitive Processes of Upper Limb Use in Children with Unilateral Cerebral Palsy. *J Vis Exp*, 107, e53420, doi:10.3791/53420. Published. Video Link: <http://www.jove.com/video/53420/>



### 3.1. INTRODUCTION

Cerebral Palsy (CP) is defined as a group of neurodevelopmental disorders related to movement and posture impairments that are caused by disturbances to the developing fetal or infant brain (Rosenbaum et al., 2007). Even though these impairments are non-progressive, they are associated with lifelong disabilities (Aisen et al., 2011; Rosenbaum et al., 2007). One of the most common subtypes of CP is unilateral CP, accounting for more than one third of all cases (Odding, Roebroek, & Stam, 2006). It is characterized by pronounced motor deficits on one side of the body that are frequently more prominent in the upper limb (Odding et al., 2006; Rosenbaum et al., 2007). Next to the reduced movement capacity of the affected upper limb, several children with unilateral CP also seem to fail to spontaneously use the remaining capacity of their affected hand (AS) in daily life (Boyd et al., 2010; Deluca, Echols, Law, & Ramey, 2006; Hoare, Wasiak, Imms, & Carey, 2007; Houwink, Aarts, Geurts, & Steenbergen, 2011; Taub, Ramey, DeLuca, & Echols, 2004). This disregard of the remaining capacity of the affected upper limb in unilateral CP has frequently been referred to as developmental disregard (Boyd et al., 2010; Deluca et al., 2006; Hoare et al., 2007; Houwink et al., 2011; Sutcliffe, Logan, & Fehlings, 2009; Taub et al., 2004; Zielinski, Jongasma, Baas, Aarts, & Steenbergen, 2014; Zielinski, Steenbergen, Baas, Aarts, & Jongasma, 2014).

Apart from the traditional explanations of developmental disregard based on behavioral reinforcement theories (Taub et al., 2004), more recent studies have emphasized the importance of cognitive factors for understanding developmental disregard (Houwink et al., 2011; Sutcliffe et al., 2009; Zielinski, Jongasma, et al., 2014; Zielinski, Steenbergen, et al., 2014). These theories are based on the idea that certain motor deficits in children with unilateral CP are actually caused by dysfunctional cognitive processes that are necessary for successful goal-directed motor behavior, rather than by the movement restrictions itself. In this respect developmental disregard has been compared to the phenomenon of post-stroke motor neglect, suggesting visuo-spatial attention deficits (Saevarsson, 2013; Sutcliffe et al., 2009; Zielinski, Steenbergen, et al., 2014). Alternatively, it has been proposed that the lack of use of the AS during crucial developmental periods does not only affect motor development, but is also associated with a delay of cognitive processes related to motor behavior (Houwink et al., 2011; Zielinski, Jongasma, et al., 2014).

Although developmental disregard has been extensively described in the literature and different theories have emphasized the possible contribution of altered cognitive processes (Houwink et al., 2011; Sutcliffe et al., 2009; Zielinski, Jongasma, et al., 2014; Zielinski, Steenbergen, et al., 2014), these cognitive

processes related to goal-directed motor behavior have never been directly studied in unilateral CP. The current protocol was developed to assess cognitive aspects related to upper limb control in children with unilateral CP. The protocol describes the use of Event-Related Potentials (ERPs) extracted from the ongoing EEG during manual target-response tasks.

ERPs offer the unique opportunity to measure neural responses that are time locked to distinct processing stages related to an overt response. That is, they allow to study different cognitive processes related to goal directed motor responses, such as response selection, response preparation, and response inhibition processes. Furthermore, ERPs consist of several components, each of them associated with different cognitive processes (e.g., the N1 with early attention processes, the N2 with cognitive control and the P3 with cognitive load and mental effort). Likewise, using ERPs during a simple manual target-response task enables us to directly study different cognitive processes related to different processing stages of upper limb control in children with unilateral CP with and without developmental disregard.



### 3.2. PROTOCOL

Approval for different experiments using this experimental design was obtained from the local Ethical Committee of the Faculty of Social Sciences (ECSW) from the Radboud University Nijmegen as well as by the regional Medical Research Ethics Committee, the CMO Arnhem-Nijmegen (Registration number: 2012/049; NL nr.: 39607.091.12).

#### 3.2.1 Participants

1. Only include children that are diagnosed with unilateral CP as diagnosed by a medical specialist (i.e., neurologist, pediatrician).

NOTE: The ERP protocol to assess cognitive aspects underlying upper limb motor control has been developed for children with unilateral CP, but is not restricted to this group only.

2. Only include children older than 5 years old (Zielinski, Jongasma, et al., 2014; Zielinski, Steenbergen, et al., 2014).

NOTE: Younger children might not be able to pay attention to the task during the whole procedure.

3. Exclude children with severe visual and auditory impairments.

NOTE: It is recommended to include children who only have slight visual and auditory impairments if they are able to perform the task and show no differences with respect to response speed or accuracy compared to children

participating without visual impairments. However, possible impairments need to be specified in a later report and possibly controlled for in the final analyses.

4. Finally, exclude children that are unable to comply to the task due to possible cognitive impairments and/or behavioral disorders.

5. Prior to the EEG measurement, have a trained occupational therapist and/or physiotherapist assess the children with respect to the manual ability (MACS) of the AS (Eliasson et al., 2006) as well as the possible presence of developmental disregard.

a) To assess developmental disregard, calculate an index comparing the typical amount of use of the AS and arm during spontaneous daily activities (performance) with the quality of hand/arm skill under ideal conditions (capacity) (Houwink, Geerdink, Steenbergen, Geurts, & Aarts, 2013; Sutcliffe et al., 2009). To do so use valid and reliable tests for assessing hand capacity and hand performance (Klingels et al., 2010). Recommendation: Use indices that have previously been used and preferably validated (Houwink et al., 2013; Sutcliffe et al., 2009). The use of the VOAA-DDD-R for determining developmental disregard is highly recommended, as the psychometrics of this task have been published (Houwink et al., 2013).

b) Since manual ability as well as developmental disregard may change over time (e.g., due to therapy results), schedule this assessment shortly before or after the EEG measurement (preferably within the same week).

6. Furthermore, collect demographical data of the children (e.g., age, gender, medication and seizure history) to be able to take these variables into account (e.g., when matching groups or interpreting results).

### 3.2.2 Developing the Visual Target-response Task

1. Write a script for the computerized visual target-response task. See Supplemental Code Files for an example script.

a) To present the visual stimuli on a computer screen, use a stimulus delivery and experimental control program that is time accurate enough to send time-locked markers to the EEG signal whenever a stimulus is presented. For registering responses, use a device that registers time accurate (1 msec) button presses and delivers related stimulus markers to the EEG computer.

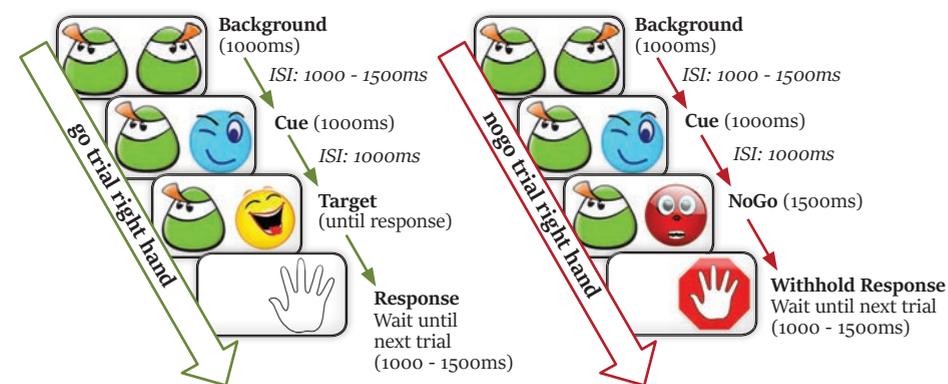
b) For visual stimuli use clear shapes presented on a white background that are easy to recognize (examples are shapes or simple objects) and easy to distinguish (e.g., based on color, shape, size). Recommended are simple graphic designs instead of complex stimuli like photographs.

c) Follow the recommendations below to design ERP experiments for children. Note: Designing ERP experiments for children is often challenging, because children may have a limited capacity to comply to long repetitive experiments.

aa) Present stimuli that are big enough to be easily recognized by the child (recommended size: 7 x 7 cm).

bb) Furthermore, preferably use stimuli that are attractive for the children to keep children's attention to the task (e.g., smiley's).

**Figure 3.1.** displays an experimental protocol that can be used in young children to study different cognitive processes during simple hand movements.



**Figure 3.1.** Example of a target-response task experiment suitable for a broad age range. The example consists of visual stimuli of pairs of smiley figures presented against a white background. Two different types of trials are shown: target-trials for the right hand (left) and nogo-trials for the right hand (right). Both trials include background- and cue- stimuli. ISI, inter-stimulus interval.

d) Make sure to include clearly different stimuli for right vs. left hand movement initiation. This allows comparing the distinct processing stages involved in movements of both the affected and the less-AS in children with unilateral CP. This within-subject design allows participating children to serve as their own control participant (AS vs. less-AS).

aa) Recommendation: Present stimuli to the left or the right side of the screen to respectively induce left or right hand movements. To control for stimulus lateralization, include a background-stimulus to the other side of the screen.

- e) Present the same amount of stimuli to the affected as to the less affected side. Use a minimum of 20 repetitions per stimulus-category to allow averaging of the Event-Related Potentials (Zielinski, Steenbergen, et al., 2014). However, ensure that the length of the experiment does not exceed 10 min as children might not be able to attend to a longer task procedure. Earlier ERP studies in children with CP report protocols between 4.5 and 10 min (Maitre, Barnett, & Key, 2012; Maitre et al., 2014; Zielinski, Jongsma, et al., 2014; Zielinski, Steenbergen, et al., 2014). If a longer protocol is used, allow the child to take a break after 10 min and continue afterwards.
2. For recording the responses to the presented stimuli, provide two big response buttons (recommended: diameter: 9.5 cm; height: 5.5 cm) with very low response force requirements to make sure that even children with substantial movement restrictions are easily able to respond.
3. Adapt the study paradigm to measure cognitive processes of interest and rule out possible alternative explanations of the data.
4. Example of experimental design: Cued Go/Nogo Task (**Figure 3.1.**)
  - a) For a cued go/nogo task to study response selection, response preparation as well as response inhibition, present four different types of visual stimuli: background-stimuli (implemented as a baseline measure of visual stimulus processing), cue-stimuli for the left and the right side (implemented to study stimulus selection processes), go/target-stimuli for the left and the right side (implemented to study response preparation processes) and nogo-stimuli for the left and the right side (implemented to study response inhibition processes).
  - b) Recommendation: Present background- and cue-stimuli for 1,000 msec. Present target- stimuli until a response is made. Present nogo-stimuli for 1,500 msec. Keep the inter-stimulus interval (ISI) between cue- and target/nogo-stimuli fixed (recommended: 1,000 msec). Keep the ISI after each correct response following target or go stimuli random (recommended: between 1,000-1,500 msec).
  - c) In order to avoid confounding oddball activity, present target- and nogo-stimuli in an equiprobable manner. NOTE: Although this paradigm diminishes effects of inhibition on the nogo-stimuli (Lavric, Pizzagalli, & Forstmeier, 2004), it allows a more direct comparison of the ERPs elicited by both the target- and nogo-stimuli.
  - d) After each correct response to a target-stimulus or a correct inhibited response to a nogo-stimulus, present some form of motivating feedback (e.g., a short laughing sound).

### 3.2.3 The Data Acquisition System

NOTE: For measurements with children a mobile EEG lab is highly recommended. A mobile lab allows conducting the study in an environment that is familiar to the child (e.g., school, rehabilitation centre, home). If a mobile EEG setup is not available, ensure that the child is comfortable with the testing environment. During EEG preparation it is recommended to have some distraction/entertainment for the child (e.g., watching a film).

1. Use two computers: one presenting the stimuli and a second computer to record and digitize the EEG. Connect the computers so that event codes can be sent to the EEG digitization computer whenever an event of some sort occurs (e.g., stimulus, response).
2. When choosing the electrode-amplifier system use an active electrode system (highly recommended) to reduce the signal to noise ratio.

NOTE: Active electrodes improve the signal to noise ratio, because the first step of amplification is conducted at the site of the electrode, thus minimizing the impact of intervening noise signals. A great benefit of this active electrode system is that an electrically isolated chamber is not necessary during EEG recording allowing to measure in almost every environment.

- a) Even with an active electrode system, be careful not to measure close to electrical or mechanical devices.
3. Choose the number of the electrodes based on the research question and study population. A 32-channel electrode system (together with a 32-channel EEG amplifier) is sufficient for studying most cognitive processes related to different processing stages of upper limb control in children.

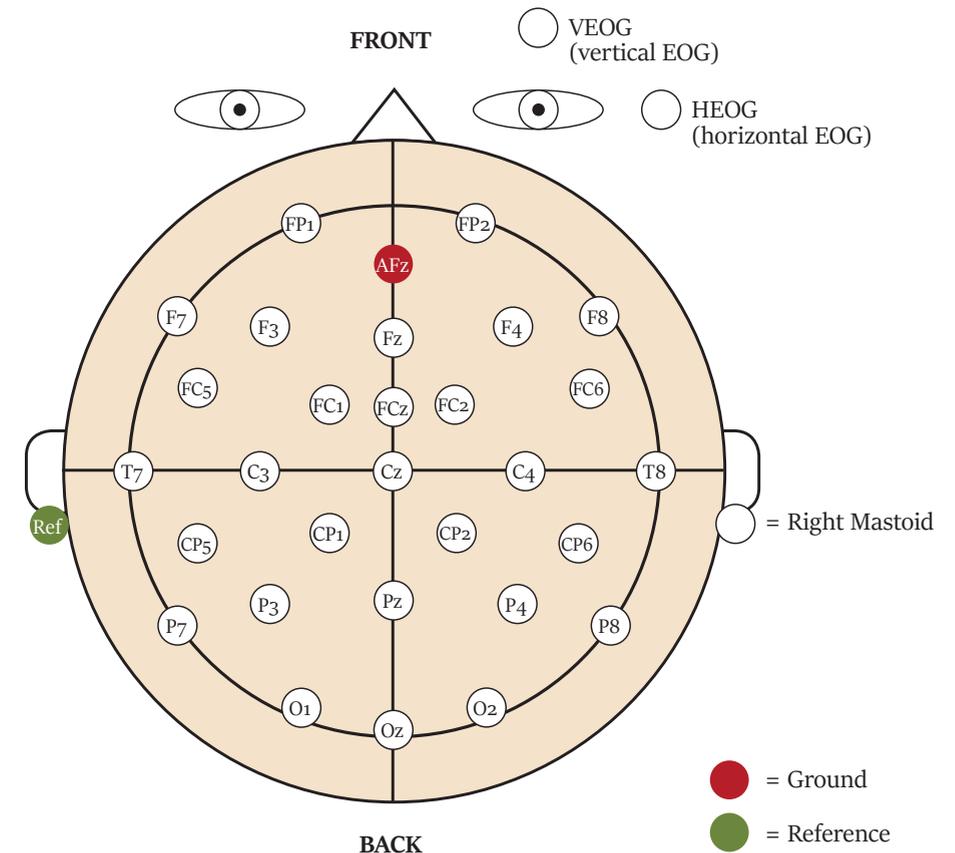
### 3.2.4 Electrophysiological Recordings

1. Start with cleaning the skin at the position where the reference electrode is placed to reduce the impedance (recommendation: place the reference electrode on the left mastoid bone and another active electrode on the right mastoid bone for offline re-referencing to linked mastoids).
  - a) Clean the skin at the reference electrode placement by gently applying scrub cream to remove dead skin cells and clean it with alcohol to remove oily substances.
  - b) In addition, clean the forehead and the skin surrounding the eyes for the EOG (electro-oculogram) electrodes (more information on EOG recordings in step 6). Be careful when scrubbing the face, the skin here may be very sensitive.
2. Before putting the cap on the participants head, measure the head circumference to determine the cap size. To determine the circumference, place a measuring tape around the widest part of the head, just above the ears.



3. Apply the cap with the corresponding size and check if it is in the right position.
  - a) To do this, measure the distance between Inion (bulging part of the occipital bone at the back of the skull) and Nasion (point where the top of the nose meets the ridge of the forehead) and between the left and right inter-aural indentations. Place the Cz electrode at exactly 50% of these distances. Using a cap ensures that if Cz is correctly located over the central vertex, all the other electrodes are automatically positioned at the standard locations according to the international 10-20 system („American Electroencephalographic Society guidelines for standard electrode position nomenclature,” 1991).
4. Place the electrodes according to the International 10-20 system by using the numbers on the cap and electrodes.
  - a) Locate electrodes at five midline sites (Fz, FCz, Cz, Pz and Oz) and 24 lateral sites (FP1/2, F7/8, F3/4, FC5/6, FC1/2, C3/4, CP5/6, CP1/2, P7/8, P3/4, T7/8, O1/2) to allow estimations of scalp distributions for finding spatial maxima of the ERP components of interest during the offline data processing (see **figure 3.2.**).
  - b) If the reference electrode is placed on the left mastoid bone, place one more electrode on the right mastoid bone for linked-reference recording. Place the Ground electrode on AFz (see **figure 3.2.** for schematic of electrode placement).
5. Fill the electrodes with conductive gel by inserting a blunt needle through the electrodes. The gel maximizes skin contact and acts as a malleable extension of the electrodes. In order to lower the impedance, gently abrade the skin under the electrode. Be careful to not apply too much conductive gel as gel might get in contact with gel of an adjacent electrode, thus distorting the signal.
6. Co-register an EOG to correct the EEG signal for eye movements during the offline data processing. NOTE: Especially with children it is difficult to avoid eye movement artifacts through instruction only. Co-registering this EOG signal to subsequently correct for the electrical activity produced by the eyes, therefore is highly recommended for these participants.
  - a) For this purpose, place EOG electrodes around the eyes of the children.
  - b) As children’s skin is very sensitive, try to avoid the placement of four EOG electrodes. Instead, place only two EOG electrodes by using one of the active electrodes below the right eye and one on the outer canthus of the right eye. When applying an ocular correction during the offline data processing, use F7 and FP2 electrodes as reference electrodes for EOG recording.
7. Keep the electrode impedance below 20 k $\Omega$  by using an impedance meter while attaching the electrodes.

- NOTE: It is recommended to use an amplification system that has this as a built-in function.
8. Use digitization software to digitize and record the EEG signal according to the manufacturer’s instructions. Use the following recommended settings for the recording: digitize at 1,000 samples/sec and online filter between 0.016 and 250 Hz.



**Figure 3.2. Schematic of electrode placement based on the international 10-20 system.** The white electrodes represent the applied placement of the 32 active electrodes with linked mastoid reference placement and two active electrodes used for EOG measurement. The green electrode represents the reference electrode. The red electrode represents the ground electrode. EOG, electro-oculogram.

### 3.2.5 Executing Target-response Task During EEG Recording

1. Place the laptop or computer screen approximately 40 cm in front of the child. Locate the two red buttons next to the laptop keyboard, one at the right side and one at the left side. Keep the distance between the buttons at 30 cm to

obviate the possibility that the wrong hand is used to press the button. Locate children's hands slightly above the two red buttons with elbows resting on the table.

2. Instruct the child to respond as quickly as possible to the target-stimuli by pressing the red button on the side of the target-stimulus (right button for right stimulus presentation, left button for left stimulus presentation). If nogo-stimuli are included, instruct the child to inhibit their response whenever a nogo-stimulus is presented.
3. Conduct a short trial session. Make sure that all stimuli that are used in the experiment appear at least once during this trial session. However, keep this trial session as short as possible (approximately 1 min without unnecessary repetitions) to prevent inducing fatigue later in the protocol.

### 3.2.6 Offline Data Processing

#### 3.2.6.1 Behavioral data processing

1. Define behavioral variables (e.g., errors, reaction times) before processing the EEG data. It is important that ERP data correspond to the behavioral data (e.g., that only trials with correct responses are used for averaged ERPs).
2. Recommendations: Define errors as false hits (e.g., response following cue- and nogo-stimuli within 2,000 msec), omissions following target-stimuli (recommended: no response within 2,000 msec) as well as erroneous responses (wrong button or both buttons pressed simultaneously). Depending on the research question, researchers may wish to exclude these errors in the RT and ERP data.

#### 3.2.6.2 Electrophysiological data processing for ERP analyses (recommended steps)

NOTE: Choose a data analysis system that is suitable for analyzing the data aiming at answering the specific research question. Different systems are better suitable for different analyses purposes (e.g., ERP analyses vs. frequency analyses). It is possible to independently program this software as well as using a commercial EEG analysis system. The instructions provided below are specific for BrainVision Analyzer. Using BrainVision Analyzer is only one out of many available options to analyze ERP data.

1. If a linked-reference recording was chosen (reference electrode placed on one of the mastoid bones and another active electrode placed on the other mastoid bone), re-reference the signal of every EEG electrode to linked mastoids. Select the channel placed on the right mastoid bone as a new reference channel and include the implicit reference into calculation of the new reference (Transformations→Channel Preprocessing→New Reference).

2. Apply an ocular correction by using the signal recorded from the vertical and horizontal EOG channels (e.g., Gratton, Coles, & Donchin, 1983). If only two EOG channels were used, use F7 and Fp2 electrodes as reference electrodes for the EOG channels (Transformations→Ocular Correction).
3. Apply an appropriate filter (Transformations→Data Filtering→IIR Filters). For ERPs recorded in children it is recommended to use a high-pass filter with a cutoff of 0.5 Hz and a low-pass filter that does not exceed 40 Hz.
4. Segment the signal related to the different stimuli into equal segment epochs based on the different marker positions (Transformations→Segment Analysis Functions→Segmentation→Create new Segments based on a marker position). For ERPs following the presentation of visual stimuli use segments from 250 msec prior to the stimulus till at least 750 msec after the stimulus (recommended). Furthermore, exclude the epochs of incorrect trials (false hits & omissions) by means of Boolean selection.
5. Detrend the signal to correct for drifts in the signal (Transformation→Segment Analysis Functions→DC Detrend).
6. Apply an artifact rejection to screen each segment for motor and ocular artifacts such as high frequency muscle activity and remove segments containing artifacts exceeding  $\pm 150 \mu\text{V}$ . Recommendation: use the semiautomatic mode to have more insight into what data is removed (Transformations→Artifact Rejection→Semiautomatic Segment Selection).
7. Apply an appropriate baseline correction (Transformations→Segment Analysis Functions→Baseline Correction). Recommendation: For ERPs following the presentation of visual stimuli use a baseline correction from -250 msec until the presentation of the stimulus.
8. Average the segments per stimulus type and hand (affected vs. less-affected) (Transformations→Segment Analysis Functions→Average).
9. Finally, export mean amplitudes for various peaks of interest (Export→Area Information). Recommendation: To allow blind scoring, define the averaged value within a fixed latency window. To determine the appropriate latency window for the studied group, find the maximum of the peak of interest in the grand-averaged ERPs of all children and define a window reaching 50% of this value before and after the peak. Use this window to export the averaged value of this component window for all individual participants (Picton, 1992).
10. Recommendation: As the current research protocol is directed at studying differences in information processing and cognitive abilities, include data from midline electrodes. Endogenous components reflecting differences in information processing and cognitive abilities are clearly visible and identifiable over the vertex due to the widespread activity and smeared scalp topography of the signals.



NOTE: In prior studies using this protocol, data from Fz, FCz, and Cz electrodes were used for data analyses (Zielinski, Jongmsa, et al., 2014; Zielinski, Steenbergen, et al., 2014).

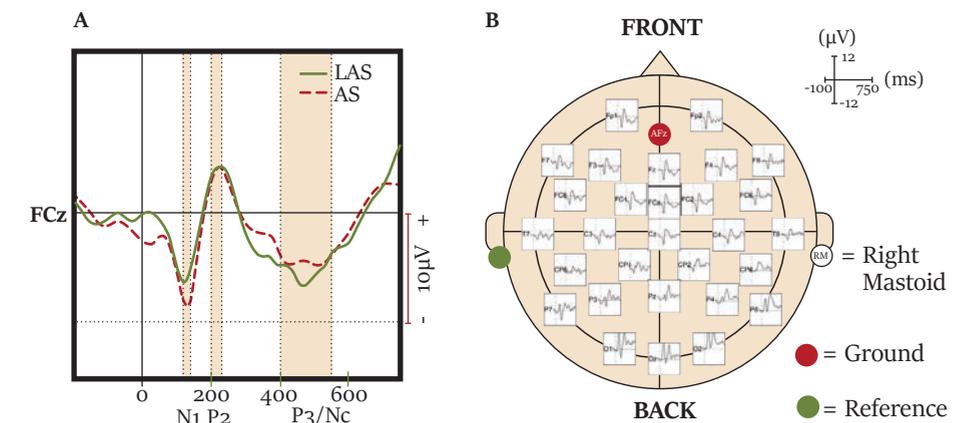
### 3.3 REPRESENTATIVE RESULTS

The described protocol has been used in previously published research that studied the underlying cognitive factors contributing to the phenomenon of developmental disregard in children with unilateral Cerebral Palsy (CP) (Zielinski, Jongmsa, et al., 2014; Zielinski, Steenbergen, et al., 2014). Two slightly different protocols have been used in these publications to disentangle different cognitive processes involved in a goal-directed hand response towards a target. In both articles significant differences in cognitive processes between groups (developmental disregard and no developmental disregard) were found in reaction to target-stimulus presentation on midline electrodes (Fz, FCz, Cz). The representative results therefore show Event-Related Potentials (ERPs) elicited by target-stimuli (elicited in a go/nogo-task as shown in **figure 3.1.**) in children with unilateral CP with and without developmental disregard. The figures presented are based on recordings of 24 children with unilateral CP between 5 and 11 years old.

Averaging across trials and participants produces an ERP waveform that consists of a series of positive and negative deflections: the ERP components. **Figure 3.3.** shows the grand-averaged ERPs of 24 children with unilateral CP in response to visual target-stimuli (as presented in **figure 3.1.**). **Figure 3.3.A** shows the grand-averaged ERPs at FCz electrode position for a detailed view of the different potentials. It shows separate potentials for stimulus presentation to the affected side (AS) and to the less-AS. **Figure 3.3.B** shows the representation of the potentials across the scalp. These grand-averaged ERPs show the mean reaction to stimuli presented to both sides, the AS and the less-AS. The grand-averages shown in **figures 3.3.A** and **3.3.B** contain a clear N1 and P2 component. Instead of a classic P3, a late latency negative component (Nc) is observed at fronto-central scalp position following target-stimuli. This fronto-central negative wave in children was reported earlier to be comparable to the classic P3 wave in adults (Picton, 1992) and has repeatedly been observed in target-response tasks in children with unilateral CP (Zielinski, Jongmsa, et al., 2014; Zielinski, Steenbergen, et al., 2014).

**Figure 3.4.** depicts group differences in ERPs between children with unilateral CP with and without developmental disregard. **Figure 3.4.A** depicts the grand-averaged ERPs for both groups (developmental disregard and

no developmental disregard) and each side (affected and less-affected side) separately. For both groups the N1 and P2 components as well as the late latency negative component can be observed. However, the negative wave in the P3 domain is significantly larger in the developmental disregard group ( $p < .05$ ). Furthermore, significant differences between the amplitude of the N1 component can be observed between groups. For statistical analyses the averaged values within fixed latency windows were analyzed. To depict significant differences, bar graphs are frequently used as shown in **figure 3.4.B**. To interpret the differences between the two groups, there is abundant literature that relates each ERP component to a specific cognitive operation. Whenever significant group differences are found existing literature should be used for appropriate interpretation of the meaning of these differences. How the findings of these representative results have been interpreted related to the research questions is documented in the corresponding publications (Zielinski, Jongmsa, et al., 2014; Zielinski, Steenbergen, et al., 2014).

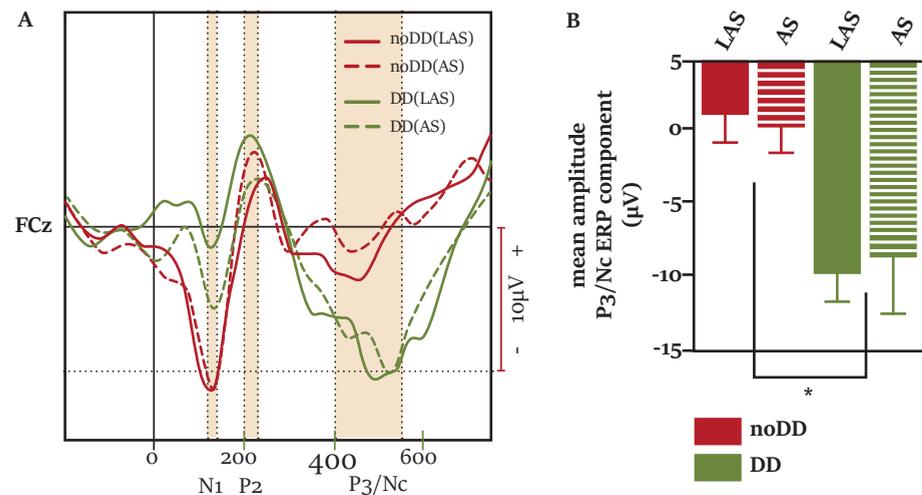


**Figure 3.3. Representative grand-averaged ERPs following target-stimuli.** Grand-averaged ERP waveforms of 24 children with unilateral CP time locked to target-stimuli. (A) Grand-averaged ERPs at FCz electrode position. The continuous green line represents the ERPs following target-stimulus presentation to the less-affected side (less-AS). The red dashed line represents the ERPs following target-stimulus presentation to the affected side (AS). The time windows around the maxima of the different components of interest (N1, P2, and P3/Nc) are highlighted. (B) The representation of the grand-averaged ERPs across the scalp. LAS, less-affected side; AS, affected side.

In addition to the data derived from the ERP recordings, the different target-response tasks also generate behavioral data that can be used for additional analyses. Reaction times (time from target presentation to button press) and

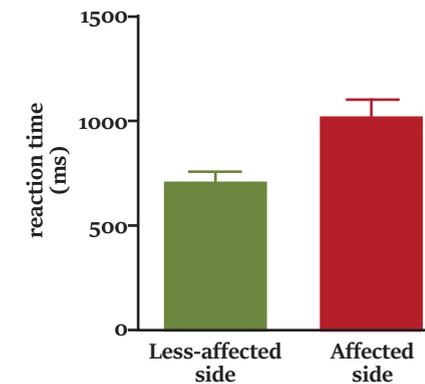


errors (e.g., omissions following target-stimuli) can be used as separate additional dependent variables. When studying children with unilateral CP, differences in reaction times between both hands (affected vs. less-affected) can be expected (Zielinski, Jongasma, et al., 2014; Zielinski, Steenbergen, et al., 2014) as shown in **figure 3.5**. However, even if differences on ERPs are observed, it is possible that behavioral measurements show no differences between groups (Zielinski, Jongasma, et al., 2014).



**Figure 3.4. Representative grand-averaged ERPs following target-stimuli displaying differences between two groups.** (A) Grand-averaged ERP waveforms of the same 24 children with unilateral CP as presented in **figure 3.3.**, time locked to target-stimuli. Twelve children were classified as having developmental disregard. The red lines represent the ERPs of children with unilateral CP without developmental disregard (noDD;  $N = 12$ ). The green lines represent the ERPs for children with developmental disregard (DD;  $N = 12$ ). The continuous lines represent the ERPs following target-stimulus presentation to the less-affected side (LAS). The dashed lines represent the ERPs following target-stimulus presentation to the affected side (AS). The time windows around the maxima of the different components of interest (N1, P2, and P3/Nc) are highlighted. (B) P3/Nc amplitudes (mean  $\pm$  SEM  $\mu$ V) to target-stimuli as depicted in **figure 3.4.A**. The red bars represent the mean values of P3/Nc amplitude for children without developmental disregard. The green bars represent the mean values of P3/Nc amplitude for children with developmental disregard. The filled bars represent the results of the less-affected side (LAS). The striped bars represent the results of the affected side (AS). The asterisk indicates a significant ( $p < .05$ ) difference between both groups concerning the P3/Nc amplitude. noDD, no developmental disregard; DD, developmental disregard; LAS, less-affected side; AS, affected side.

Another possibility to using reaction times and error scores as separate dimensions is to use a combined score by calculating the Inverse Efficiency Scores (IES). The IES are determined by the mean reaction time divided by the proportion of correct responses expressed in milliseconds (Bruyer & Brysbaert, 2011). This method is considered to be especially useful in tasks with low ( $< 10\%$ ) error rates (Bruyer & Brysbaert, 2011). As the current protocol suggests very easy target-response procedures, a low error rate is anticipated and has been documented in prior published work (Zielinski, Jongasma, et al., 2014; Zielinski, Steenbergen, et al., 2014).



**Figure 3.5. Representative reaction time data displaying differences between AS and less-AS.** Depicted are means  $\pm$  SEMs. The green bar shows the mean reaction time to target-stimuli of 24 children with unilateral CP with their less-AS. The red bar shows the mean reaction time to target-stimuli of the same children with their AS.

### 3.4 DISCUSSION

This article presents a protocol developed to directly assess cognitive processes related to movement control during simple upper limb movements in children with unilateral Cerebral Palsy (CP) and developmental disregard. Unilateral CP is a non-progressive neurodevelopmental disorder that is characterized by movement deficits on one side of the body, primarily affecting the upper limb (Odding et al., 2006; Rosenbaum et al., 2007). Children with developmental disregard show a disregard of the preserved capacity of their AS during spontaneous daily activities (Houwink et al., 2011). The current protocol was developed to unravel the related cognitive mechanisms that might contribute to the phenomenon of developmental disregard with the goal of improving existing rehabilitation procedures for these children. By using this protocol valuable new



insights were obtained about the underlying cognitive processes related to simple upper limb movements in children with developmental disregard (Zielinski, Jongsma, et al., 2014; Zielinski, Steenbergen, et al., 2014).

Critical to this protocol is the use of Event-Related Potentials (ERPs) during a very easy executable target-response task. The simplicity of conducting the task allows for the inclusion of young children with movement restrictions. Recording ERPs during the task is used as a powerful non-invasive neuroimaging technique that measures neural activity with a high temporal resolution. Using this protocol allows for the study of the cognitive aspects related to distinct processing stages of upper limb control in children with unilateral CP. As such, it extends behavioral examinations to the neurophysiological level. Furthermore, the protocol can be easily adapted by presenting different stimuli (e.g., cue-stimuli, nogo-stimuli) or adapting stimulus presentation time as well as inter-stimulus intervals. It is therefore possible to directly assess different cognitive processes involved in upper limb control (e.g., response preparations vs. response inhibition).

Next to the idea that certain motor deficits in children with unilateral CP are actually caused by dysfunctional cognitive processes, another important aspect that might contribute to the observed motor deficits in children with developmental disregard is a possible sensory deficit (Maitre et al., 2012). Due to injury to specific thalamo-cortical and cortico-cortical pathways some children with unilateral CP do not receive accurate sensory feedback from their movements (Auld, Ware, Boyd, Moseley, & Johnston, 2012). This in turn has been proposed to lead to an underuse of the AS, i.e. developmental disregard. The current protocol does not directly assess this possible sensory deficit. For the detailed assessment of different sensory processing in children with movement disabilities, we refer to the work of Maitre and Key (2014).

To ensure accurate and valid results, there are a few critical points to keep in mind. Before starting an EEG experiment, it is first of all important to understand the associated limitations of this technique. The relatively poor spatial resolution as well as the difficulty of inferring subcortical activity are important issues to consider. If the research question is aimed at neuro-anatomically localizing specific processes during upper limb control, alternative neuroimaging methods should be considered (e.g., (f)MRI). However, it should be clearly stated that the non-invasiveness of EEG as well as the possibility of using a mobile lab to measure at locations that are familiar to the child offers a tremendous advantage over other techniques.

Next to the poor spatial resolution of EEG measurements, the noise introduced by blinks and muscle activity is also disadvantageous. Especially in children it is very difficult to give appropriate instructions to reduce these

artifacts. It is therefore very important to use a protocol that keeps children's attention and does not take too long.

#### 3.4.1 Conclusion

The current protocol offers new empirical insights into the underlying cognitive processes that contribute to the phenomenon of developmental disregard in children with unilateral CP (Zielinski, Jongsma, et al., 2014; Zielinski, Steenbergen, et al., 2014). These insights might be of high value not only for further understanding of developmental disregard, but also for individualizing the current therapies. Furthermore, the capability of this protocol to directly assess underlying cognitive factors of upper limb control could give rise to a possible broader implementation for research on cognitive aspects related to movement development in children.



### 3.5 ACKNOWLEDGEMENTS

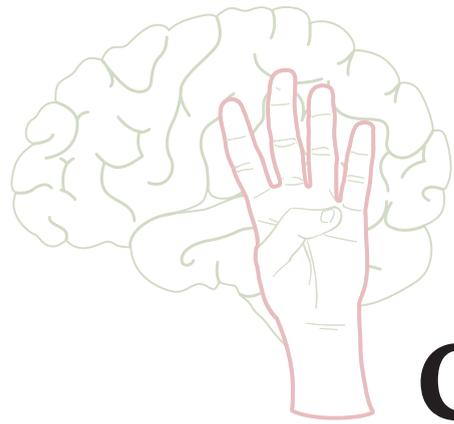
This work is part of a doctoral dissertation that was supported by grants from (in alphabetical order): Hersenstichting Nederland, Johanna KinderFonds, Stichting Rotterdams Kinderrevalidatie Fonds Adraanstichting, Phelps Stichting voor Spastici, and Revalidatie fonds.

# PART 1

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## THE OPERANT CONDITIONING FRAMEWORK

Developmental disregard as a  
“learned” phenomenon



# CHAPTER IV

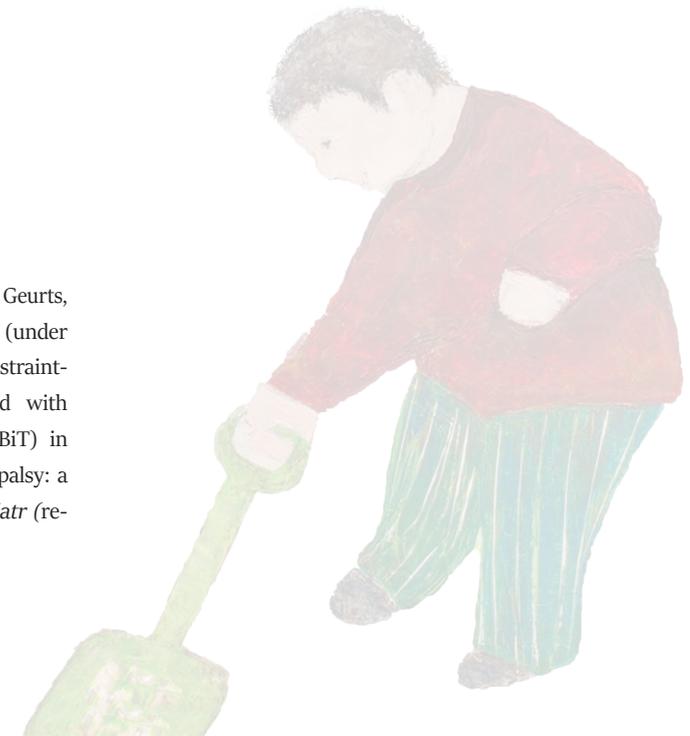
## The Effects of Modified Constraint-induced Movement Therapy Combined with Intensive Bimanual Training (mCIMT-BiT) in Children with Obstetric Brachial Plexus Palsy: a Retrospective Data Base Study

### Abstract

Developmental disregard, the non-use of the affected side (AS) despite sufficient capacity, is sometimes observed in children with obstetric brachial plexus palsy (OBPP), even though originally described in children with unilateral cerebral palsy (CP). The combination of modified constraint-induced movement therapy with bimanual training (mCIMT-BiT) is frequently applied to overcome this lack of spontaneous AS use in unilateral CP. In the current study the effects of mCIMT-BiT on spontaneous upper limb use and bimanual performance will be investigated in children with OBPP and compared to children with unilateral CP. We hypothesize that children with OBPP also benefit from this therapy. For this aim data of 19 children with OBPP (mean age: 4.1 years) and 18 with unilateral CP (mean age: 4.5 years) were compared. Spontaneous use (AHA) and bimanual performance (ABILHAND-kids, COPM) were assessed at three time points (pre-treatment, post-treatment, follow-up: 8-12 weeks). Outcome measures were analyzed using repeated measures analysis with group as between-subject factor. The results showed that children with OBPP present significant improvements on all outcome measures following mCIMT-BiT. These effects sustained at follow-up. Improvements on bimanual performance (ABILHAND-kids, COPM) were comparable to those in unilateral CP. Contrary to unilateral CP, children with OBPP showed additional improvement of spontaneous use (AHA) at follow-up ( $M=69.47$ ) compared to post-treatment assessment ( $M=68.05$ ;  $t(18)=-2.156$ ,  $p=.045$ ). These results indicate improved bimanual performance in children with OBPP following mCIMT-BiT, comparable to the improvement observed in unilateral CP. Additionally, in children with OBPP spontaneous AS use further improved after therapy. This might suggest that children with OBPP have effectively overcome their developmental disregard following mCIMT-BiT. These results suggest that mCIMT-BiT is effective in OBPP.

### This chapter is based on:

Zielinski, I.M., van Delft, R., Voorman, J.M., Geurts, A.C.H., Steenbergen, B., & Aarts, P.B.M (under review). The effects of modified constraint-induced movement therapy combined with intensive bimanual training (mCIMT-BiT) in children with obstetric brachial plexus palsy: a retrospective data base study. *BMC Pediatr* (re-submitted).



## 4.1 INTRODUCTION

Obstetric brachial plexus palsy (OBPP) is a flaccid paresis or paralysis of the upper limb caused by traction on the brachial plexus during delivery (Pondaag, Malessy, van Dijk, & Thomeer, 2004; Zafeiriou & Psychogiou, 2008). The incidence ranges from 0.4 - 3 per 1000 live births (Bialocerkowski, Kurlowicz, Vladusic, & Grimmer, 2005; Pondaag et al., 2004; Zafeiriou & Psychogiou, 2008). In 70-92% of these children complete recovery is observed (Pondaag et al., 2004; Zafeiriou & Psychogiou, 2008). If the lesion is permanent, however, functional limitations are seen related to the degree of injury, the degree of motor weakness, muscle contractures, and co-contractions (Bialocerkowski et al., 2005; Santamato, Panza, Ranieri, & Fiore, 2011). In children with a permanent lesion, reduced active range of motion and grip strength are frequently observed, directly limiting their manual performance (Hulleberg, Elvrum, Brandal, & Vik, 2014; Strombeck, Krumlinde-Sundholm, & Forssberg, 2000). As a consequence, these children experience difficulties in activities of daily living (Hulleberg et al., 2014), with more severely injured children frequently also requiring assistance (Kirjavainen et al., 2007).

The mainstream therapy for children with a permanent OBPP consists of physio- and occupational therapy stimulating passive and active movement of the AS in order to enhance neuromuscular function and prevent complications attributed to lack of movement (e.g. contractures) (Bialocerkowski et al., 2005). Unfortunately, in the Netherlands there is no treatment protocol specifying the intensity of this usual care, causing a range of varying procedures and intensities of treatment between treatment centers. As addition to this usual care focusing on the reduced upper limb capacity, it has recently been suggested that children with OBPP might as well benefit from intensive therapies aimed at overcoming a phenomenon called developmental disregard by inducing spontaneous upper limb use. This phenomenon, where children seem to 'forget' using the remaining capacity of their AS during spontaneous daily activities, has been suggested to partly explain the functional upper limb limitations observed in children with OBPP (Abdel-Kafy, Kamal, & Elshemy, 2013; Vaz et al., 2010).

Developmental disregard has first been described in children with unilateral cerebral palsy (CP) (Deluca, Echols, Law, & Ramey, 2006; Hoare, Wasiak, Imms, & Carey, 2007). It refers to a phenomenon where, despite preserved motor capacity that allows or would predict the use of the AS, this upper limb is in fact frequently not used during the performance of daily activities. Two underlying mechanisms have been suggested to cause developmental disregard in children with OBPP: learned non-use and neurodevelopmental delay or deficiency (Santamato et al., 2011; Vaz et al., 2010). Learned non-use explains the underuse

of the AS by a negative reinforcement phenomenon (Taub et al., 1994). Following this theory, children experience negative feedback each time they use their AS. This is suggested to lead to a progressive suppression of movements of the AS (Taub et al., 1994). Neurodevelopmental delay or deficiency, in turn, is thought to result from a lack of movement stimulation and/or sensory feedback during crucial or even critical developmental periods (Deluca et al., 2006; Santamato et al., 2011). Due to the primary movement restrictions caused by the brachial plexus injury, children with OBPP suffer a critical lack of movement stimulation during developmental periods when movement repertoires are rapidly acquired in typically developing children. Furthermore, due to potential damage of afferent axons in OBPP, children might also suffer a lack of sensory feedback related to their movement production (Brown et al., 2000). As a consequence, typical developmental milestones are delayed or even deficient for the AS (e.g. transferring objects from one hand to the other) potentially leading to delayed or deficient neurodevelopmental processes (Anguelova, Maessy, Buitenhuis, van Zwet, & van Dijk, 2016; Boyd et al., 2010; Brown et al., 2000; Deluca et al., 2006).

In children with unilateral CP one of the most promising treatments aimed at reducing the symptoms of developmental disregard and therefore increasing the spontaneous use of the AS is constraint-induced movement therapy (CIMT) (Hoare et al., 2007). This therapy was originally developed to overcome learned non-use in adult stroke patients (Taub & Wolf, 1997). It is based on the idea of re-learning the use of the upper limb through processes of operant conditioning (Taub et al., 1994). It involves constraining of the less- or non-AS, while at the same time stimulating the use of the AS via intensive and repetitive training. When this therapy was introduced in pediatrics, concerns were raised about the feasibility of applying strict CIMT programs to children, as original therapy programs were very intensive, not child-friendly, and potentially invasive (Aarts, Jongerius, Geerdink, van Limbeek, & Geurts, 2010; Gordon, Charles, & Wolf, 2005). Therefore, modified ( $\leq 3$  hours/day) and child friendly versions of the CIMT program (mCIMT) were developed, which were reported to be effective and tolerated by children with unilateral CP (Aarts et al., 2010; Brady & Garcia, 2009; Gordon et al., 2005; Taub et al., 2007). Even though originally developed for children with unilateral CP, a few case reports and one randomized controlled trial recently reported promising results exploring the effectiveness of applying mCIMT programs to children with OBPP (Abdel-Kafy et al., 2013; Berggren & Baker, 2015; Buesch et al., 2010; Santamato et al., 2011; Vaz et al., 2010). However, most studies solely concentrated on the improvement of functional capacity of the AS (e.g. muscle strength, shoulder movement, range of movement) (Abdel-Kafy et al., 2013; Buesch et al., 2010;



Santamato et al., 2011), while only a few case reports reported changes in actual upper limb performance (Berggren & Baker, 2015; Buesch et al., 2010; Vaz et al., 2010).

Next to overcoming learned non-use, therapies aiming at reducing symptoms of developmental disregard also need to focus on the proposed developmental delay or deficiency underlying this phenomenon. As opposed to adult stroke patients that experience symptoms of learned non-use, children may have never learned to effectively use their AS during bimanual daily activities. Even though initial unimanual practice might transfer to improvements in bimanual coordination, motor learning principles suggest that improvement in using the two hands together can only be accomplished by repetitive practice of bimanual tasks (Charles & Gordon, 2005; Gordon, Schneider, Chinnan, & Charles, 2007). It has therefore been suggested that combining mCIMT with intensive bimanual training (BiT) is critical to effectively overcome developmental disregard in children (Zielinski, Jongsma, Baas, Aarts, & Steenberg, 2014). When applying mCIMT protocols to children with unilateral CP, programs were therefore frequently and successfully combined with BiT (Aarts et al., 2010; Geerdink, Aarts, van der Burg, Steenberg, & Geurts, 2015; Gelkop et al., 2015). As of yet, the efficacy of a combined mCIMT-BiT program when treating upper limb performance in children with OBPP has not yet been established. However, as in children with unilateral CP, BiT as being added to the mCIMT programs seems to be indispensable to effectively treat the proposed developmental delay or deficiency affecting the children's upper limb performance.

In the current study the effects of a combined mCIMT-BiT program on spontaneous upper limb use and upper limb performance in a group of children with OBPP will be investigated. To evaluate the effectiveness of mCIMT-BiT, the therapy outcomes will be compared to a group of children with unilateral CP that followed the same therapy program. Based on the hypothesis that developmental disregard might partly explain the functional upper limb limitations and promotes the reduced upper limb performance in children with OBPP, we expect that a combined program of mCIMT-BiT focusing on overcoming developmental disregard will enhance the spontaneous use of the AS as well as improve bimanual performance. We expect these therapy related improvement to be similar among both patient groups, because learned non-use as well as developmental delay or deficiency are thought to contribute to developmental disregard in both children with OBPP and unilateral CP. Specifically, we expect this improvement to be observed for 1. spontaneous use of the AS during bimanual activities, 2. bimanual performance and 3. subjective performance and satisfaction of problematic bimanual activities.

## 4.2 METHODS

### 4.2.1 Participants and design

For this retrospective database study, data of 19 children with OBPP that had participated in a combined mCIMT-BiT program based on the "Pirate group intervention" (Aarts et al., 2010) between 2008 and 2015 were obtained from Dutch rehabilitation centers participating in the "Dutch implementation of the Pirate concept", initiated by the Sint Maartenskliniek Nijmegen, The Netherlands. The "Pirate group intervention" consists of a total of 54 hours mCIMT based therapy and 18 hours goal directed and task specific BiT in a pirate themed group setting (4-6 children). During this whole period children wear pirate costumes and train their arms and hands in a meaningful way by applying various pirate themed activities (Aarts, Jongerius, Geerdink, van Limbeek, & Geurts, 2010).

To participate, the children needed to be between 2.5 and 9 years of age when starting to participate at the mCIMT-BiT program and have sufficient manual ability to perform therapy related tasks (i.e. had to be able to grasp with their AS). The contraindications for participating at the current therapy program were the same as for usual care: children should not experience any pain in their affected hand, arm, or shoulder, they should be motivated, and their parents should be able to come to the revalidation center 3 times per week. Unfortunately, we did not have information on the children's surgical history, even though we do know that most of the children did undergo an operation at early age. We did however only include children that did not receive upper limb surgery or botulinum toxin injections during a 3-month period before starting the program.

Children with unilateral CP were 1:1 matched to the 19 children with OBPP for upper limb performance and age. For this purpose, we used the clinical database of the Sint Maartenskliniek, Nijmegen that includes all children with unilateral CP that had earlier participated in the "Pirate group intervention". Initially, children were matched to the pre-treatment "Assisting Hand Assessment" (AHA) (Krumlinde-Sundholm, Holmefur, Kottorp, & Eliasson, 2007) scores as accurately as possible (max +/-3 logit-based units). Secondly, children were age-matched as accurately as possible (max +/- 3 years). Because one of the OBPP children did not perform the pre-treatment AHA measurement, only 18 children with unilateral CP were included. The exact matching and children's demographic characteristics are presented in **table 4.1**.

The internal review board of the Sint Maartenskliniek Nijmegen approved the use of the reported data for the current retrospective database study. Furthermore, all parents signed written informed consent to allow use of the clinical data for scientific purposes.



A pretest - posttest design was used with children with unilateral CP serving as control group. Data were assessed at three different time points related to treatment onset: 1. pre-treatment (T1: 2-3 weeks prior to treatment), post-treatment (T2: 2-3 weeks after treatment) and follow-up (T3: 8-12 weeks following treatment).

**Table 4.1.** Demographics of children with OBPP and matched children with unilateral CP

OBPP					matched unilateral CP				
Nr	AS (L/R)	gender (M/F)	age (y/m)	AHA (T1)	Nr	AS (L/R)	gender (M/F)	age (y/m)	AHA (T1)
1	R	F	3y 8m	65	20	L	F	4y 10m	65
2	R	F	3y 11m	77	21	R	F	3y 9m	77
3	L	M	5y 1m	82	22	L	M	5y 6m	83
4	L	M	2y 9m	missing data (imputed: 82)	no match				
5	L	M	5y 3m	87	23	L	F	3y 10m	84
6	L	F	2y 8m	68	24	R	M	3y 9m	69
7	R	M	3y 7m	67	25	L	M	3y 9m	67
8	R	M	2y 9m	59	26	R	M	4y 5m	59
9	R	M	7y 0m	53	27	R	M	9y 0m	52
10	R	M	5y 3m	42	28	R	F	4y 3m	42
11	L	M	7y 7m	55	29	R	F	4y 7m	57
12	R	M	2y 10m	48	30	L	M	4y 0m	48
13	L	F	3y 6m	53	31	L	M	3y 3m	53
14	R	F	4y 1m	39	32	L	F	4y 3m	39
15	R	M	3y 1m	68	33	R	M	3y 8m	69
16	L	F	3y 11m	65	34	L	M	3y 1m	64
17	R	F	5y 5m	77	35	R	F	3y 5m	77
18	R	F	4y 4m	41	36	L	M	5y 3m	40
19	R	F	2y 10m	65	37	L	M	4y 8m	64
L/R	M/F	mean±SD	mean±SD		L/R	M/F	mean±SD	mean±SD	
7/12	10/9	4y 2m ±1y 5m	60.94 ±13.96		10/8	11/7	4y 7m ±1y 6m	62.79 ±14.96	

**Abbreviations:** OBPP, obstetric brachial plexus palsy; CP, cerebral palsy; AS, affected side; L, left; R, right; M, male; F, female; y, year; m, month; AHA, assisting hand assessment; SD, standard deviation

#### 4.2.2 Intervention

The mCIMT-BiT program was based on the child friendly “Pirate intervention protocol” (Aarts et al., 2012). The duration of the program was 54 hours of mCIMT and 18 hours of BiT during 8 to 10 weeks (either 2 or 3 times a week for a duration of 4.5 or 3 hours accordingly). The majority of the treatment was provided in a group setting by experienced occupational- and physiotherapists that were usually unknown to the children. Next to the group therapy, 1 hour per day was allocated to individual training to work on the children’s specific goals. Intensive, repetitive, task-specific and goal-oriented training strategies were used (Hubbard, Parsons, Neilson, & Carey, 2009; Loring, Bexelius, & Brogren Carlberg, 2009; Vaz et al., 2010). During the training program, parents were informed and advised on how to stimulate their child to use the affected upper-limb.

During the first 6 to 8 weeks, the less-AS was restrained using a splint or a sling while at the same time providing intensive structured training for the AS (based on CIMT principles) (Eliasson et al., 2014). In this training, the principles of shaping and repetitive task practice were applied (Aarts et al., 2012; Eliasson et al., 2014). The total time of mCIMT was 54 hours (6 weeks: 2 x 4.5 hours or 6 weeks: 3 x 3 hours). In the last 2 to 4 weeks bimanual activities were trained with special attention for specific goals set by the parents (BiT). During this period the children were stimulated to use both hands during typical bimanual activities and thus prompted to use the affected upper-limb. The total time for this BiT was 18 hours (2 weeks: 3 x 3 hours or 4 weeks: 2 x 2 hours).



#### 4.2.3 Outcome measures

##### 4.2.3.1 Spontaneous use of the AS during bimanual activities

The AHA (Krumlinde-Sundholm et al., 2007) was selected as the primary outcome measure. It is a video-based semi structured play session validated for children with unilateral CP and OBPP. It evaluates the spontaneous use of the AS during daily activities that require bimanual handling. For the analyses, the logit-based unit scores were used (range: 0-100).

##### 4.2.3.2 Bimanual performance

To assess bimanual performance, the ABILHAND-Kids Questionnaire (Arnould, Penta, Renders, & Thonnard, 2004) was chosen as secondary outcome measure. This is a Rasch-based parent-reported questionnaire assessing independency during bimanual activities at home. It is a valid and reliable scale focusing on the child’s manual ability to execute 21 daily activities. These activities are scored on a three level scale (‘impossible’, ‘difficult’, ‘easy’). For the analyses, scores were transferred to logits.

#### 4.2.3.3 Subjective performance and satisfaction of problematic bimanual activities

As a third outcome measure, the two scales of the Canadian Occupational Performance Measure (COPM) (Law et al., 1990) were selected. These scales assess both the subjective level of performance (COPM-Performance) and satisfaction (COPM-Satisfaction) on different self-reported activities. In the current study, children and their parents were asked to name five problematic bimanual daily activities that they considered to be important for the child's daily performance and rate them on a scale from 1 to 10 for both scales (COPM-Performance & COPM-Satisfaction).

#### 4.2.4 Data handling

The assessments were administered and scored by a trained occupational therapist. Two of the 19 parents of the children with OBPP did not fill in the ABILHAND-Kids Questionnaire. One of these parents did also not fill in the COPM. Furthermore, the parents of one child with OBPP did not fill in the satisfaction scale of the COPM. Of the remaining 429 values (37 participants: 19 with OBPP, 18 with unilateral CP, and 4 outcome variables: AHA, ABILHAND-Kids, COPM-Performance & COPM-Satisfaction, on three different time points: T1, T2, T3), 24 values were missing because of incomplete responses or non-interpretable results. These values were missing without any specific pattern. Before data analysis, these missing values were imputed using linear regression multiple imputation (5 times) based on all available values within variables. The 24 missing values were replaced using the mean values of the 5 imputations.

For the final analyses, data from 37 children were included for the analyses of the AHA scores (19 OBPP, 18 unilateral CP), data from 35 children for the analyses of the ABILHAND-Kids Questionnaire outcomes (17 OBPP, 18 unilateral CP), 36 for the analyses of the COPM-Performance score (18 OBPP, 18 unilateral CP) and 35 for the analyses of the COPM-Satisfaction score (17 OBPP, 18 unilateral CP).

#### 4.2.5 Statistical analysis

Primary (AHA) and secondary outcome measures (ABILHAND-Kids Questionnaire, COPM-Performance & COPM-Satisfaction) were analyzed separately using a repeated measures general linear model analysis with time point related to treatment onset (T1, T2, T3) as independent within-subject variable and group (OBPP vs. unilateral CP) as between-subject factor.

Whenever significant treatment effects were found, post-hoc paired samples t-tests were performed to compare outcomes between individual time points. Whenever treatment\*group interaction effects were observed, these post-

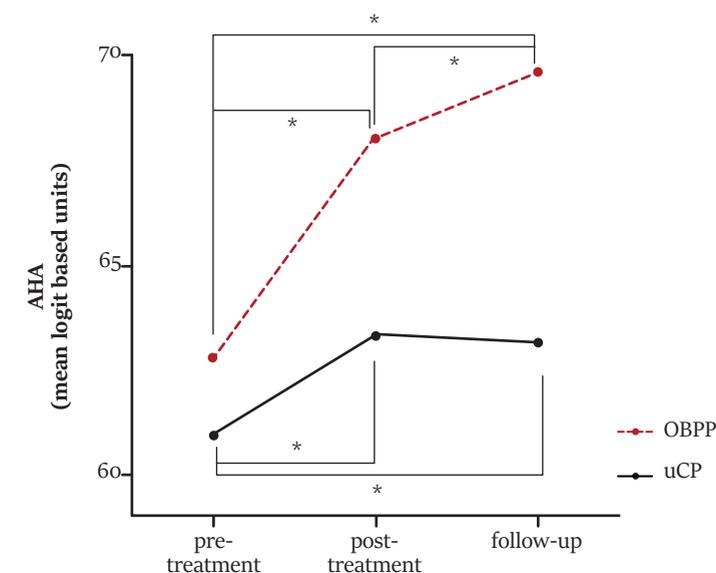
hoc paired samples t-tests were performed for both groups separately. For all analyses, the significance level was set at  $\alpha < .05$ .

## 4.3 RESULTS

### 4.3.1 Spontaneous use of the AS during bimanual activities (AHA)

The repeated measures analysis revealed a significant and strong effect of time ( $F(2,34)=15.211$ ,  $p < .001$ ,  $\eta^2=.472$ ) reflecting a significant improvement on the AHA scores over time for both groups. Next, a significant and moderate time\*group interaction ( $F(2,34)=3.565$ ,  $p = .039$ ,  $\eta^2=.173$ ) was found.

For the OBPP group, post-hoc paired samples t-tests revealed significant differences between T1 ( $M=62.79$ ) and T2 ( $M=68.05$ ;  $t(18)=-4.774$ ,  $p < .001$ ,  $d=-1.15$ ), between T1 ( $M=62.79$ ) and T3 ( $M=69.47$ ;  $t(18)=-4.9534$ ,  $p < .001$ ,  $d=-1.15$ ) as well as between T2 ( $M=68.05$ ) and T3 ( $M=69.47$ ;  $t(18)=-2.156$ ,  $p = .045$ ,  $d=-0.55$ ), reflecting differences between all three assessments (pre, post, and follow-up).



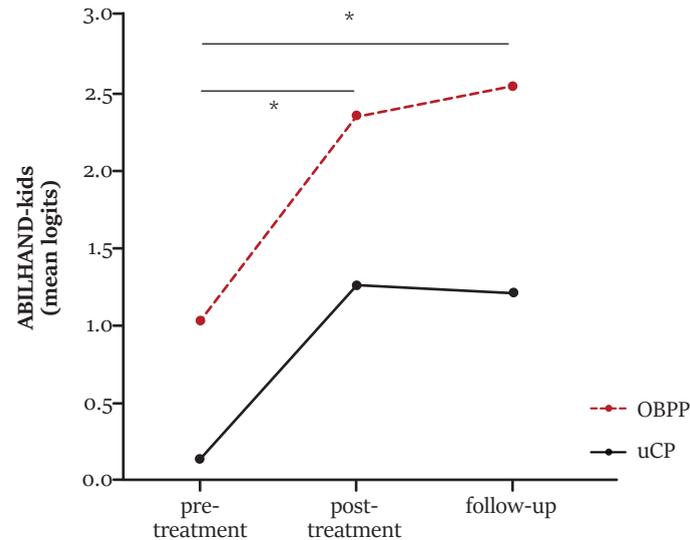
**Figure 4.1. Assisting Hand Assessment outcomes.** Mean Assisting Hand Assessment (AHA) outcomes of both groups on three assessments. Data of children with obstetric brachial plexus palsy (OBPP) are depicted in red; data of children with unilateral cerebral palsy (CP) are shown in black. Statistical significant differences ( $p < .05$ ) are shown per group and are indicated by the asterisks.

For the unilateral CP group post-hoc paired samples t-tests revealed significant differences between T1 (M=60.94) and T2 (M=63.33;  $t(17)=-2.719$ ,  $p=.015$ ,  $d=-0.64$ ) as well as between T1 (M=60.94) and T3 (M=62.61;  $t(17)=-2.169$ ,  $p=.045$ ,  $d=-0.51$ ), reflecting differences between pre-treatment and both following assessments. No significant difference was found between T2 (post; M=63.33) and T3 (follow-up, M=62.61). For data presentation of the AHA data, see **figure 4.1**.

#### 4.3.2 Bimanual performance (ABILHAND-kids)

The repeated measures analysis revealed a significant and strong effect of time ( $F(2,32)=30.468$ ,  $p<.001$ ,  $\eta^2=.656$ ) as well as a significant and moderate effect of group ( $F(1)=8.605$ ,  $p=.006$ ,  $\eta^2=.207$ ). However, no group\*time interaction was found.

The post-hoc paired samples t-tests across both groups revealed significant differences between T1 (M=0.577) and T2 (M=1.791;  $t(34)=-7.916$ ,  $p<.001$ ,  $d=-1.34$ ) and between T1 (M=0.577) and T3 (M=1.859;  $t(18)=-7.004$ ,  $p<.001$ ,  $d=-1.18$ ), reflecting differences between pre-treatment and both following assessments. No differences between T2 (post; M=1.791) and T3 (follow-up; M=1.859) were found. For data presentation of the ABILHAND-kids data, see **figure 4.2**.



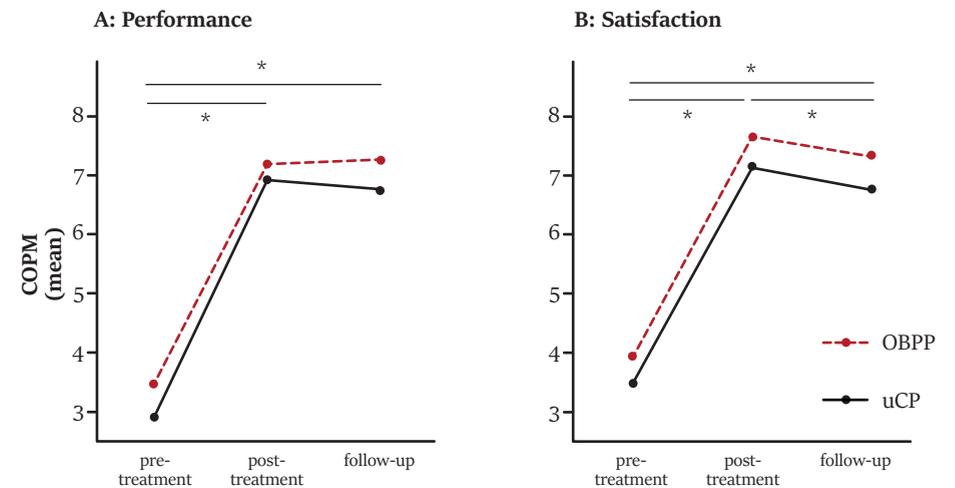
**Figure 4.2. ABILHAND-kids outcomes.** Mean ABILHAND-kids outcomes of both groups on three assessments. Data of children with obstetric brachial plexus palsy (OBPP) are depicted in red; data of children with unilateral cerebral palsy (CP) are shown in black. Statistical significant differences ( $p < .05$ ) are shown across both groups and are indicated by the asterisks. Trials of go/nogo paradigm.

#### 4.3.3 Subjective performance and satisfaction of problematic bimanual activities (COPM)

The repeated measures analysis of the COPM-Performance data revealed a significant and strong effect of time ( $F(2,33)=185.743$ ,  $p<.001$ ,  $\eta^2=.918$ ). No group difference or group\*time interaction was found. The post-hoc paired samples t-tests across both groups revealed significant differences between T1 (M=3.186) and T2 (M=7.050;  $t(35)=-18.765$ ,  $p<.001$ ,  $d=-3.13$ ) and between T1 (M=3.186) and T3 (M=7.011;  $t(35)=-18.040$ ,  $p<.001$ ,  $d=-3.01$ ), reflecting differences between pre-treatment and both following assessments. Again, no differences between T2 (post; M=7.050) and T3 (follow-up; M=7.011) were observed.

The repeated measures analyses of the COPM-Satisfaction data revealed a significant and strong effect of time ( $F(2,32)=145.169$ ,  $p<.001$ ,  $\eta^2=.901$ ). No group difference or group\*time interaction was observed. The post-hoc paired samples t-tests across both groups revealed significant differences between T1 (M=3.694) and T2 (M=7.397;  $t(34)=-15.951$ ,  $p<.001$ ,  $d=-2.70$ ) and between T1 (M=3.694) and T3 (M=7.063;  $t(34)=-17.027$ ,  $p<.001$ ,  $d=-2.88$ ), reflecting differences between pre-treatment and both following assessments. Furthermore, a significant difference between T2 (M=7.397) and T3 (M=7.063;  $t(34)=2.302$ ,  $p=.028$ ,  $d=0.39$ ) was found, showing reduced scores on the T3 compared to the T2 measurement.

**Figure 4.3.** shows COPM outcomes for both scales.



**Figure 4.3. ABILHAND-kids outcomes.** Mean ABILHAND-kids outcomes of both groups on three assessments. Data of children with obstetric brachial plexus palsy (OBPP) are depicted in red; data of children with unilateral cerebral palsy (CP) are shown in black. Statistical significant differences ( $p < .05$ ) are shown across both groups and are indicated by the asterisks. Trials of go/nogo paradigm.



## 4.4 DISCUSSION

In the current study the effects of modified constraint-induced movement therapy combined with intensive bimanual training (mCIMT-BiT) on upper limb performance were studied in a group of children with obstetric brachial plexus palsy (OBPP). The therapy outcomes were compared to the outcomes of a group of children with unilateral cerebral palsy (CP) where this treatment has been proven to be effective over usual care (Aarts et al., 2010). It was expected that in children with OBPP, as in children with unilateral CP, a combined program of mCIMT-BiT improves bimanual performance and enhances the spontaneous use of the AS.

In line with our hypothesis children with OBPP showed significant positive treatment effects following mCIMT-BiT. These effects were comparable to the effects observed in the control group of children with unilateral CP. Both children with OBPP and children with unilateral CP showed positive treatment effects on bimanual performance (ABILHAND-kids) as well as on subjectively reported performance and satisfaction of problematic bimanual activities (COPM). This was evidenced by significant differences between pre-treatment and post-treatment assessments. Importantly, retention of these effects was found at follow-up. These effects indicate that children with OBPP also benefit from mCIMT-BiT to improve bimanual performance. This extends earlier case reports solely focusing on the effects of mCIMT programs on individual case levels (Berggren & Baker, 2015; Buesch et al., 2010; Vaz et al., 2010), as well as studies solely focusing on the improvement of functional capacity of the AS (e.g. muscle strength, shoulder movement, range of movement) (Abdel-Kafy et al., 2013; Buesch et al., 2010; Santamato et al., 2011).

For the primary outcome measure reflecting the spontaneous use of the AS during bimanual activities (AHA), children with OBPP showed a significant increase in spontaneous upper limb use following mCIMT-BiT, as did the group of children with unilateral CP. Again, this increase exemplifies improved bimanual use following the combined mCIMT-BiT program. However, children with OBPP showed an additional improvement of spontaneous use of the AS when comparing post-treatment and follow-up assessments. For children with unilateral CP no such additional improvement at follow-up was established. This additional improvement for children with OBPP was not anticipated a priori, although similar results have earlier been reported on a case level (Buesch et al., 2010).

One possible explanation for these group differences might be related to the different mechanisms supposed to underlie the reduced spontaneous upper limb use in children with OBPP as compared to children with unilateral CP. In

both groups of children it has been suggested that, on top of the injury related reduced upper limb capacity, a phenomenon called developmental disregard might provoke reduced spontaneous AS use. However, next to the proposed underlying mechanisms causing developmental disregard in OBPP (i.e. learned non-use and neurodevelopmental delay/ deficiency) (Santamato et al., 2011; Vaz et al., 2010), in children with unilateral CP, additional cognitive mechanisms related to their central nervous system damage have been suggested to cause and maintain developmental disregard (Houwink, Aarts, Geurts, & Steenbergen, 2011; Zielinski, Jongsma, et al., 2014; Zielinski, Steenbergen, Baas, Aarts, & Jongsma, 2014). In the current study children participated in a combined mCIMT-BiT program. Whereas mCIMT is specifically focused on overcoming learned non-use by aiming at reversing the behavioral suppression of movement in the AS and by inducing cortical re-organization (Hoare et al., 2007; Taub et al., 1994), BiT is suggested to be crucial to effectively treat the developmental delay or deficiency related to the lack of experience of bimanual activities (Zielinski, Jongsma, et al., 2014). Both suggested underlying mechanisms causing and maintaining developmental disregard in OBPP therefore seemed to be targeted when applying mCIMT-BiT. However, no extra attention seems to be devoted to the possible additional cognitive mechanisms that cause and maintain developmental disregard in unilateral CP. Therefore, it can be argued that, next to effectively increasing bimanual performance in both groups, mCIMT-BiT helped children with OBPP to effectively overcome their symptoms of learned non-use and neurodevelopmental delay or deficiency (i.e. developmental disregard), leading to a continuous enhancement of spontaneous AS use. This continuous enhancement would in turn explain the additional improvement at follow-up. However, as developmental disregard was not directly assessed, this interpretation of the results needs further verification.

The current study was the first to report positive effects of a mCIMT-BiT program for children with OBPP. Furthermore, it was the first group study to report positive effects on actual upper limb performance following a mCIMT program. However, next to assessing developmental disregard to verify the interpretation of the differences between both groups, future research is needed to find the best balance between mCIMT and BiT for children with OBPP. This is important as concerns may rise about the manifestation of complaints caused by overuse of the musculoskeletal system when treating children with OBPP with intensive treatment programs. Attention needs to be paid to possible complaints when treating children with OBPP with similar programs and the ideal dose and balance of both types of therapy need to be determined. However, in line with the existing literature applying similar intensive mCIMT programs to children with OBPP (Abdel-Kafy et al., 2013; Buesch et al., 2010; Santamato et al., 2011;



Vaz et al., 2010), no related complaints were raised by children or parents in our population.

The current study was limited by the fact that no direct assessment of developmental disregard was performed. To substantiate the interpretations of the results that children with OBPP have indeed overcome developmental disregard, future studies should include an assessment of developmental disregard (Houwink, Geerdink, Steenbergen, Geurts, & Aarts, 2013). Furthermore, in the current study no direct comparison was made with a control group of children with OBPP receiving usual care. Therefore, we cannot conclude that mCIMT-BiT is more effective than usual care. Additionally, no extra baseline measurement preceding the pre-treatment measurement was included. Therefore, spontaneous recovery might have influenced our data. The fact that the effect size of the difference between post and follow-up measurement is smaller compared to the effect size of the difference between pre and post measurement might indicate that the direct effect of the therapy can be considered as stronger. This indicated support for the hypothesis that the smaller difference between post and follow-up measurement may be explained by the natural development of OBPP. Furthermore, we did not focus on the possible additional effect of adding BiT for children with OBPP. Even though the need of adding bimanual training is based on a solid theoretical background, this added value has not been tested systematically and the ideal dose and balance of both types of therapy were not assessed. Finally, even though no negative effects of the treatment were reported in the current study, future studies should consider to directly assess this, in order to rule out potential harmful effects of a treatment. We would furthermore advise future studies to control for improvements of hand capacity. This is more likely to occur in children with a less severe underlying damage and might give an alternative explanation for the improvement in hand performance (instead of overcoming developmental disregard).

#### 4.4.1 Conclusion

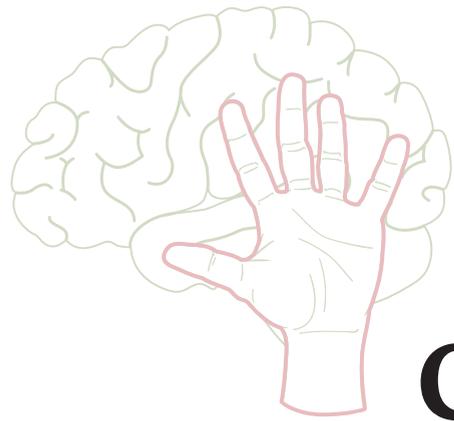
The results of the current study indicate improved bimanual performance and spontaneous AS use in children with OBPP following a mCIMT-BiT program. This improvement was comparable to the improvement of a group of children with unilateral CP, where this treatment has been proven to be effective over usual care. This suggests that mCIMT-BiT is an effective treatment method to enhance upper limb performance in children with OBPP. Furthermore, in children with OBPP, spontaneous AS use seems to further gradually increase after therapy. This might indicate that these children have overcome their symptoms of developmental disregard. Further research is needed to verify that mCIMT-BiT is more effective than usual care, to find out whether positive therapy effects are

due to overcoming developmental disregard, and to rule out that the observed effects are due to spontaneous recovery.

## 4.5 ACKNOWLEDGEMENTS

We want to thank all children and their families who allowed us for using these data.





# CHAPTER

# V

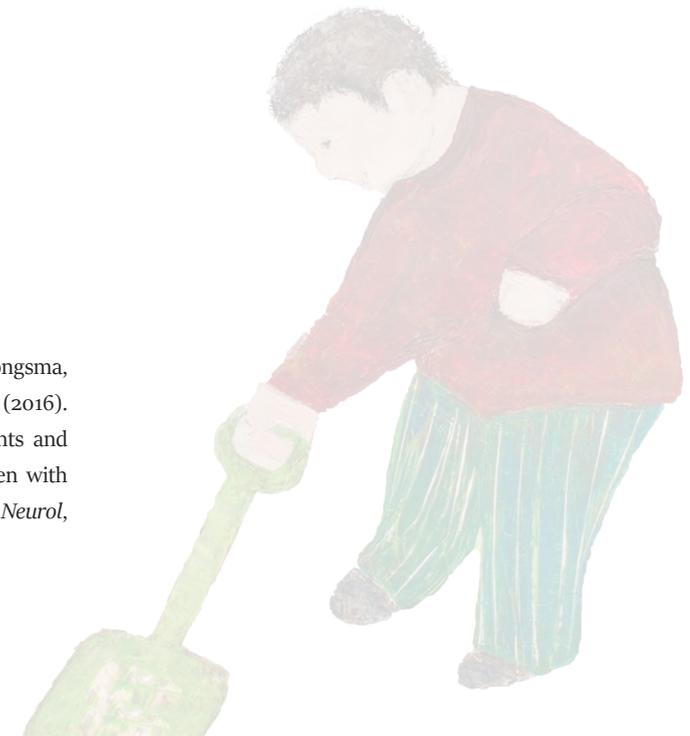
## The Relation Between Mirror Movements and Non-use of the Affected Hand in Children with Unilateral Cerebral Palsy

### Abstract

In children with unilateral cerebral palsy (CP), it is widely believed that mirror movements contribute to non-use of the affected side (AS) despite preserved capacity, a phenomenon referred to as developmental disregard. We aimed to test whether mirror movements are related to developmental disregard, and to clarify the relation between mirror movements and bimanual function. A repetitive squeezing task simultaneously measuring both hands' grip-forces was developed to assess mirror movements by using maximum cross-correlation coefficient ( $CCC_{max}$ ) as well as strength measures ( $MM_{strength}$ ). Developmental disregard, bimanual performance, and capacity were assessed using a validated video-observation method. Twenty-one children with unilateral CP participated (Median age 10y 7mo, interquartile range [IQR] 10y 1mo–12y 9mo). Outcome measures of mirror movements were correlated to developmental disregard, bimanual performance, and capacity scores using Spearman-rank correlations (significance level:  $\alpha < 0.05$ ). Mirror movements were not related to developmental disregard. However, enhanced mirror movements in the less-AS were related to reduced performance ( $CCC_{max}$ :  $q = -0.526$ ,  $p = 0.007$ ;  $MM_{strength}$ :  $q = -0.750$ ,  $p < 0.001$ ) and capacity ( $CCC_{max}$ :  $q = -0.410$ ,  $p = 0.033$ ;  $MM_{strength}$ :  $q = -0.679$ ,  $p < 0.001$ ). These relations were only moderate (performance:  $MM_{strength}$ :  $q = -0.504$ ,  $p = 0.010$ ), low (capacity:  $MM_{strength}$ :  $q = -0.470$ ,  $p = 0.016$ ) or absent for mirror movements in the AS. Additionally, seven children showed stronger movements in their less-AS when actually being asked to move their AS. These findings show no relation between mirror movements and developmental disregard, but support an association between mirror movements and bimanual function.

### This chapter is based on:

Zielinski, I.M., Green, D., Rudisch, J., Jongsma, M.L.A., Aarts, P.B.M., & Steenbergen, B. (2016). The relation between mirror movements and non-use of the affected hand in children with unilateral cerebral palsy. *Dev Med Child Neurol*, doi: 10.1111/dmcn.13204



## 5.1 INTRODUCTION

In some children with unilateral cerebral palsy (CP), bimanual performance is more restricted than would be expected based on the capacity of the affected side (AS) (Hoare, Wasiak, Imms, & Carey, 2007; Houwink, Aarts, Geurts, & Steenbergen, 2011). These children appear to disregard their AS during typical bimanual daily activities. This non-use during spontaneous daily activities, in combination with preserved AS capacity, is frequently referred to as developmental disregard (Deluca, Echols, Law, & Ramey, 2006; Houwink et al., 2011). Next to the direct negative impact of developmental disregard on spontaneous daily functioning, the lack of use of the AS might in turn also lead to reduced upper-limb function. This is because movements are not being automated and neural substrates serving entire classes of behaviors might not be established during development (Deluca et al., 2006).

One suggested underlying cause for developmental disregard is the persistence of mirror movements occurring in the upper-limbs (Hoare et al., 2007; Kutzt-Buschbeck, Sundholm, Eliasson, & Forssberg, 2000). Mirror movements are simultaneous involuntary movements that accompany voluntary movements of homologous muscles on the opposite side of the body (Kutzt-Buschbeck et al., 2000). For example, when one hand moves voluntarily, the other hand involuntarily performs the same action. Even though mirror movements are considered to be a normal feature of motor behavior in young children due to immaturity of the central nervous system, they are known to gradually disappear during the first decade of life (Connolly & Stratton, 1968). However, in many children with unilateral CP these mirror movements are more pronounced and persistent (Woods & Teuber, 1978). They are more frequently observed in the less-AS when actively moving the AS and are reported to be stronger compared to mirror movements in the AS (Kutzt-Buschbeck et al., 2000; Woods & Teuber, 1978).

There are two proposed mechanisms which may underlie mirror movements in children with unilateral CP. First, the motor cortex of the less-affected hemisphere is controlling the two hands via both contralateral projections to control the less-AS, and preserved ipsilateral projections to control the AS movements, causing mirror movements in both, but especially in the AS (Jaspers, Byblow, Feys, & Wenderoth, 2015; Staudt et al., 2004). Second, widespread and bilateral cortical activation occurs when actively moving the AS related to the sensorimotor impairments of this AS. This lack of interhemispheric inhibition leads to motor overflow causing mirror movements in the less-AS (Jaspers et al., 2015; Klingels et al., 2015; Staudt et al., 2004). Mirror movements in the AS have thus been proposed to be indicative for one motor cortex controlling both hands

(Jaspers et al., 2015), while mirror movements in the less-AS might simply be explained by sensorimotor impairments of the AS.

Mirror movements presented in the upper-limbs and their relation with upper-limb function has repeatedly been studied in children with unilateral CP (Adler, Berweck, Lidzba, Becher, & Staudt, 2015; Holmstrom et al., 2010; Islam, Gordon, Skold, Forssberg, & Eliasson, 2011; Klingels et al., 2015; Kutzt-Buschbeck et al., 2000). Even though results vary, they generally point towards an association between pronounced manual mirror movements and diminished bimanual performance (Adler et al., 2015; Klingels et al., 2015; Kutzt-Buschbeck et al., 2000). However, findings are inconclusive, with some studies showing associations between diminished bimanual performance and mirror movements in either hand (Adler et al., 2015; Kutzt-Buschbeck et al., 2000), while others only report this association for mirror movements in the less-AS (Klingels et al., 2015). Still, the reported findings led authors to conclude that the symmetric nature of mirror movements hinders efficient bimanual task execution (Adler et al., 2015; Klingels et al., 2015; Kutzt-Buschbeck et al., 2000). Because most daily activities require asymmetrical actions of both hands (typically with the AS having a holding or stabilizing function), it was repeatedly suggested that pronounced mirror movements might even lead to the exclusion of the AS in spontaneous bimanual activities (Hoare et al., 2007; Kutzt-Buschbeck et al., 2000). In the typical stabilizing function of the AS, mirror movements in this AS will result in difficulties in stabilizing objects when performing manipulative tasks with the less-AS. Furthermore, when actively moving the AS during bimanual asymmetric activities, mirror movements in the less-AS cause a reduction in independent control of this 'good hand' (Kutzt-Buschbeck et al., 2000). It has therefore been suggested repeatedly that mirror movements in either hand contribute to the phenomenon of developmental disregard in children with unilateral CP through a process of learned non-use (Adler et al., 2015; Hoare et al., 2007; Klingels et al., 2015; Kutzt-Buschbeck et al., 2000).

Although some studies have explored the relation between mirror movements and bimanual performance while controlling for the capacity of the AS (Adler et al., 2015; Klingels et al., 2015), the relation between mirror movements and developmental disregard has never been studied directly. By using a standardized measurement to assess developmental disregard (Houwink, Geerdink, Steenbergen, Geurts, & Aarts, 2013), the main aim of the current study was to test whether enhanced manual mirror movements are related to a greater degree of developmental disregard in children with unilateral CP. Second, by using a newly developed continuous scale with which distal manual mirror movements in both hands are registered separately (i.e. mirror movements in the AS when actively moving the less-AS and mirror movements in the less-



AS when actively moving the AS), we aimed to clarify the relationship between mirror movements in either hand and the previously reported impact on bimanual performance (Adler et al., 2015; Klingels et al., 2015; Kuhtz-Buschbeck et al., 2000).

## 5.2 METHODS

### 5.2.1 Participants

Children and adolescents with unilateral CP, aged 7 to 18 years were recruited from different rehabilitation centres in the Netherlands and the UK. Inclusion criteria were diagnosis of unilateral CP with a Manual Ability Classification System (MACS) level of I to III (Eliasson et al., 2006). Many children were part of larger studies exploring neurocognitive processes, brain structures, and/or functions related to upper-limb movements using electroencephalogram (EEG), neuroimaging, and/or transcranial magnetic stimulation. The study was approved by the National Research Ethics Service (NRES), UK, as well as by the local Ethical Committee (CMO) of the region Arnhem-Nijmegen, the Netherlands. All parents provided written informed consent for participation of their children at the study as well as for publication of the results. Children over 12 also provided written assent.

### 5.2.2 Clinical assessment of upper-limb capacity, performance, and developmental disregard

For the clinical assessment of developmental disregard, upper-limb capacity, and performance, the ‘revised Video-Observation Aarts and Aarts module: Determine Developmental Disregard’ was used (Houwink et al., 2013). Here, capacity is defined as the frequency of AS-use during a task that requires bimanual hand-use. Performance is defined as the frequency of AS-use during a task that stimulates bimanual hand-use, but is not essential to performance of the task (i.e. it is possible to perform the task with only one hand). Developmental disregard is defined as the difference between the duration of AS-use between both tasks, the ‘demanding’ and the ‘stimulating’ task (Houwink et al., 2013). Whenever this developmental disregard score was higher than a previously validated cut-off score (i.e. 17.2%) (Houwink et al., 2013), children were classified as having developmental disregard.

### 5.2.3 Quantitative assessment of mirror movements

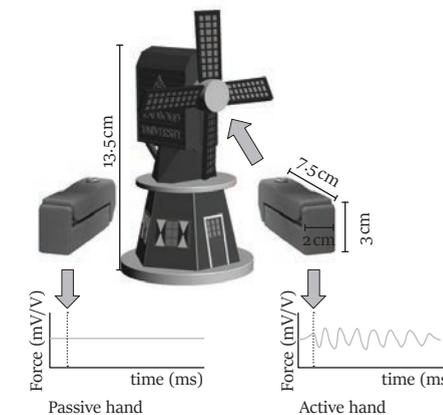
A custom-made repetitive squeezing task was developed to quantitatively register distal manual mirror movements. During this so-called ‘Windmill-task’, mirror

movements were assessed by placing two grip-force transducers (equipped with micro load cells: 0–5 kg; weight: 45 g; circumference: 10 cm) between thumb and index- plus middle-finger of the children’s hands. When the child was not able to hold the transducer with these three fingers (e.g. due to muscle weakness or spasticity), additional fingers were allowed to stabilize the grip. The grip of the less-AS was always matched to the grip of the AS: when using additional fingers with the AS the same fingers were used with the less-AS. One of the transducers was connected to a little windmill (**figure 5.1**). The motor of the windmill was programmed so the mill started rotating once the connected transducer was pressed beyond a certain threshold (approximately 1.5 kg). To speed up the rotation of the mill, the grip had to be returned to a lower threshold by loosening the grip (approximately 1 kg) and again reach the upper threshold within 1000 ms, so that a repetitive squeezing pattern was induced ( $\geq 1$  Hz frequency). Children were instructed to hold the transducers in both hands with the hands lifted to chest level. With one hand (active hand) they were asked to repetitively squeeze the transducer in order to rotate the mill of the windmill as fast as possible. With the other hand, children were asked to simply lift and hold the second transducer (passive hand, tested for mirror movements).



A: Schematic of windmill and handles

B: Participant performing Windmill-task



**Figure 5.1.** (A) The Windmill-task as positioned for a right-hand active squeezing. The two objects next to the windmill represent the grip-force transducers with the right transducer being connected to the windmill. Both transducers are connected to a computer, digitizing and storing the data recorded of both hands time-locked grip-force (in mV/V). This figure represents a squeezing pattern with the passive hand showing no mirror movements. (B) Participant performing the Windmill-task.

To measure the grip-force, the grip objects were equipped with strain-gauge load cells that converted the force into an electrical signal (mV/V). The time-locked grip-force signal of both hands was sampled at 50 Hz, digitized, and stored on a computer.

#### 5.2.4 Procedure

After administering the ‘revised Video-Observation Aarts and Aarts module: Determine Developmental Disregard’ (Houwink et al., 2013), (participants were seated on a chair in front of a table upon which the windmill was placed. A standardized protocol of 5 seconds of squeezing and 5 seconds of rest with a total of 20 repetitions was conducted for each hand (100s of squeezing data for each hand). A pre-recorded voice indicated the start and stop for rotating the mill. Both hands were tested separately, always with the less-AS first (less-AS-squeezing condition) to prevent early frustration. Thus, distal manual mirror movements in both hands were tested separately: (1) mirror movements in the AS during less-AS-squeezing; and (2) mirror movements in the less-AS during AS-squeezing. A short practice session for each condition was conducted prior to the task (two trials of 5s of squeezing).

#### 5.2.5 Data pre-processing

First, to quantify mirror movements, the force pattern of both hands during each squeezing session (20x5s) was compared by cross-correlating both signals (Nelson-Wong, Howarth, Winter, & Callaghan, 2009). Both grip-force signals were correlated by iteratively shifting one signal forwards in time against the other signal. A correlation-coefficient (Pearson’s  $r$ ) was calculated for each phase shift (steps of 20ms at a 50Hz sampling rate), resulting in a time series of Pearson’s  $r$  values. This time series was representing a correlation function at each increment of the phase shift between the two input signals (Nelson-Wong et al., 2009). In a second step, an average cross-correlation function was obtained from all squeezing sessions. The maximum correlation-coefficient of this averaged function ( $CCC_{max}$ ) was used as an index of the similarity between the two squeezing signals. Hence,  $CCC_{max}$  is indicative of the intensity of mirror movements, with  $r=0$  reflecting no mirroring of the passive hand during active hand movement, and  $r=1$  reflecting that the passive hand is performing the exact same movement as the active hand. Whenever  $CCC_{max}$  was  $\geq 0.30$ , children were classified as having mirror movements, as a correlation-coefficient  $< 0.30$  is considered negligible (Mukaka, 2012).

To further operationalize the intensity of the mirror movements, the mean grip-force of the passive hand during each squeezing session was calculated

as the difference between the peaks and the troughs of the force signal. These values were averaged across all trials and normalized by dividing them by the mean force values of the same hand when actively squeezing ( $MM_{strength}$ ). A higher  $MM_{strength}$  indicated increased strength in the passive hand during the squeezing period, hence pronounced mirror movements.

$CCC_{max}$  and  $MM_{strength}$  calculations were performed separately for both conditions (AS-squeezing vs. less-AS-squeezing). The active squeezing period started 500ms after the ‘start’ signal and lasted 5 seconds to control for the slight delay following the auditory ‘start’ signal. All trials were individually inspected and excluded from the analyses if the active hand did not show a repetitive squeezing pattern (at least five repetitions  $\geq 1$ Hz) within this period (3.1% data exclusion in the AS-squeezing condition; 1.2% in the less-AS-squeezing condition).

#### 5.2.6 Statistical analysis

Shapiro–Wilk tests indicated that most variables were not normally distributed (only the  $CCC_{max}$  variables for both conditions were normally distributed). Furthermore, only small numbers of participants ( $n < 30$ ) were included for the current study. Therefore, for statistical analysis non-parametric tests were applied.

Aim 1: To test the relation between enhanced distal hand mirror movements and higher developmental disregard scores,  $CCC_{max}$  and  $MM_{strength}$  values were related to the individuals’ developmental disregard scores for both conditions separately (AS-squeezing vs. less-AS-squeezing) using one-tailed Spearman-rank ( $\rho$ ) correlations.

Aim 2: To clarify the relation between mirror movements in either hand and upper-limb function, we first verified whether mirror movements were stronger in the less-AS when the AS was actively moving. Two Wilcoxon Signed-Rank tests were used to compare  $CCC_{max}$  and  $MM_{strength}$  scores between both hands.

Subsequently, one-tailed Spearman-rank ( $\rho$ ) correlations were applied between ‘revised Video-Observation Aarts and Aarts module: Determine Developmental Disregard’ (Houwink et al., 2013) outcomes of upper-limb performance and  $CCC_{max}$  and  $MM_{strength}$  scores for both conditions separately (AS-squeezing vs. less-AS-squeezing). The same was done for the ‘revised Video-Observation Aarts and Aarts module: Determine Developmental Disregard’ (Houwink et al., 2013) upper-limb capacity scores. For all analyses, the significance level was set at a  $< 0.05$ . Correlation coefficients  $> 0.70$  were considered as high, 0.50 to 0.70 as moderate, 0.30 to 0.50 as low, and  $< 0.30$  as negligible (Mukaka, 2012).



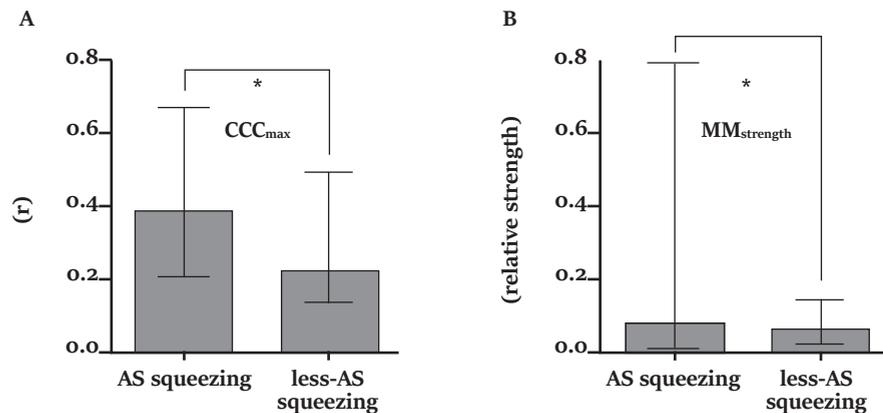
## 5.3 RESULTS

### 5.3.1 Participants

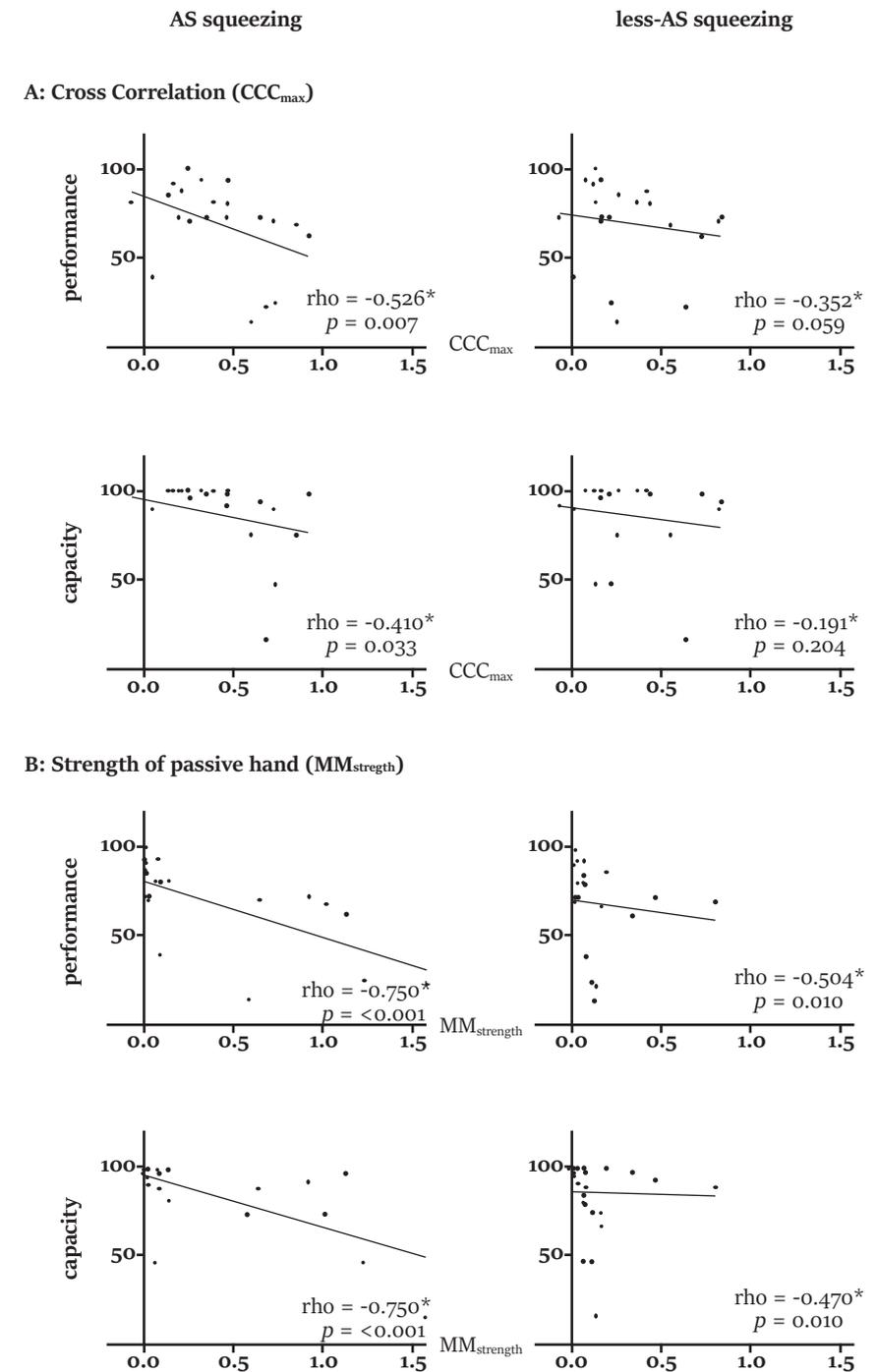
Twenty-three children and adolescents with unilateral CP participated. Two were excluded as they were not able to perform the task with their AS (MACS III). For the remaining 21 participants (12 males; 5 MACS I, 14 MACS II, 2 MACS III) the median age was 10 years and 7 months (IQR 10y 1mo–12y 9mo; 12 AS right). Nine participants were classified as having developmental disregard (developmental disregard score  $\geq 17.2\%$ ; 6 males; 6 AS right;  $M_{age}=10y 8mo$ ). Seven children did not show any mirror movements ( $CCC_{max} < 0.30$ ; 4 males; 4 AS right;  $M_{age}=11y 1mo$ ); six children showed mirror movements only in the less-AS when the AS was actively moving (4 male; 4 AS right;  $M_{age}=10y 6mo$ ); seven children showed mirror movements in both hands (4 male; 4 AS right;  $M_{age}=12y 10mo$ ), and one child showed only mirror movements in the AS when the less-AS was actively moving (male; AS right; age=7y 1mo).

### 5.3.2 Mirror movements

Aim 1: Developmental disregard scores were not related to mirror movements in the AS ( $CCC_{max}$ :  $\rho=0.091$ ,  $p=0.348$ ;  $MM_{strength}$ :  $\rho=0.201$ ,  $p=0.191$ ) or less-AS ( $CCC_{max}$ :  $\rho=0.113$ ,  $p=0.313$ ;  $MM_{strength}$ :  $\rho=0.129$ ,  $p=0.289$ ).



**Figure 5.2.**  $CCC_{max}$  (A) and  $MM_{strength}$  (B) values representing the intensity of mirror movements per condition (left: AS actively squeezing; right: less-AS actively squeezing) represented by the medians and interquartile ranges.  $CCC_{max}$  values indicate the averaged maximum cross-correlation between both hands force signals, with higher values reflecting more similarity between both force patterns, hence more mirror movements.  $MM_{strength}$  values indicate the strength of the passive hand during the active squeezing period, with higher values indicating stronger mirror movements; AS, affected side.



**Figure 5.3.** Depicted are correlations between upper-limb function (performance and capacity) and mirror movements, with \* representing significance ( $p < 0.05$ ) and # representing a statistical trend ( $p < 0.1$  and  $> 0.05$ ). (A) Correlations between upper-limb function (upper graphs: performance; lower graphs: capacity) and the cross-correlation between both hands force signals ( $CCC_{max}$ ). (B) Correlation between upper-limb function (upper graphs: performance; lower graphs: capacity) and the strength of the passive hand during the active squeezing.  $CCC_{max}$ , maximum cross correlation coefficient;  $MM_{strength}$ , mean strength of the passive hand; AS, affected side.

Aim 2: More mirror movements were observed in the less-AS, evidenced by significantly higher  $CCC_{max}$  and  $MM_{strength}$  values when the AS was actively moving ( $CCC_{max}$ : Median=0.39, IQR 0.20–0.67;  $MM_{strength}$ : Median=0.077, IQR 0.009–0.792) compared with when the less-AS was actively moving ( $CCC_{max}$ : Median=0.22, IQR 0.13–0.49,  $p=0.046$ ;  $MM_{strength}$ : Median=0.065, IQR=0.019–0.144,  $p=0.035$ ; see **figure 5.2.**).

For mirror movements in the less-AS, correlation analyses showed moderate to high associations between low scores on upper-limb performance and enhanced mirror movements. This was evidenced by a significant negative correlation between performance and  $CCC_{max}$  scores ( $\rho=0.526$ ,  $p=0.007$ ) as well as between performance and  $MM_{strength}$  values ( $\rho=0.750$ ,  $p < 0.001$ ). For upper-limb capacity, low to moderate significant negative correlations were observed ( $CCC_{max}$ :  $\rho=0.410$ ,  $p=0.033$ ;  $MM_{strength}$ :  $\rho=0.679$ ,  $p < 0.001$ ; see **figure 5.3.**, ‘AS-squeezing’).

Mirror movements in the AS also showed significant, low to moderate negative correlations with bimanual performance ( $MM_{strength}$ :  $\rho=0.504$ ,  $p=0.010$ ) and capacity scores ( $MM_{strength}$ :  $\rho=0.470$ ,  $p=0.016$ ; see **figure 5.3.**, ‘less-AS squeezing’). Correlations between  $CCC_{max}$  scores and bimanual performance ( $\rho=0.352$ ,  $p=0.059$ ) as well as capacity ( $\rho=0.191$ ,  $p=0.204$ ) did not reach significance.

### 5.3.3 Additional findings

During the ‘AS-squeezing’ condition seven children (five male, 3 AS right, Median age: 11y 10mo) displayed a stronger force pattern in the passive, less-AS (Median 2831.35, IQR 2275.01–2924.79) compared with the active, AS (Median 1655.80, IQR 1065.66–1949.10). In all of these seven children, the time-lag information of the  $CCC_{max}$  values were negative, indicating that the less-AS was moving slightly before the AS. This pattern was only observed in children with greater impairments in manual ability ( $MACS \geq 2$ ).

## 5.4 DISCUSSION

The main finding of the current study is that distal manual mirror movements during a unimanual squeezing task in unilateral CP are not related to the phenomenon of developmental disregard. Earlier studies have suggested a direct relation between manual mirror movements and non-use or disregard of the AS (Adler et al., 2015; Hoare et al., 2007; Klingels et al., 2015). This suggestion was based on the observed association between pronounced mirror movements and diminished bimanual performance (Adler et al., 2015; Klingels et al., 2015; Kuhtz-Buschbeck et al., 2000). It has been argued that when mirror movements occur in the AS, which mostly has a holding or stabilizing function, mirror movements cause less stability; furthermore, mirror movements cause a reduction in independent control of the less-AS when occurring while actively moving the AS during bimanual asymmetric activities (Kuhtz-Buschbeck et al., 2000). Our findings concur with these hypotheses, showing a relation between pronounced mirror movements in either hand and diminished bimanual performance. Previous hypotheses have posited that mirror movements may therefore lead to a non-use of the AS in spontaneous bimanual activities, i.e. developmental disregard (Adler et al., 2015; Klingels et al., 2015). The present study is the first to directly test this suggested relation between manual mirror movements and developmental disregard, and results show a lack of this association.

The factors contributing to the phenomenon of developmental disregard are not yet fully understood. Originally, it was argued that developmental disregard is a behavioral phenomenon, resulting from the negative experience each time the AS is used (Taub, Uswatte, Mark, & Morris, 2006). However, recent experimental findings aimed at unraveling developmental disregard (Zielinski, Jongsma, Baas, Aarts, & Steenbergen, 2014; Zielinski, Steenbergen, Baas, Aarts, & Jongsma, 2014), as well as related theoretical frameworks (Deluca et al., 2006; Hoare et al., 2007; Sutcliffe, Logan, & Fehlings, 2009; Weinstein et al., 2014), suggest that this phenomenon may also be the result of compromised visuo-spatial attention as well as a developmental delay related to higher order motor executive functions, thereby challenging the earlier accounts of developmental disregard (Mukaka, 2012). Our current finding – that mirror movements are not related to developmental disregard – adds to this body of knowledge by showing that reduced bimanual efficiency does not necessarily lead to developmental disregard in children with unilateral CP.

Another important facet of our study was the clarification of the nature of the relationship between distal manual mirror movements and bimanual performance. This was done by using an objective quantitative assessment tool to assess distal hand mirror movements in both hands separately and relating



this data to a bimanual performance measure. Previously reported results have been inconclusive, with some study results showing associations between diminished bimanual performance and mirror movements in both hands (Adler et al., 2015; Kutzt-Buschbeck et al., 2000), while other findings only report this association for mirror movements appearing in the less-AS (Klingels et al., 2015). However, these earlier studies either used only a subjective, ordinal rating scale for assessing mirror movements (Adler et al., 2015; Klingels et al., 2015) or lacked standardized testing when assessing bimanual performance (Kutzt-Buschbeck et al., 2000). We were able to show significant moderate to high correlations between bimanual performance and mirror movements appearing in the less-AS when the AS was actively moving. Additionally, low to moderate correlations were also observed between bimanual performance and mirror movements appearing in the AS when the less-AS was actively moving. By confirming these relations, we showed that mirror movements in either hand might be related to reduced performance during bimanual asymmetric activities. At the same time, our finding of a lack of relation between these mirror movements and developmental disregard indicates that this does not necessarily lead to a non-use or disregard of the AS during spontaneous daily activities.

Next to the explanation that mirror movements are directly related to a reduced performance during bimanual asymmetric activities, the negative correlation between bimanual performance and mirror movements might also simply be explained by the type and/or severity of the children's lesion. The neuropathology would then in turn explain both, the reduced bimanual performance as well as the enhanced mirror movements (due to widespread bilateral activation during unimanual movements or even ipsilateral cortico-spinal connections from the less-affected hemisphere to the AS) (Jaspers et al., 2015; Klingels et al., 2015; Staudt et al., 2004). This interpretation is supported by the current finding that mirror movements were also correlated to hand capacity, as has been reported previously (Klingels et al., 2015). However, without details of the extent and location of the individual lesions or direct unimanual capacity measures, it is not possible to elaborate on the cause of the observed reduction in bimanual performance.

Our results furthermore replicated earlier findings that many children with unilateral CP display significantly more mirror movements in the less-AS compared with the AS (Klingels et al., 2015; Kutzt-Buschbeck et al., 2000; Woods & Teuber, 1978). There are three potential explanations for this finding. First, the more dextrous use of the less-AS compared with the AS might contribute to a more discrete and lateralized pattern of neural control of the less-AS compared with the AS, leading to reduced mirror movements in the AS when the less-AS is

actively moving (Klingels et al., 2015; Kutzt-Buschbeck et al., 2000). Second, the enhanced mirror movements in the less-AS might be related to the sensorimotor impairments of the AS, and evolve due to inefficient interhemispheric inhibition from the affected hemisphere, resulting in bilateral excitatory activity (Zielinski, Steenbergen, et al., 2014). Third, mirror movements appearing in the less-AS might represent a non-specific motor overflow phenomenon which indirectly assists AS movements (Klingels et al., 2015). This latter explanation is based on the notion that children with reduced manual ability of the AS may move both hands simultaneously when asked to only move their AS, in order to overcome the lack of selectivity and strength of their AS. This is because symmetrical movements are performed more easily (Swinnen & Wenderoth, 2004). This possible assisting strategy might be especially useful during predominantly symmetric bimanual activities and potentially also during the less frequently observed phenomenon of unimanual AS movements (e.g. releasing an object by actively opening the less-AS). Thus, mirror movements in the less-AS may in some cases be considered to assist controlled movements of the AS.

In line with the suggestion that mirror movements appearing in the less-AS might occur to assist AS movement, we found that seven children displayed a stronger force pattern in the less-AS when they were asked to actively move their AS. These children also started moving their less-AS slightly earlier. This additional finding may imply that these children facilitate the movement of their AS by moving their less-AS. That is, they appear to 'use' their mirror movements as a strategy to facilitate movements of the AS. This pattern was only observed in children with reduced manual ability ( $MACS \geq 2$ ). Therefore, the slight delay of the AS movement might also be explained by biomechanical processes related to this reduced manual ability. Further research is warranted to unravel the possible strategic use – in particular, to answer the question of whether this possible strategic use of mirror movements leads to a better unimanual or bimanual control of the AS during some daily activities.

The current study was limited by the small group size, especially of the more severely impaired children (i.e. MACS III). Additionally, two children had to be excluded as they were not able to complete the task with their AS. For future studies, the task needs to be adapted in a way that the thresholds for moving the windmill are scaled to the individuals' maximal force capacities. Another limitation affecting performance is our block design, where the less-AS always started. This may have led to possible carry-over effects that would have been avoided with a randomized design. Finally, and inherent to the studied population, is the heterogeneity of the studied group (e.g. aetiology, underlying differences in brain injury).



#### 5.4.1 Conclusion

No relation between mirror movements and developmental disregard in children with unilateral CP was observed. Using a newly developed quantitative tool to assess mirror movements, earlier findings on mirror movements were supported: mirror movements were related to reduced manual performance. Furthermore, mirror movements were shown to be stronger in the less-AS during AS movement. Finally, in a subset of the children, our new quantitative measurement uncovered a possible strategy to use mirror movements to control movements of the AS.

### 5.5 ACKNOWLEDGEMENTS

We want to thank all the children and their families who took part in this study. We also want to kindly acknowledge Mark van de Hei and Pascal de Water from the technical support group of the Radboud University Nijmegen for their valuable and professional assistance in developing the 'Windmill-task'. Furthermore, we kindly thank Sabine Vincon for her help in collecting the clinical data. This work is part of a doctoral dissertation that was supported by grants from (in alphabetical order): Hersenstichting Nederland, Johanna KinderFonds, Stichting Rotterdams Kinder-revalidatie Fonds Adriaanstichting, Phelps Stichting voor Spastici, and Revalidatiefonds. The authors have stated that they had no interests which might be perceived as posing a conflict or bias.

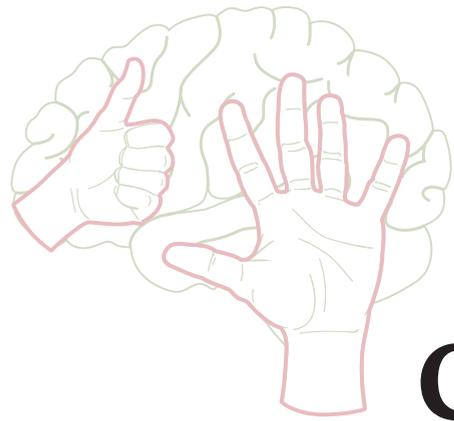


# PART 2

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## **THE INFORMATION PROCESSING FRAMEWORK**

developmental disregard as a  
phenomenon of a deficient and/or  
delayed development of cognitive  
processes involved in movement control



# CHAPTER VI

## Developmental Disregard in Unilateral Cerebral Palsy: No EEG Mu-restoration Following Hand Movements

### Abstract

Many children with unilateral Cerebral Palsy (uCP) show a non-use of the preserved capacity of their affected side (AS), known as developmental disregard (DD). It has been hypothesized that DD is related to a delayed or deficient development of neural circuits involved in motor control, caused by a lack of use of the AS during sensitive developmental periods. The typically observed EEG mu-restoration following movements is thought to reflect top-down control processes that prepare functional neural circuits of motor control to perform new relevant tasks. It is hypothesized that in DD this mu-restoration after voluntary AS-movements is reduced. Twenty-four children with uCP (10 with DD) performed a unimanual squeezing task. Mean EEG mu-rhythm (7-13.5Hz) was extracted from the EEG above the sensorimotor cortex (C3 and C4) during rest and movement of each hand. A repeated-measures GLM was conducted with group (noDD vs. DD) as between- and side (AS vs. less-AS), condition (rest vs. movement), and electrode (C3 vs. C4) as within-subject variables. The repeated-measures GLM revealed a significant condition\*group interaction ( $F(22)=4.617$ ,  $p=.043$ ). Post-hoc analysis revealed no difference between conditions for the DD group, whereas significant differences between rest and movement across both hands were observed in children without DD ( $F(13)=7.412$ ,  $p=.017$ ). While a typical EEG mu-restoration after voluntary hand movements was observed in children without DD, no mu-restoration was observed in children with DD after both AS- and less-AS-movements. This finding suggests a deficiency of top-down processes related to voluntary movement control of both the hands in children with DD.

### This chapter is based on:

Zielinski, I.M., Steenbergen, B., Aarts, P.B.M., Green, D., & Jongsma, M.L.A. *Adv Cogn Psychol* (submitted). Developmental Disregard in unilateral Cerebral Palsy: no EEG mu-restoration following hand movements. *Adv Cogn Psychol* (submitted).



## 6.1 INTRODUCTION

A reduced use of the existing upper limb capacity in children with unilateral cerebral palsy (CP) is frequently observed (Taub, Ramey, DeLuca, & Echols, 2004). This phenomenon is generally referred to as developmental disregard (DeLuca, Echols, Law, & Ramey, 2006; Houwink, Aarts, Geurts, & Steenbergen, 2011). When performing typical bimanual tasks, children with developmental disregard show a preference for unimanual performance, even when recruiting the preserved capacity of the affected side (AS) would have resulted in a more efficient performance (DeLuca et al., 2006; Houwink et al., 2011). Although these children frequently manage to perform typical bimanual tasks with only one hand (employing strategies such as using the teeth or stabilizing objects against the body), time for task completion is often prolonged (Van Zelst, Miller, Russo, Murchland, & Crotty, 2006). As a consequence, these children seek assistance from others, or even avoid certain activities, which may eventually lead to reduced participation in physical and social activities (Chorna et al., 2015; Skold, Josephsson, & Eliasson, 2004). Understanding of the underlying mechanism for this non-use of the remaining upper limb capacity is therefore important to promote children's independence and participation in daily life.

One common explanation for the symptoms of non-use observed in children with developmental disregard is based on operant conditioning processes (Crocker, MacKay-Lyons, & McDonnell, 1997; Taub, 1980). It compares developmental disregard to the phenomenon of learned non-use frequently observed in adult stroke patients (Taub & Wolf, 1997). It is defined as a learned suppression of movements of the AS, suggesting that hemiplegic patients have learned not to use the AS based on the negative experiences of unsuccessfully using this hand in combination with the positive experiences when successfully using (only) the less-AS (Taub & Wolf, 1997).

Despite the similar behavioral symptoms of reduced upper limb use observed in adult stroke patients and children with unilateral CP, the origins of these two appearances of "non-use" are likely different. This is because in children with unilateral CP developmental aspects play an important additional role. Principally, these children have never had the experience of successfully using their affected upper limb. Therefore, insufficient and/or incomplete motor learning may additionally cause the observed non-use in children with unilateral CP and developmental disregard (DeLuca et al., 2006; Hoare, Wasiak, Imms, & Carey, 2007; Houwink et al., 2011; Zielinski, Jongsma, Baas, Aarts, & Steenbergen, 2014; Zielinski, Steenbergen, Baas, Aarts, & Jongsma, 2014). In this context we recently showed that the preparation of voluntary hand movements during tasks involving both hands is accompanied by enhanced cognitive effort

in children with developmental disregard (Zielinski, Jongsma, et al., 2014; Zielinski, Steenbergen, et al., 2014). This increased effort was ascribed to a lack of automation of this bimanual performance (DeLuca et al., 2006; Fitts & Posner, 1967; Houwink et al., 2011). Thus, diminished experience in performing manual tasks involving the AS during development reduces successful automation of these (bi)manual tasks (Fitts & Posner, 1967; Floyer-Lea & Matthews, 2004).

Similar, but from a neurodevelopmental perspective, developmental disregard might be explained by a delayed or deficient development and refinement of brain circuits typically involved in motor control (DeLuca et al., 2006; Grefkes, Eickhoff, Nowak, Dafotakis, & Fink, 2008). Specifically, the intra- and interhemispheric circuits involved in volitional upper limb movement control are known to only effectively develop when actively moving the limb (Sanes & Donoghue, 2000). Furthermore, different lines of research suggest sensitive periods for this motor development in early childhood (between 6 months and 3 years), emphasizing the importance of actively moving the limbs during early developmental periods (Roerber, Gunnar, & Pollak, 2014; Watanabe, Savion-Lemieux, & Penhune, 2007). A non-use of the AS in children with unilateral CP, especially during these early sensitive periods, might therefore result in a lack of establishment, refinement, and effective connectivity of these neural circuits typically involved in the motor control of the AS (DeLuca et al., 2006; Zielinski, Steenbergen, et al., 2014).

EEG and MEG studies have repeatedly shown that the execution of movements is associated with changes in oscillatory neuronal activity in bilateral sensorimotor areas, which is observed by a suppression of the mu-rhythm (Pfurtscheller & Lopes da Silva, 1999; Pfurtscheller, Stancak, & Neuper, 1996). The synchronization of this mu-rhythm (i.e. enhanced mu) has originally been interpreted as a physiological correlate of deactivated cortical areas, or cortical "idling", while the de-synchronization of this mu-rhythm (i.e. reduced mu) has been interpreted as the physiological correlate of neuronal activation related to voluntary motor control (Pfurtscheller & Lopes da Silva, 1999; Pfurtscheller et al., 1996). However, recent theories suggest that the presence of a synchronous mu-rhythm reflects top-down control processes that inhibit irrelevant information and prepare the functional neural circuit to perform new relevant tasks (Klimesch, Sauseng, & Hanslmayr, 2007). The mu-restoration above the sensorimotor areas following movements is therefore of key interest when studying top-down cognitive control mechanisms typically involved in voluntary movement production.

To study if developmental disregard is related to a diminished refinement of neural circuits typically involved in voluntary motor control, we studied the patterns of mu-activations related to repetitive hand movements by means of



EEG. An earlier study on the movement related mu-rhythm in children with unilateral CP already reported a reduced or even absent state of preparedness for voluntary upper limb movement in these children (Daly et al., 2014). This was interpreted to be the result of an insufficient ability to develop relevant functional connectivity patterns during early developmental stages (Daly et al., 2014). However, the authors did not differentiate between children with and without developmental disregard. We argue here that this lack of preparedness may be especially present in children with developmental disregard due to a deficient development of neural circuits involved in motor control causing the symptoms of non-use in developmental disregard. We hypothesize that the movement related mu-restoration, reflecting the integrity of the complex functional system involved in voluntary motor control, is reduced in children with developmental disregard as compared to children with unilateral CP but without developmental disregard.

## 6.2 METHODS

### 6.2.1 Participants

Twenty-four children and adolescents with unilateral CP (Mage=10y, 10m; range:7y-18y; right hand affected: N=16; female: N=10) were recruited from different rehabilitation centers in the Netherlands and the UK. Inclusion criteria were a diagnosis of unilateral CP with a Manual Ability Classification System (MACS) level of I to III (I: N=6, II: N=17, III: N=1; MMACS=1.8). Many children were part of larger studies exploring neurocognitive processes, brain structures, and/or functions related to upper limb movements using EEG, neuroimaging, and/or transcranial magnetic stimulation.

The study was approved by the National Research Ethics Service (NRES; 10/Ho804/40/Am02), UK, as well as by the local Ethical Committee (CMO; NL44687.000.13) of the region Arnhem-Nijmegen, the Netherlands. All parents provided written informed consent for participation of their children at the study as well as for publication of the results. Children over 12 also provided written assent.

### 6.2.2 Procedure

First, developmental disregard was assessed using the “Video-Observation Aarts and Aarts module: Determine Developmental Disregard” (VOAA-DDD-R) (Houwink, Geerdink, Steenbergen, Geurts, & Aarts, 2013). This structured video observation with known psychometric properties (Houwink et al., 2013) assesses both the overall duration and frequency of AS-use during two standardized

tasks: one designed to demand the use of both hands, and one to merely stimulate bimanual activity. Developmental disregard is defined as the difference between the duration of AS-use among both tasks, so that children are diagnosed with developmental disregard when showing a distinct enhanced use of the AS during the ‘demanding’ as compared to the ‘stimulating’ task (i.e. 17.2%).

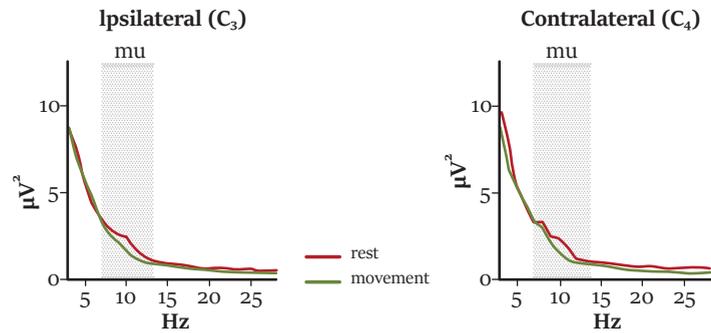
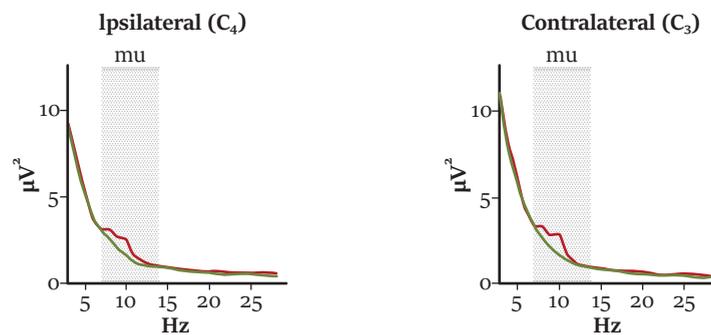
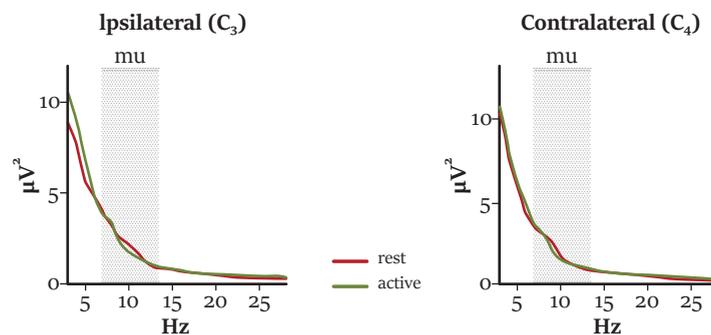
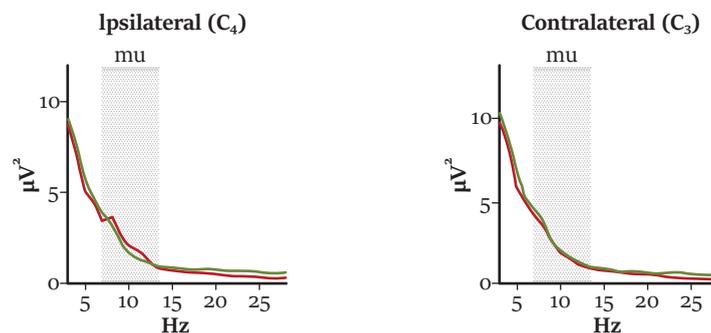
To compare the mean mu-rhythm between movement and rest, the children performed the Windmill-task (Zielinski et al., 2016). This unimanual repetitive squeezing task (originally designed to assess mirror movements) consisted of a standardized protocol of 5 seconds of squeezing and 5 seconds of rest with a total of 20 repetitions for each hand (100s of squeezing and 100s of rest data for each hand). A pre-recorded voice indicated the “start” and “stop” for the squeezing. Both hands were tested separately (AS squeezing vs. less-AS squeezing), always with the less-AS first to prevent early frustration.

### 6.2.3 EEG recording and pre-processing

EEG signals were recorded with a 32-channel active electrode system (actiCap MedCaT B.V. Netherlands) and amplified by a 32-channel BrainAmp EEG amplifier with electrode placement according to the international 10–20 system at Fz, FCz, Cz, Pz, Oz, Fp1/2, F3/4/7/8, FC1/2/5/6, C3/4, T7/8, CP1/2/5/6, P3/4/7/8, O1/2 (Klem, Luders, Jasper, & Elger, 1999). A ground electrode was placed over AFz. Electrooculography (EOG) was recorded from channels placed above and below the right eye and on the outer canthi of each eye. Electrode impedance was kept below 20 k $\Omega$ . The signal was digitized at 1000 Hz between 0.016–250 Hz.

Offline analyses were performed using Brain Vision Analyser (Brain Products GmbH, Munich). The EEG signal was re-referenced to linked mastoids and filtered between 1–35 Hz. For each participant an ocular correction was applied (Gratton, Coles, & Donchin, 1983). For children that were left-hand affected (N=8), the electrode positions were inverted (i.e. C3 was re-defined as C4 and C4 was re-defined as C3), so that for every child the C4 electrode was located contralaterally to less-AS movements and ipsilaterally to AS-movements. Next, the EEG was segmented into epochs of 3072ms, for the rest and movement condition. These epochs started 1000ms after the “start” or “stop” signal to control for potential delays to start or stop a movement after hearing the related signals. Incorrect trials (i.e. containing movements during rest periods or no movements during movement condition) and segments containing artifacts exceeding  $\pm 150 \mu\text{V}$  were removed (developmental disregard: total of 8.4% of trials; no developmental disregard: total of 4.8% of trials). A further segmentation on retained segments was performed creating segments of 1024 ms, to perform a Fast Fourier transformation including 512 samples (Power Density; 1Hz resolution; 10% Hanning Window). Epochs were averaged for both conditions



**A: noDD****Less-AS moving****AS moving****B: DD****Less-AS moving****AS moving**

**Figure 6.1. Averaged power spectra no developmental disregard (1A), and developmental disregard (1B).** Depicted are the power distributions of the frequency bands between 3 and 28 Hz for both groups separately (no developmental disregard vs. developmental disregard) with the mu-rhythm (7-13.5Hz) being highlighted. The upper panels of both figures (1A and 1B) show the mean distribution during the less-AS movement (green) and following rest periods (red), above the ipsilateral (C<sub>3</sub>) and contralateral (C<sub>4</sub>) sensorimotor cortex. The lower panels show the mean distribution during the AS movement (green) and following rest periods (red), again ipsilaterally (C<sub>4</sub>) and contralaterally (C<sub>3</sub>). noDD, no developmental disregard; DD, developmental disregard; AS, affected side.

(rest vs. movement). Finally, mean EEG mu-rhythm (7-13.5Hz) (Klimesch et al., 2007) was extracted from the EEG over the sensorimotor cortex (C<sub>3</sub> & C<sub>4</sub>) during rest and movement of each hand for further analysis. For a distribution of the frequency bands above the sensorimotor cortex (C<sub>3</sub> & C<sub>4</sub>) comparing both conditions (rest vs. movement) for the no developmental disregard group see **figure 6.1.A** and for the developmental disregard group **figure 6.1.B**.

**6.2.4 Statistical analysis**

A repeated measures GLM analyses was conducted using the mean EEG mu-rhythm (7-13.5Hz) with group (no developmental disregard vs. developmental disregard) as between- and hand (AS vs. less-AS), condition (rest vs. movement), and electrode (C<sub>3</sub> vs. C<sub>4</sub>) as within- subject variables. Whenever interaction effects were observed, appropriate post-hoc analyses were performed. For all analyses, the significance level was set at  $\alpha < .05$ . When applicable, Bonferroni correction was applied for multiple testing.

**6.3 RESULTS**

Ten children were classified with developmental disregard (Mage=10y, 6m; right hand affected: N=7; female: N=4; MMACS=1.9). The other fourteen children served as control group (unilateral CP without developmental disregard; Mage=11y, 1m; right hand affected: N=9; female: N=6; MMACS=1.7). A Mann-Whitney U-Test revealed that groups did not differ in age. To test differences between groups concerning gender, AS, and manual ability (MACS), Fisher's Exact Tests were conducted and revealed no differences between groups on either variable. For group characteristics, see **table 6.1**.

The repeated measures GLM revealed a significant condition\*group interaction ( $F(22)=4.617$ ,  $p=.043$ ,  $\eta^2=.173$ ).

Post-hoc repeated measures GLM analysis were performed per group



(developmental disregard vs. no developmental disregard) with side (AS vs. less-AS), condition (rest vs. movement), and electrode (C<sub>3</sub> vs. C<sub>4</sub>) as within-subject variables.

Table 6.1. Group characteristics

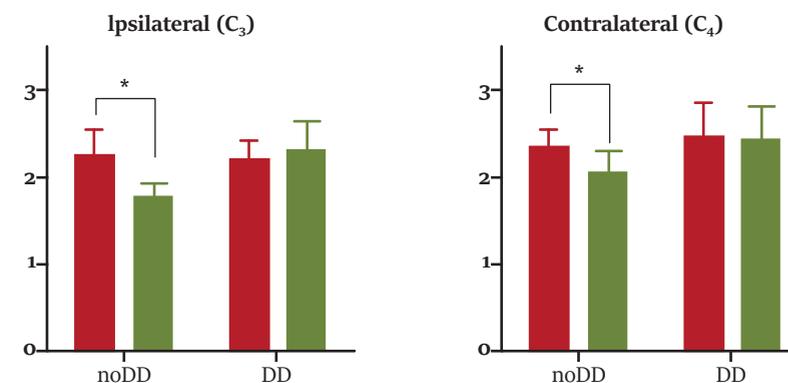
	noDD (N=14)	DD (N=10)	Statistics
Age (years; months)	11; 1	10; 6	Mann-Whitney U Test:
(range (years; months))	6; 8 - 17; 2	7; 9 - 18; 0	n.s.
Gender (male/female)	8/6	6/4	Fisher's Exact Tests: n.s.
AS (left/right)	5/9	3/7	Fisher's Exact Tests: n.s.
MACS (range)	1.7 (1 - 2)	1.9 (1 - 3)	Fisher's Exact Tests: n.s.

**Abbreviations:** DD, developmental disregard; AS, affected side; MACS, Manual Ability Classification System; n.s., non-significant

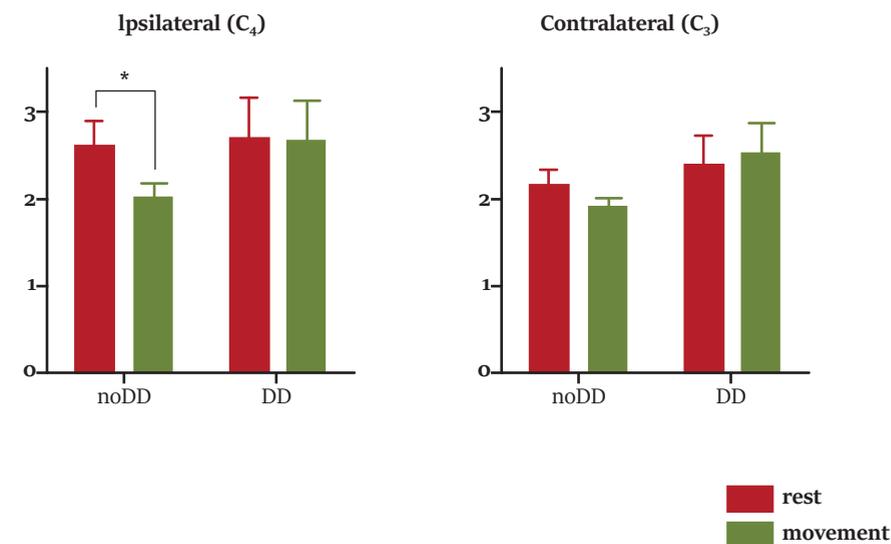
For the no developmental disregard group, the post-hoc GLM analysis revealed a significant and strong condition effect ( $F(13)=7.412$ ,  $p=.017$ ,  $\eta^2=.363$ ), showing a significant reduced mu-rhythm during the movement condition ( $M=1.94$ ) compared to the rest condition ( $M=2.33$ ). Furthermore, a significant and strong hand\*condition\*electrode interaction was found ( $F(13)=6.169$ ,  $p=.027$ ,  $\eta^2=.322$ ). Post-hoc GLM analyses were performed per hand with condition (rest vs. movement) and electrode (C<sub>3</sub> vs. C<sub>4</sub>) as within-subject variables. For both hands, a significant and strong condition effect was found (less-AS:  $F(13)=5.214$ ,  $p=.040$ ,  $\eta^2=.286$ ; AS:  $F(13)=6.278$ ,  $p=.026$ ,  $\eta^2=.326$ ), revealing a reduced mu-rhythm during the movement compared to the rest condition. Only for the AS a further condition\*electrode trend was found ( $F(13)=3.847$ ,  $p=.072$ ). Post-hoc paired sample t-test comparing rest and movement condition for this AS per electrode (C<sub>3</sub> vs. C<sub>4</sub>) only revealed a significant effect of condition of the sensorimotor cortex above the side ipsilateral (C<sub>4</sub>) to the moving AS ( $t(13)=3.165$ ,  $p=.007$ ). When moving the AS, a reduced mu-rhythm during the movement compared to the rest condition was only observed above the less-affected sensorimotor cortex.

The post-hoc GLM analysis for the developmental disregard group revealed no significant difference between the mu-rhythm of the rest and movement condition. For a distribution of the mean mu-rhythm per group comparing rest and movement conditions, see **figure 6.2**. Different graphs are presented per electrode location and hand.

### Less-AS moving



### AS moving



**Figure 6.2. Mu-power (mean + SEM; C<sub>3</sub> and C<sub>4</sub>).** The mean mu-power is compared between movement (green) and rest periods (red) for both groups separately (no developmental disregard: left; developmental disregard: right). The upper panel shows the mean mu-power during the less-AS movement and following rest periods, above the ipsilateral (C<sub>3</sub>) and contralateral (C<sub>4</sub>) sensorimotor cortex. The lower panel shows the mean mu-power during AS movement and following rest periods, again ipsilaterally (C<sub>4</sub>) and contralaterally (C<sub>3</sub>). AS, affected side; noDD, no developmental disregard; DD, developmental disregard.

## 6.4 DISCUSSION

The results of the current study show that children with unilateral CP with developmental disregard show a lack of typical EEG mu-restoration after voluntary hand movements. In contrast, this typical mu-restoration was present in children with unilateral CP but without developmental disregard. The restoration of the synchronous mu-rhythm above the sensorimotor areas after movement is suggested to reflect top-down control processes that inhibit irrelevant information and prepare the functional neural circuit to perform new relevant tasks (Klimesch et al., 2007). An earlier study on the movement related mu-rhythm in children with unilateral CP already reported a reduced or even absent state of preparedness for voluntary upper limb movement in these children (Daly et al., 2014). As an extension of this finding we differentiated between children with and without developmental disregard. The current results suggest a lack of integrity of the complex functional inhibitory system typically involved in preparing voluntary movements in developmental disregard, but not universally in unilateral CP.

Earlier studies have demonstrated differences in cognitive processes related to voluntary movement preparation between children with unilateral CP with and without developmental disregard (Zielinski, Jongasma, et al., 2014; Zielinski, Steenbergen, et al., 2014). These findings have predominantly been interpreted as evidence of insufficient motor learning in children with developmental disregard, arguing that different (bi)manual tasks have never been sufficiently automated (Deluca et al., 2006; Hoare et al., 2007; Houwink et al., 2011; Zielinski, Jongasma, et al., 2014; Zielinski, Steenbergen, et al., 2014). The current results illustrate the potential neural origins of these differences between children with and without developmental disregard. The finding of a lack of mu-restoration after voluntary hand movements is in line with the hypothesis that developmental disregard might result from a lack of refinement of the typical intra- and/or interhemispheric functional neural circuits of motor control (Grefkes et al., 2008). This is likely related to a non-use of the AS, as these circuits are thought to only effectively develop when actively moving the limb (Sanes & Donoghue, 2000). A non-use of the AS during early childhood might be particularly harmful, as neural systems are suggested to be extra responsive for refinement during sensitive periods of early childhood (between 6 months and 3 years) (Roeber et al., 2014; Watanabe et al., 2007). Motor deprivation during these sensitive periods has earlier been suggested to potentially result in long lasting impairments (Watanabe et al., 2007). Following this line of reasoning, early intervention programs actively stimulating upper limb movement during the specific sensitive refinement periods might be of special interest (Martin,

2005). This would enhance the effective development and refinement of the neural circuits involved in successful upper limb control, potentially preventing the suggested failure to refine neural circuits involved in motor control (Basu, Pearce, Kelly, Wisher, & Kisler, 2014).

Interestingly, the observed lack of mu-restoration in children with developmental disregard was not restricted to voluntary AS-movements, but also observed after less-AS movements. In line with this, an earlier study demonstrated enhanced cognitive effort related to voluntary unimanual movement preparation of both hands in children with developmental disregard (Zielinski, Steenbergen, et al., 2014). We therefore argue that the proposed diminished refinement and coupling of neural circuits involved in motor control is not restricted to the AS, but may also affect the motor development of the less-AS. This proposed “bimanual” involvement in children with unilateral CP has earlier been reported to affect many children with unilateral CP with a direct negative influence on their ability to manage daily manual activities (Arnould, Bleyenheuft, & Thonnard, 2014; Tomhave, Van Heest, Bagley, & James, 2015). It might potentially be related to the fact that due to early symptoms of non-use of the AS, several typical (bimanual) daily activities are not, or rarely performed, also affecting the typical development of the less-AS. However, this hypothesis of a certain bimanual involvement underlying developmental disregard warrants further validation.

Alternatively to the hypothesis that a non-use during development causes a diminished maturation and refinement of involved neural circuits, in children with developmental disregard these neural circuits might have already been affected as a consequence of their primary brain injury. Following this hypothesis, the lack of mu-restoration might thus be caused by damage of involved connective tissue, leading to alterations of the mu-rhythm and possible related symptoms of developmental disregard (Klimesch et al., 2007; Leocani et al., 2005). This would suggest the primary brain injury to be the initial cause for clinical symptoms of developmental disregard as well as potentially the altered underlying mechanisms detected in the current and earlier studies (Zielinski, Jongasma, et al., 2014; Zielinski, Steenbergen, et al., 2014). If the symptoms observed in developmental disregard are indeed caused by the primary brain injury, this might challenge many approaches that were earlier suggested to treat developmental disregard. Future studies need to investigate the possibility of primary damage to specific brain structures that might be affected in children with developmental disregard.

Another interesting finding of the current study is that in children with unilateral CP but without developmental disregard, the mu-restoration after voluntary movement of the AS was only observed over the ipsilateral, less-



affected hemisphere. Apparently, within the periods of rest following the periods of active squeezing only the less-affected hemisphere returned to the proposed state of preparedness. This suggests that this dominant hemisphere plays an important role in top-down inhibitory control processes involved in voluntary movement to control the AS in children with unilateral CP. This is in line with other reports stating that a reorganization of the motor cortex in many children with unilateral CP with the less-affected hemisphere may play a crucial role for the voluntary movement of the AS (Carr, 1996; Holmstrom et al., 2010; Staudt et al., 2004).

The current study is limited by the small number of participants and especially the smaller amount of children being diagnosed with developmental disregard as compared to those serving as control group (N=10 vs. N=14). Also, no information with respect to the differences in etiology or underlying brain injury was available preventing the opportunity to explain group differences related to these factors.

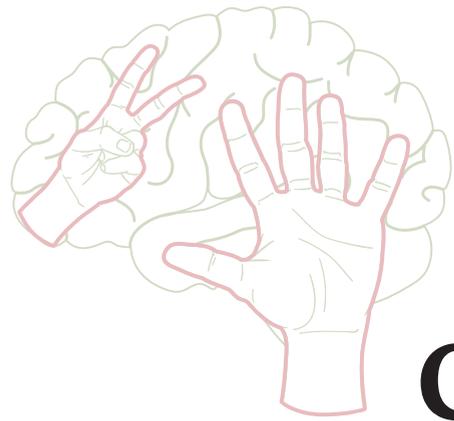
#### 6.4.1 Conclusion

The current results show a lack of typical EEG mu-restoration following voluntary hand movements in children with unilateral CP with developmental disregard. This suggests a general diminished refinement of neural circuits underlying volitional upper limb movement in these children. This diminished refinement is proposed to be directly related to the symptoms of non-use these children experience during typical bimanual daily activities. Alternatively, it is suggested that clinical symptoms of developmental disregard as well as the observed lack of mu-restoration are both related to specific characteristics of the initial brain lesion. Both hypotheses warrant further investigation including bigger sample sizes as well as additional information about the etiology and underlying brain injury.

## 6.5 ACKNOWLEDGEMENTS

We want to kindly acknowledge all the children and their families who took part at this study. Furthermore, we kindly thank Sabine Vincon and Julian Rudisch for their valuable help during data collection.





# CHAPTER

# VII

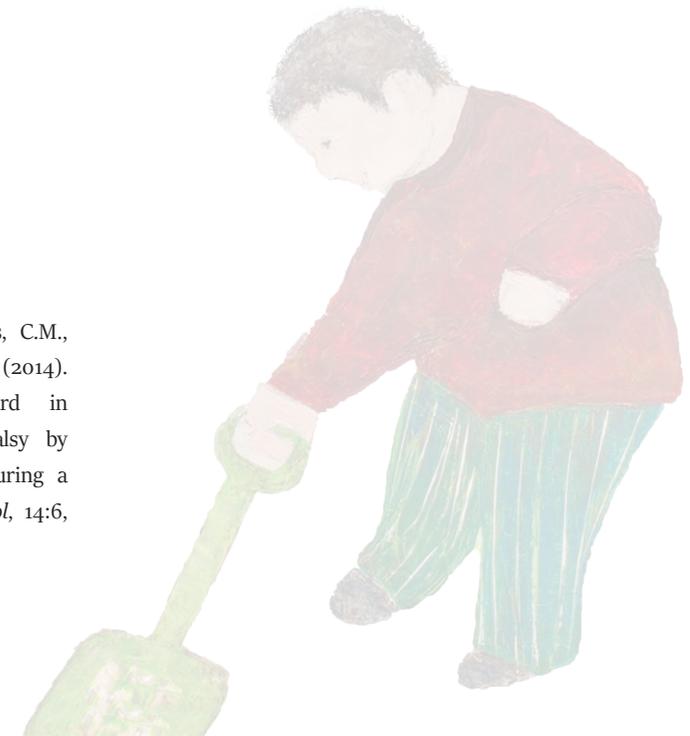
## Abstract

In a subset of children with unilateral Cerebral Palsy (CP) a discrepancy between capacity and performance of the affected side (AS) can be observed, known as developmental disregard. Though this phenomenon has been well documented, its underlying cause is still under debate. It has originally been explained based on principles of operant conditioning. Alternatively, it has been proposed that developmental disregard results from a diminished automaticity of movements, resulting in an increased cognitive load when using the AS. To investigate the amount of involved cognitive load we studied Event-Related Potentials (ERPs) preceding task-related motor responses during a unimanual capacity and a bimanual performance task. It was hypothesized that children with developmental disregard show alterations related to long-latency ERP components when selecting a response with the AS, reflecting increased cognitive load in order to generate an adequate response and especially so within the bimanual task. To test this hypothesis, fourteen children with unilateral CP were tested, seven with developmental disregard. The other seven children served as a control group. All participants performed two versions of a cue-target paradigm, a unimanual capacity and a bimanual performance task. The ERP components linked to target presentation were inspected: the mid-latency P2 component and the consecutive long-latency N2b component. The results displayed that in the bimanual performance task children with developmental disregard showed an enhancement in mean amplitude of the long-latency N2b component when selecting a response with their AS. No differences were found regarding the amplitude of the mid-latency P2 component. No differences were observed regarding the unimanual capacity task. The control group did not display any differences in ERPs linked to target evaluation processes between both hands. These electrophysiological findings show that developmental disregard is associated with increased cognitive load when movements are prepared with the AS during a bimanual performance task. These findings confirm behavioral observations, advance our insights on the neural substrate of developmental disregard and have implications for therapy.

## Unraveling Developmental Disregard in Children with Unilateral Cerebral Palsy by Measuring Event-related Potentials During a Unimanual Capacity and Bimanual Performance Task

### This chapter is based on:

Zielinski, I.M., Jongsma, M.L.A., Baas, C.M., Aarts, P.B.M., & Steenbergen, B. (2014). Unravelling developmental disregard in children with unilateral cerebral palsy by measuring event-related potentials during a simple and complex task. *BMC Neurol*, 14:6, doi: 10.1186/1471-2377-14-6.



## 7.1 INTRODUCTION

Cerebral Palsy (CP) is defined as a group of non-progressive disorders related to the development of movement and posture, caused by damage to the developing foetal or infant brain (Rosenbaum et al., 2007). A large group (between 21 and 40%) of children with CP is formed by those with unilateral CP, having substantially greater motor deficits in one upper extremity than the other (Odding, Roebroek, & Stam, 2006). The observed unilateral motor impairments are related to damage of brain regions involved in planning, controlling, and execution of movements leading to a reduced movement capacity in children with unilateral CP (Taub, Ramey, DeLuca, & Echols, 2004). Apart from the reduced movement capacity, a subset of children with unilateral CP also seem to disregard the preserved capacity of their affected side (AS), leading to a failure to use this AS according to its full capacity in daily life (Deluca, Echols, Law, & Ramey, 2006; Hoare, Wasiak, Imms, & Carey, 2007; Houwink, Aarts, Geurts, & Steenbergen, 2011; Taub et al., 2004). This discrepancy between capacity and performance is defined as developmental disregard (Deluca et al., 2006; Houwink et al., 2011; Taub et al., 2004).

To date, different explanations have been put forward to explain developmental disregard in children with unilateral CP. A common explanation is based on the theory of operant conditioning (Crocker, MacKay-Lyons, & McDonnell, 1997; Taub, 1980). It compares developmental disregard to the phenomenon of learned non-use, defined as a learned suppression of movement, reported in the literature in adults who suffered a cerebrovascular accident (CVA) (Taub & Wolf, 1997). Following this theory, it is suggested that children with developmental disregard have experienced too little incentive to use the AS, because using the opposite, less-AS is less demanding (Deluca et al., 2006). Thus, positive reinforcement resulting from the successful use of the less-AS is combined with negative reinforcement from the unsuccessful use of the AS. This leads to a behavioral bias favoring the less-AS disproportional to the capacities of both the less-AS and AS.

Despite the similarity of the behavioral symptoms associated with learned non-use in CVA patients and developmental disregard in children with unilateral CP, recent studies emphasize that in developmental disregard both the developmental aspect and related cognitive aspects of information processing pose an important conceptual difference to the pure behavioral phenomenon described in learned non-use (Boyd et al., 2010; Deluca et al., 2006; A.-C. Eliasson, Bonnier, & Krumlinde-Sundholm, 2003; Hoare et al., 2007; Houwink et al., 2011; Taub et al., 2004). In this respect, Deluca and colleagues (2006) have postulated that children with developmental disregard have suffered a critical

lack of movement stimulation during developmental periods when movement repertoires are rapidly acquired in typically developing children. As a consequence of this lack of movement that starts at perinatal periods, in combination with the earlier mentioned effects of reinforcement, typical developmental milestones are delayed or even deficient for the AS. In line, the neural substrates involved in motor control as well as in sensori-motor integration of the AS experience a similar lack in development and refinement (Boyd et al., 2010; Deluca et al., 2006; Sutcliffe, Logan, & Fehlings, 2009). It has even been stated that developmental disregard might be a neurologically based phenomenon similar to poststroke neglect syndrome (Sutcliffe et al., 2009).

In a recent explanation to account for developmental disregard this protracted development of motor control, sensorimotor integration and linked neural substrates is suggested to cause certain movement patterns of the AS to be not sufficiently automated (Houwink et al., 2011). Based on Fitts and Posner's (Fitts & Posner, 1967) theory of motor skill acquisition, Houwink and colleagues (2011) hypothesized that due to the lack of automaticity, using the AS requires a disproportional amount of attention (Houwink et al., 2011). They argue that a disproportional amount of attention coincides with an excess in cognitive load that is associated with motor control of the AS. The increased cognitive load in turn leads to a reduced spontaneous use of the AS in daily life (Houwink et al., 2011). This hypothesis was already verified in several studies with CVA patients. These studies showed that patients, who have to relearn a lost motor skill, need a disproportional level of attention when moving the AS in the early stages of rehabilitation when relearned movements are not yet (re)automated (Cockburn, Haggard, Cock, & Fordham, 2003; Houwink, Steenbergen, Prange, Buurke, & Geurts, 2013). Thus, a lack of automaticity of movements is associated with increased cognitive load in adult CVA patients.

To be able to assess cognitive load related to movement, Event-Related Potentials (ERPs) offer the unique opportunity to directly measure neural responses associated with distinct processing stages preceding an overt response (Brandeis & Lehmann, 1986). Whereas mid-latency components (e.g. N1 & P2) have been associated with orienting and perception, the long-latency components of ERPs (e.g. N2, P3) are known to reflect processes associated with cognitive control and attention allocation (Norman, 1984; Salisbury, O'Donnell, McCarley, Shenton, & Benavage, 1994). To assess the possible role of cognitive load in the impaired motor performance of developmental disregard, the current study therefore focussed on the long-latency N2b component. Next to generally being known to reflect processes associated with cognitive control and attention allocation, the N2b has also already directly been linked to cognitive control of response-related processes (Folstein & Van Petten, 2008).



In order to investigate the aspects of information processing preceding goal directed motor responses, ERPs were extracted from the ongoing EEG during a unimanual task as an index of the individuals hand capacity and a bimanual task, to estimate the hand performance. Based on the cognitive load theory of developmental disregard we reasoned that children with developmental disregard will show alterations linked to the higher order cognitive control processes when preparing a response with their AS during the bimanual performance task. We therefore hypothesize that children with developmental disregard show alterations related to the N2b component when selecting a response with the AS, reflecting increased cognitive load in order to generate an adequate response. We furthermore hypothesize this effect to be especially pronounced during the more demanding bimanual performance task.

## 7.2 METHODS

### 7.2.1 Participants

Fifteen children diagnosed with unilateral Cerebral Palsy (CP; 5 girls, 10 boys,  $M_{age} = 8$  years, 1 month, age range: 5 years, 3.5 months - 11 years, 1.5 months) were recruited from the Sint Maartenskliniek, Nijmegen, the Netherlands. One participant was excluded from the final analyses due to major visual impairments (diagnosed with hemianopsia), which may have confounded our results. Side of AS, manual ability, as well as developmental disregard, of each individual child was assessed by an occupational therapist prior to the EEG measurements. Manual ability of each child was assessed using the Manual Ability Classification System (MACS) for children with CP (Eliasson et al., 2006). Groups were classified using the “Video-Observation Aarts and Aarts module: Determine Developmental Disregard” (VOAA-DDD-R) (Houwink, Geerdink, Steenbergen, Geurts, & Aarts, 2013).

Seven children were classified as having developmental disregard ( $M_{VOAA-DDD-R} = 21.4$ ,  $SD_{VOAA-DDD-R} = 6.7$ ;  $M_{age} = 7y,9m$ ,  $SD_{age} = 1y,11m$ ; 6 male, left AS:5;  $M_{MACS} = 1.6$ ,  $SD_{MACS} = 0.5$ ). The other seven children served as the control group, that is, children with unilateral CP but without developmental disregard ( $M_{VOAA-DDD-R} = 4.8$ ,  $SD_{VOAA-DDD-R} = 10.6$ ;  $M_{age} = 8y,11m$ ,  $SD_{age} = 2y,1m$ ; 3 male; left AS:5;  $M_{MACS} = 1.9$ ,  $SD_{MACS} = 0.7$ ).

To test whether the groups did not differ with respect to age, gender, side of the AS, and manual ability (MACS), independent-samples Mann-Whitney U Test were conducted. No differences were observed for either of these variables.

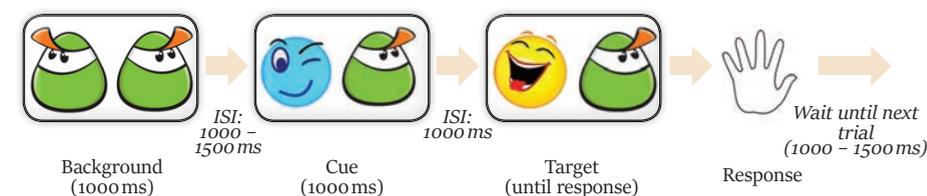
Approval for the experiment was obtained from the local Ethical Committee of the Faculty of Social Sciences (EC), Radboud University Nijmegen (Registration

number: 2012/049; NL nr.: 39607.091.12). The parents of all participants signed a written informed consent form prior to the study for their children to participate in the study and for the participant information to be used for research purposes.

### 7.2.2 Design

In this experiment two versions of a cue-target paradigm were used. Cue and target stimuli were embedded within a train of background stimuli. The stimuli were sequentially presented in a semi-random order so that every cue stimulus was followed by a target stimulus but the occurrence of the cue stimulus within the train of background stimuli was random. The probability of the occurrence of both the cue and target stimuli was 0.25 (half of the stimuli were background stimuli).

All stimuli consisted of a pair of “smiley” figures: one on the left side of the screen and one on the right side of the screen. Cue stimuli consisted of a blue (cue) smiley figure paired with a green (background) smiley figure. Target stimuli consisted of a yellow (target) smiley figure paired with a green (background) smiley. The target was always presented at the same side as the preceding cue. Background stimuli consisted of two paired green smiley figures. Smiley figures (size 7 x 7 cm) were presented at a fixed position with a white background on a laptop screen approximately 40 cm in front of the child. **Figure 7.1.** provides a visual presentation of the stimuli.



**Figure 7.1. Stimuli of cue-target paradigm.** Schematic of the cue-target paradigm shown on the left side of the screen. For presentation on the right side, the smiley figures were mirrored horizontally. ISI, inter-stimulus interval.

The stimulus duration of background- and cue-stimuli was 1000 ms. Target stimuli were presented until the child responded. The inter-stimulus interval (ISI) between cue and target stimuli was kept fixed at 1000 ms. The ISI after background stimuli and after responses was set randomly between 1000 and 1500 ms. Participants were instructed to respond to target stimuli by pressing a button at the same side at which the target was presented (right or left) as quickly as possible with the corresponding hand. For this purpose two red buttons (diameter: 9.5 cm; height: 5.5 cm) were located next to the laptop keyboard, one

at the right side and one at the left side. The distance between these buttons was kept at 30 cm to prevent that the wrong hand was used to press the according button. Only after a response was recorded (correct or incorrect) the next trial was started. After each correct response a short laughing sound was presented to provide feedback. No sound was presented after incorrect responses. Incorrect responses were defined as erroneous responses to cue or background stimuli, incorrect responses following target stimuli (using the wrong hand), as well as omissions following target stimuli (no response within 2000 ms). The experiment was divided into two blocks related to the two different tasks (unimanual capacity vs. bimanual performance task). In the first block the trains of cue and target stimuli were only presented at one side of the screen (unimanual task), starting with the side corresponding to the less-AS and followed by the side corresponding to the AS. Each run contained 25 trains of cue-target stimuli (a total of 50 target stimuli, 25 for both sides). In the second block, the cue and target stimuli were shown in a semi-random order at either the left or right side of the screen (bimanual task), demanding alternating responses of either the right or left hand. Twenty trains of cue-target stimuli were presented on the left side and 20 trains of cue-target stimuli at the right side of the screen (a total of 40 target stimuli).

### 7.2.3 EEG recordings

EEG signals were recorded with a 32-channel actiCap (MedCaT B.V., the Netherlands) and subsequently amplified by a 32-channel BrainAmp EEG amplifier with electrode placement according to the International 10-20 system (Jasper, 1958; American Encephalographic Society, 1994). A ground electrode was placed over AFz and a reference over the left mastoid bone. The EEG signal was offline re-referenced to linked mastoids and stored on disk for offline analyses. Vertical and horizontal eye movements were recorded by two additional bipolar channels placed above and below the right eye and on the outer canthi of each eye. Electrode impedance was kept below 5 k $\Omega$ . The signal was digitized at 1000 Hz and filtered online between 0.016 Hz (i.e. 10 s time-constant) and 250 Hz. Electrodes were located at five midline sites (Fz, FCz, Cz, Pz and Oz) and 24 lateral sites (FP1/2, F7/8, F3/4, FC5/6, FC1/2, C3/4, CP5/6, CP1/2, P7/8, P3/4, T7/8, O1/2) to allow estimations of scalp distributions for finding spatial maxima of the ERP components of interest.

### 7.2.4 Procedure

Prior to the EEG measurements children were assessed by a clinician to be tested for side of AS and developmental disregard. Next, the EEG and Electrooculography (EOG) electrodes were placed (approximately 30 to 45 minutes) and the child

was seated in front of the laptop screen on a comfortable chair adjusted to the correct height. Recordings were done at a familiar setting (Rehabilitation Centre Sint Maartenskliniek, Nijmegen, the Netherlands). At least one of the parents was always present during recordings.

The child received instructions before each block of the experiment by showing the stimuli and pointing out which button to press. A short practice session preceded each block to familiarize the child with the task. The whole procedure did not exceed 90 minutes.

### 7.2.5 Data processing and analysis

EEG data were analyzed using the software BrainVision Analyzer v. 2.0 (Brain Products GmbH). For each participant an ocular correction was applied using a semi-automatic correction procedure based on the logarithm of Gratton and Coles (Gratton, Coles, & Donchin, 1983). Next, the EEG signal was high-pass filtered at 0.5 Hz and low-pass filtered at 30 Hz. Based on the onset of all cue and target stimuli the EEG was segmented into epochs from -250 ms pre-stimulus to 750 ms post-stimulus. Only ERPs corresponding to correct responses following cue (no response) and target stimuli (response within 2000 ms) were included using the Advanced Boolean Expression (total of 93.04% of the trials). After segmentation epochs were de-trended and artifacts related to gross motor movement and muscle tension were removed manually. Next, a baseline correction (-250 - 0 ms) was applied to all segments.

All segments were averaged per stimulus type (cue vs. target), hand (AS vs. less-AS), and task (unimanual vs. bimanual). ERP components were defined in terms of their polarity, latency, and scalp distribution. The grand average ERPs following both cue and target stimuli contained a clear N1 (mean latency: 130 ms), P2 (mean latency: 215 ms), and N2b component (mean latency 355 ms) component. Based on conventionally reported and observed scalp distributions of the N1, P2, and N2b, component amplitudes at FCz were further analyzed (Jonkman, Kenemans, Kemner, Verbaten, & van Engeland, 2004; Patel & Azzam, 2005; van Elk et al., 2010). To allow blind scoring, ERP amplitudes were defined as the averaged value within a fixed latency window: N1 (120 - 140 ms), P2 (200 - 230 ms), and N2b (330 - 380 ms) (Picton, 1992). ERP mean amplitude of the cue and target ERP components were analyzed separately using repeated measures GLM analyses with handedness (AS vs. less-AS) and task (unimanual vs. bimanual) as independent within-subject variables and group (control group vs. developmental disregard group) as between-subject factor. Whenever interaction effects were observed appropriate Paired-Samples T-Tests were performed. For all analyses the significance level was set at  $\alpha < .05$ .



Analysis of behavioral responses focused on Inverse Efficiency Scores (IES) determined as the mean reaction time (RT) divided by the proportion of correct responses expressed in ms (Bruyer & Brysbaert, 2011). This method is considered to be especially useful in tasks with low (<10%) error rates (Bruyer & Brysbaert, 2011). Indeed, error rates of the current experiment remained below 7% for the whole group. IES scores were analyzed using repeated measures GLM analyses with handedness (AS vs. less-AS) and task (unimanual vs. bimanual) as independent within-subject variables and group (control group vs. developmental disregard group) as between-subject factor. For all analyses the significance level was set at  $\alpha < .05$ .

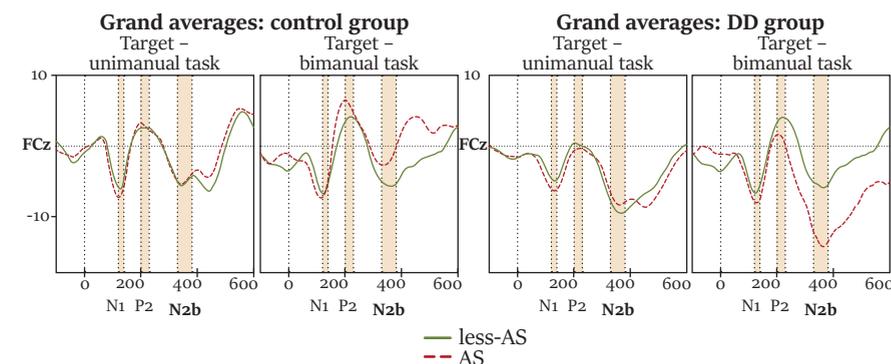
### 7.3 RESULTS

To test our first hypothesis that children with developmental disregard compared to children with unilateral CP without developmental disregard show alterations related to long-latency ERP component when selecting a response with the AS compared to the less-AS, repeated measures GLM analyses of the long-latency N2b ERP component were performed. To ensure that differences can not be ascribed to earlier processes related to the evaluation of the physical features of task relevant stimuli, the mid-latency N1 and P2 components were also inspected. To furthermore ensure that differences could also not be ascribed to early cue evaluation or general visual stimulus evaluation processes, ERP components following cue stimuli were investigated as well.

The repeated measures GLM analyses of the ERP components following cue stimuli revealed no significant interaction or main effects with respect to the N1 component (all  $p$ 's > .10), the P2 component (all  $p$ 's > .10), or the N2b component (all  $p$ 's > .10). The analyses of the ERP components following target evaluation revealed no significant interaction or main effects with respect to the mid-latency N1 (all  $p$ 's > .10) and P2 components (all  $p$ 's > .10). With respect to the long-latency N2b component this analysis did however reveal a significant task (unimanual vs. bimanual task;  $F(1,13) = 5.265$ ,  $p = .041$ ,  $\eta^2 = .288$ ) effect as well as a significant handedness x task x group interaction ( $F(1, 13) = 6.649$ ,  $p = .026$ ,  $\eta^2 = .338$ ).

To examine this interaction and to test our second hypothesis, that the long-latency effect is especially pronounced during the more demanding bimanual performance task paired sample  $t$ -tests between hands (AS vs. less-AS) were performed for each group and task separately. This revealed that the significant difference between hands was only present in the developmental disregard group and only in the bimanual task ( $t(6) = 2.469$ ,  $p < .05$ ). Specifically, only in

the bimanual task the N2b amplitude following target stimuli was significantly enhanced in the developmental disregard group when using the AS compared to using the less-AS, confirming our first and second hypothesis. Grand average ERPs to target stimuli for both the developmental disregard and the control group are depicted in **figure 7.2**. **Figure 7.3** provides a visual presentation of the mean absolute amplitude for the N2b component following target stimuli. No differences between hands were observed in the control group.



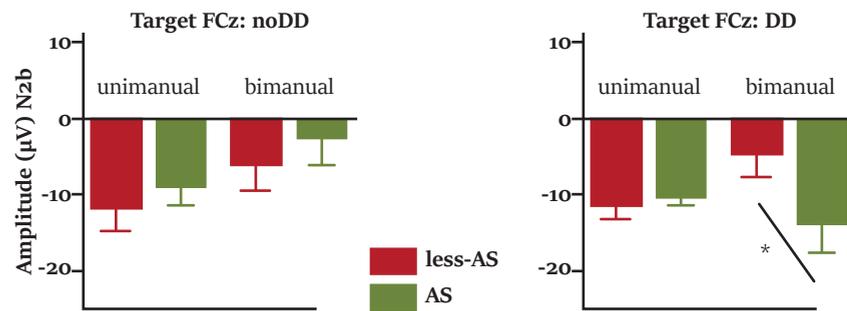
**Figure 7.2. Grand averaged ERP waveforms following target stimuli.** Grand averaged ERP waveforms elicited by target stimuli in children with unilateral CP without indications of developmental disregard (Grand Averages: control group) and children with unilateral CP and developmental disregard (Grand averages: developmental disregard group) in response to movement selection of the AS (red dashed line) compared to the less-AS (green solid line). For calculation of these grand averages all 14 participants (developmental disregard:  $N = 7$ ; control:  $N = 7$ ) were included. Highlighted temporal windows indicate N1, P2, and N2b components. The significant difference for the developmental disregard group between the movement preparations of both hands is indicated by the asterisk. DD, developmental disregard; AS, affected side.



Finally, with respect to the behavioral data the repeated measures GLM analyses of the IES scores revealed a significant main effect of hand ( $F(1, 13) = 5.715$ ,  $p = .033$ ,  $\eta^2 = .305$ ). Across both group responses were less efficient with the AS ( $M = 598.17$ ,  $SD = 256.48$ ) compared to responses with the less-AS ( $M = 558.38$ ,  $SD = 227.28$ ). No GLM interaction effects with respect to the IES scores were observed. The IES scores were similar for both groups.

### 7.4 DISCUSSION

The goal of the current study was to use Event-Related Potentials (ERPs) to provide a direct measure of cognitive load associated with movements of the AS in



**Figure 7.3. Mean absolute amplitude with SEM for the N2b (330 - 380) component following target evaluation at FCz.** Differences between sides of target presentation are depicted for children with unilateral CP without developmental disregard (control) and children with unilateral CP and developmental disregard. The mean amplitude following target presentation to the less affected side is depicted in red, for the affected side in green. The significant difference between the movement preparations of both hands for the developmental disregard group is indicated by the asterisk. noDD, no developmental disregard; DD, developmental disregard; AS, affected side.

children with unilateral Cerebral Palsy (CP) and developmental disregard. Based on Fitts and Posner's (Fitts & Posner, 1967) theory of motor skill acquisition, it has been suggested that due to a lack of automaticity of movements with the AS, children with developmental disregard experience increased cognitive load when using this limb (Houwink et al., 2011). This increased cognitive load in turn leads to an underuse of the AS in daily life performance even if sufficient limb capacity is available. In order to test this theory we recorded ERPs during two different versions of a cue-target paradigm. First, we employed a unimanual task as an index of the individuals hand capacity. Next, we recorded a bimanual task to estimate the hand performance. We first of all hypothesized that children with developmental disregard would show alterations related to the long-latency ERP components when selecting a response with the AS, reflecting increased cognitive load when generating an adequate response. Secondly, we hypothesized this effect to be especially pronounced during the bimanual performance condition, reflecting the characteristic discrepancy between hand capacity and hand performance of developmental disregard.

In line with our first hypothesis children with developmental disregard showed an enhancement in mean amplitude of the long-latency N2b ERP component when preparing a response with their AS compared to their less-AS. This component is well known to reflect the amount of activity in areas associated with cognitive load, indexes voluntary attentional processing, and is known to represent a necessary part of the information processing sequence

leading to a motor response (Näätänen & Picton, 1986; Simson, Vaughn, & Ritter, 1977). The finding of the increased N2b following target stimuli in children with developmental disregard therefore indicates that these children experience an increase in cognitive load when generating an adequate motor response with their AS compared to their less-AS. Moreover, and in line with our second hypothesis, this enhancement was only observed in the bimanual performance task and not in the unimanual capacity task.

Based on our electrophysiological results the conclusion is warranted that the discrepancy between capacity and performance in children with developmental disregard can be explained by an increased cognitive load associated with response selection in bimanual task situations. This conclusion is further strengthened by three findings of the present study. First, the enhancement of the N2b ERP component following target stimuli when generating a response with the AS was not found in the control group. Second, we did not find any differences between hands with respect to the mid-latency N1 and P2 amplitude. This indicates that there are no differences between both sides of target presentation regarding the evaluation of the physical features of task relevant stimuli (Potts, 2004; Rugg & Coles, 1995). Observed group differences can therefore not be explained due to differences in processes related to orienting and perception that regularly accompanies CP (Fazzi et al., 2012). Third, and finally, there were no differences regarding cue evaluation processes preceding the target stimuli. This finding shows that visual and cognitive evaluation processes that are not directly linked to preparing a motor response following target evaluation are not impaired in children with developmental disregard compared to children with unilateral CP without developmental disregard.

The fact that preparing a response with the AS compared to preparing a response with the less-AS increases cognitive load in a bimanual performance task is in line with the behavioral observation of the discrepancy between capacity and performance that characterizes developmental disregard (Houwink et al., 2011). The current study showed that children with developmental disregard use their AS during a unimanual capacity task without any electrophysiological or behavioral indications of increased cognitive load when preparing the response. This finding is in agreement with the behavioral observation that children with developmental disregard are indeed able to perform a particular task with their AS alone, as long as they can focus on the task and their hand capacity is sufficient (Boyd et al., 2010; Houwink et al., 2011). However, we did observe an increased ERP N2b component when preparing a response with the AS in a bimanual performance task in children with developmental disregard reflecting increased cognitive load. This finding exemplifies the behavioral observation that in spontaneous daily use, predominantly requiring both hands, children



with developmental disregard fail to use the potential motor functions of their AS and rather chose to perform a task with their less-AS alone (Boyd et al., 2010; Houwink et al., 2011). In this connection, an interesting facet of the current study regarding the behavioral observations of developmental disregard is that there were no differences between groups regarding the behavioral efficiency scores. That is, even though our electrophysiological findings indicate increased cognitive load associated with the use of the AS in a bimanual task an appropriate movement outcome could be achieved. These findings further substantiate the claim that developmental disregard is due to increased cognitive load associated with the use of the AS that only reveals itself in complex activities where attention cannot be solely focused on the effected arm and hand. Children with developmental disregard are able to use the AS efficiently even in bimanual tasks but due to the enhancement of cognitive load associated with this movements they disregard their hand in spontaneous daily live.

In sum, the results of the current study add to the accumulating evidence suggesting that cognitive aspects of information processing play a major role in the appearance of developmental disregard (Boyd et al., 2010; Deluca et al., 2006; Eliasson et al., 2003; Hoare et al., 2007; Houwink et al., 2011; Taub et al., 2004). Furthermore, these results are in line with the assumption that developmental disregard might be a neurologically based phenomenon similar to post stroke neglect syndrome (Sutcliffe et al., 2009). It is already known that motor neglect becomes worse when attention is distracted and that simultaneous movement of the opposite limbs may also increase motor neglect (Goldenberg, G., 2010). This comparison would also be in line with the theory that due to an asymmetrical development of the AS, new neural substrates for entire classes of behavior are not well established, refined, and coordinated (Boyd et al., 2010; Deluca et al., 2006; Sutcliffe et al., 2009).

Next to making a substantial step in unravelling developmental disregard in children with unilateral CP, these results have important clinical implications. To date, a very commonly applied therapy aimed at improving the upper limb capacity in all children with unilateral CP is the so called 'forced-use' or 'Constraint Induced Movement Therapy' (CIMT) (Taub et al., 1994). The main characteristic of this therapy is the immobilization of the less-AS, thus forcing the patient to use the AS exclusively (Taub et al., 1994). By applying this therapy the capacity of the effected arm and hand is intensively trained and often improves spectacularly (Aarts, Jongerius, Geerdink, van Limbeek, & Geurts, 2011; Charles, Wolf, Schneider, & Gordon, 2006; DeLuca, Echols, Ramey, & Taub, 2003; Taub, Uswatte, & Elbert, 2002). However, CIMT was originally developed to overcome learned non-use in adult CVA patients and to promote use of the limb rather than skill (Taub et al., 1994). In children, however, compared to adult patients

developmental factors play a major role in the occurrence of developmental disregard (Boyd et al., 2010; Deluca et al., 2006; A.-C. Eliasson et al., 2003; Hoare et al., 2007; Houwink et al., 2011; Taub et al., 2004) whereby they may have never learned how to effectively use their AS during many tasks (Hoare et al., 2007; Gordon, 2014). Gordon (2014) therefore concluded that treatments for children to overcome developmental disregard must be developmentally focused and must take into account the importance of motor learning. This critical view on applying CIMT to children with developmental disregard is strengthened by the findings of the current study. We showed that the performance issues typically observed in developmental disregard are directly related to increased cognitive load only when using the AS in a bimanual performance task and not when simply moving that limb in a unimanual task. It should therefore be considered to apply bimanual training instead of CIMT to children with developmental disregard to promote bimanual skill instead of unimanual use.

Recently, CIMT treatments have been combined with, or compared to, bimanual training therapies (DeLuca et al., 2003; Gordon, 2011; Gordon, 2014; Gordon, Schneider, Chinnan, & Charles, 2007; Green et al., 2013; Rostami & Malamiri, 2012). These studies show that the results of bimanual training therapies as well as a combination with CIMT are very beneficial and lead to similar improvements in hand capacity as CIMT. Furthermore, they showed that bimanual training leads to a further improvement in bimanual skill and self-determined goals.

Next to the promising consideration to apply bimanual training therapies to children with developmental disregard it should also be considered that upper-limb training should not end after an intensive rehabilitation program, but to be continued and integrated in the daily-live activities of the children with developmental disregard (Houwink et al., 2011). As been shown in adult CVA patients increased cognitive load is directly associated with a lack of automaticity of using the AS (Cockburn et al., 2003; Houwink, Steenbergen, et al., 2013). In the current study we demonstrated that during hand movements of the AS in a bimanual performance task a disproportional amount of cognitive load is activated suggesting a lack of automaticity of using that hand only during bimanual performance tasks. Continuing and integrating the rehabilitation program in the daily-live activities of the children with developmental disregard therefore has to be considered to promote further automatisation of movements of the AS during daily bimanual performance. In this respect it has already been reported that concerning the daily performance of the AS in children with unilateral CP treatment is more effective when conducted in the home setting of the children compared to the clinical setting (Rostami & Malamiri, 2012). In the study of Rostami and Malamiri (Rostami & Malamiri, 2012) it was concluded



that this natural daily-life environment provides more information about upper limb performance than other contexts such as the clinic. Considering continuing training in a home setting after completing a bimanual rehabilitation program is therefore a crucial next step in reducing developmental disregard.

Study limitations include small sample size and therefore difficulties controlling for any interaction between gender and maturation. A further limitation of the current study, also related to the small sample size, is the heterogeneity of the studied group. This latter limitation is however inherent to the participant population as unilateral Cerebral Palsy comprises a very heterogeneous group of movement disorders.

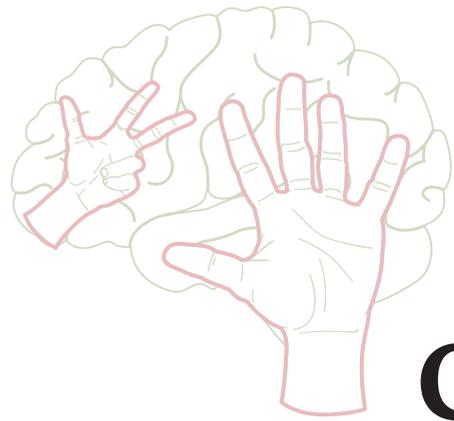
#### 7.4.1 Conclusion

The discrepancy between capacity and performance in children with developmental disregard can be explained by an increased cognitive load associated with response selection in bimanual task situations. The results of the current study therefore provide direct neurophysiological evidence to the accumulating indications suggesting that cognitive aspects of information processing play a major role in the appearance of developmental disregard. Furthermore, by showing that the performance issues typically observed in developmental disregard are directly related to increased cognitive load only when using the AS in a bimanual performance task and not when simply moving that limb in a unimanual task it can be concluded that bimanual training, instead of CIMT, should be applied as therapy to children with developmental disregard.

## 7.5 ACKNOWLEDGEMENTS

We want to thank all the children and their families who took part at this study. This work was part of a doctoral dissertation that was supported by grants from (in alphabetical order): Hersenstichting Nederland, Johanna Kinderfonds, Stichting Rotterdams Kinderrevalidatie Fonds Adraanstichting, Phelps Stichting voor Spastici and Revalidatiefonds





# CHAPTER

# VIII

## Abstract

Children with unilateral Cerebral Palsy (CP) often show diminished awareness of the remaining capacity of their affected upper limb, known as developmental disregard. One theory suggests that developmental disregard can be described as a developmental delay resulting from a lack of use of the affected side (AS) during crucial developmental periods. We hypothesize that this delay is associated with a general delay in executive functions (EFs) related to motor behavior, also known as motor EFs. To study this hypothesis 24 children with unilateral CP participated in this cross-sectional study, 12 of them with developmental disregard. To test motor EFs, a modified go/nogo task was presented in which cues followed by go- or nogo-stimuli appeared at either the left or right side of a screen. Children had to press a button with the hand corresponding to the side of stimulus presentation. Apart from response accuracy, Event-Related Potentials (ERPs) extracted from the ongoing EEG were used to register covert cognitive processes. ERP N1, P2, N2, and P3 components elicited by cue-, go-, and nogo-stimuli were further analyzed to differentiate between different covert cognitive processes. Results revealed that children with developmental disregard made more errors. Furthermore, the P3 component to go-stimuli was enhanced in children with developmental disregard. This enhancement was related to age: younger children with developmental disregard showed stronger enhancements. In addition, in developmental disregard the N1 component to cue- and go-stimuli was decreased. The behavioral results show that children with developmental disregard experience difficulties when performing the task. The finding of an enhanced P3 component to go-stimuli suggests that these difficulties are due to increased mental effort preceding movement. As age mediated this enhancement, it seems that this increased mental effort is related to a developmental delay. The additional finding of a decreased N1 component in developmental disregard furthermore suggests a general diminished visuo-spatial attention. This effect reveals that developmental disregard might be a neuropsychological phenomenon similar to post-stroke neglect syndrome that does not resolve during development. Thus, therapies aimed at reducing neglect could be a promising addition to existing therapies for developmental disregard.

## Neglect-like Characteristics of Developmental Disregard in Children with Cerebral Palsy Revealed by Event-related Potentials

### This chapter is based on:

Zielinski, I.M., Steenbergen, B., Baas, C.M., Aarts, P.B.M., & Jongsma, M.L.A. (2014). Neglect-like characteristics of developmental disregard in children with cerebral palsy revealed by event related potentials. *BMC Neurol*, 14:221, doi: 10.1186/s12883-014-0221-0



## 8.1 INTRODUCTION

Cerebral Palsy (CP) is a group of neurodevelopmental disorders accompanied by disturbances in movement and posture. It is caused by a perinatal non-progressive brain injury and is associated with lifelong motor impairments and disabilities (Aisen et al., 2011; Rosenbaum et al., 2007). Unilateral CP is among the most common subtypes of CP, comprising 20–40% of the cases (Odding, Roebroek, & Stam, 2006). Children with unilateral CP exhibit more pronounced motor deficits on one side of the body, often with the upper extremity more affected than the lower extremity (Odding et al., 2006; Rosenbaum et al., 2007). A subgroup of children with unilateral CP also seems to disregard their affected side (AS) (Deluca, Echols, Law, & Ramey, 2006; Hoare, Wasiak, Imms, & Carey, 2007; Houwink, Aarts, Geurts, & Steenbergen, 2011; Taub, Ramey, DeLuca, & Echols, 2004). This so-called developmental disregard, leads to a further reduction in using the AS in daily life (Boyd et al., 2010; Deluca et al., 2006; Houwink et al., 2011).

Different explanations have been proposed for the phenomenon of developmental disregard, all of them giving slightly different indications concerning therapy. Unravelling the underlying factors of developmental disregard therefore has high clinical value. Traditionally, developmental disregard has been explained by behavioral reinforcement theories (Taub et al., 2004). According to these theories, developmental disregard can be understood as a result of negative feedback experienced each time the AS is used (Crocker, MacKay-Lyons, & McDonnell, 1997; Taub, 1980). This behavioral phenomenon is akin to the phenomenon of learned non-use that sometimes develops in patients recovering from stroke (Taub & Wolf, 1997).

More recently, it has been hypothesized that developmental disregard could be a phenomenon similar to post-stroke motor neglect syndrome (Sutcliffe, Logan, & Fehlings, 2009). Similar to children diagnosed with developmental disregard, hemiplegic stroke patients with motor neglect show great difficulties in using their AS spontaneously, even though strength and coordination are often preserved (Gurd, Kischka, & Marshall, 2010; Saevarsson, 2013). In line, motor neglect is sometimes confused with learned non-use, leading to misdiagnosis and possible false decisions concerning therapy (Saevarsson, 2013). However, unlike learned non-use, motor neglect is thought to be the direct result of brain injury to neural networks involved in spatial attention processes (Chatterjee, 2002; Saevarsson, 2013). The relation between spatial attention and motor deficits has been explained by the premotor theory of Rizzolatti and Carmada (1987). They explain that neural networks for spatial attention are substantially connected with areas that are responsible for motor planning (Rizzolatti &

Carmada, 1987). Brain injury to these networks and resulting deficits of spatial attention therefore leads to an underutilization of the affected body parts related to deficits in motor planning, hence to motor neglect (Rizzolatti & Carmada, 1987).

Apart from the similarities between developmental disregard, learned non-use, and motor neglect, a very important factor in children with developmental disregard compared to adult stroke patients is the developmental aspect (Taub et al., 2004). Studies have increasingly emphasized the important role of developmental factors and the influence of motor learning in understanding developmental disregard in children with unilateral CP (Boyd et al., 2010; Deluca et al., 2006; Eliasson, Bonnier, & Krumlinde-Sundholm, 2003; Houwink et al., 2011; Taub et al., 2004; Zielinski, Jongsma, Baas, Aarts, & Steenbergen, 2014). More specifically, it has been argued that developmental disregard results from a lack of use of the AS during important developmental periods (Deluca et al., 2006; Houwink et al., 2011). Due to this lack of use directly related to the initial impaired hand capacity, movements are not being automated and neural substrates serving entire classes of behaviors might not yet be established, refined, or coordinated (Deluca et al., 2006). This delay in neural refinement does presumably not only affect the actual motor performance of these children, but most likely also the higher order cognitive aspects that are involved in motor behavior (Houwink et al., 2011; Zielinski et al., 2014).

Higher order cognitive aspects that are known to be important for motor learning and goal-directed motor behavior and that are strongly determined by developmental trajectories, are executive functions (EFs), also known as cognitive control (Anderson, 2002; Christ, White, Brunstrom, & Abrams, 2003). EFs is an umbrella term for different higher order cognitive abilities, such as higher order attentional processes, vigilance, and inhibitory control (Pirila, van der Meere, Rantanen, Jokiluoma, & Eriksson, 2011). It is known that EFs rely on an extensive interconnectivity between different parts of the brain especially involving the prefrontal cortex (Bottcher, Flachs, & Uldall, 2010). As the frontal lobes as well as the intricate connections from underlying brain regions are known to be the last to reach maturity, EFs are known to be the last cognitive area to mature and are therefore especially influenced by developmental periods in middle childhood (Bottcher et al., 2010). Damage to, or delays in development of these white matter tracts are associated with executive dysfunctions (Anderson, 2002; Bottcher et al., 2010; Pirila et al., 2011).

Within the realm of EFs and goal-directed motor behavior, also known as motor EFs, processes related to attentional control, response switching, as well as response inhibition, are known to be critical to the successful completion of many everyday tasks (Anderson, 2002; Mostofsky & Simmonds, 2008).



Furthermore, especially response inhibition has been repeatedly reported to show a progressive development from early childhood and to be frequently impaired in individuals with developmental disabilities (Christ et al., 2003; Jonkman, 2006; Nigg, 2000). Based on the assumption that developmental disregard can be linked to a delay in the development of motor EFs, we studied whether children with developmental disregard experience specific problems in attentional control related to response selection and response preparation as well as in response switching, and response inhibition. This was measured using an adapted go/nogo task. Stimuli within a trial appeared at the left or right side of a laptop screen inducing response switching. Children had to respond correctly to go-stimuli with the hand corresponding to the side of stimulus presentation and inhibit responses following nogo-stimuli.

In order to study motor EFs in children with unilateral CP with and without developmental disregard, we measured overt responses in terms of response accuracy. Furthermore, Event-Related Potentials (ERPs) were extracted from the ongoing EEG to register covert cognitive processes involved in this modified go/nogo task. Next to being able to reveal specific neurophysiological correlates of diminished performance, ERPs have the advantage to register covert processes involved in cognitive control even in the absence of overt behavior (e.g. when successfully refraining from responding to nogo- stimuli) (Luck, 2005).

The most commonly identified ERP components within cognitive tasks are the N1, P2, N2, and P3 components (Jonkman, 2006; Key, Dove, & Maguire, 2005; Luck, 2005). Whereas the N1 component has been associated with orienting and early spatial attention processes and the P2 component is known to be modulated by the complexity of the stimuli (Luck, 2005), the later latency N2 and P3 components are known to reflect processes associated with cognitive and attentional control (Key et al., 2005). Accordingly, ERP components that have conventionally been associated with EFs, or cognitive control, during a go/nogo task are the N2 and P3 ERP component (Liu, Xiao, Shi, & Zhao, 2011; Spronk, Jonkman, & Kemner, 2008). The nogo-N2 amplitude is associated with both conflict monitoring and response inhibition and is thought to be generated in the anterior cingulate cortex (ACC) and prefrontal lobe (Liu et al., 2011; Spronk et al., 2008). In addition, the P3 amplitude is known to be related to attentional control processes and is thought to be mostly generated in the medial temporal lobe (Key et al., 2005; Liu et al., 2011). Whereas the nogo-P3 correlates with inhibition control, the go-P3 reflects executive control and is known to be enhanced when demands on cognitive control increase (Liu et al., 2011; Luck, 2005).

If developmental disregard is indeed associated with a developmental delay in motor EFs, these children can be expected to show a diminished performance on the go/nogo task, compared to children with unilateral CP

without developmental disregard. More specifically, we hypothesized that, (1) children with developmental disregard compared to children without developmental disregard make more errors when performing the modified go/nogo task reflecting enhanced difficulties in task performance and, that (2) these difficulties would be accompanied by enhanced N2 and P3 ERP components. Next to these group differences, we furthermore expect that (3) developmental changes will be reflected in age differences within the groups.

## 8.2 METHODS

### 8.2.1 Participants

Twenty-four children with unilateral CP were recruited from the Sint Maartenskliniek, Nijmegen, the Netherlands. AS, manual ability, as well as developmental disregard was assessed by an occupational therapist prior to the EEG measurements. Manual ability was assessed using the “Manual Ability Classification System” (MACS), designed to classify how children with CP use their hands when handling objects in daily activities (Eliasson et al., 2006). Developmental disregard was assessed using the “Video-Observation Aarts and Aarts module: Determine Developmental Disregard” (VOAA-DDD-R) (Houwink, Geerdink, Steenbergen, Geurts, & Aarts, 2013). This structured video observation assesses both the overall duration and frequency of affected upper limb use. By comparing the affected upper limb use between two standardized tasks, one designed to demand the use of both hands to accomplish the task, whereas the second task is designed merely to stimulate bimanual activity, developmental disregard can be determined.

Twelve children were classified as having developmental disregard. The other twelve children served as control group (unilateral CP without developmental disregard). Even though in each group one child had a visual impairment, they were able to perform the task and showed no differences with respect to response speed or accuracy. They were therefore not excluded from the final analyses. The remaining participants had normal or corrected to normal vision. Furthermore, three of the children were visiting a special school due to an observed delay in general cognitive abilities. Two of them were diagnosed with developmental disregard.

To test whether the groups differed with respect to age a Mann-Whitney U-Test was conducted. To test whether there were differences between groups concerning gender, side of the AS, and manual ability (MACS), Fisher’s Exact Tests were conducted. For group characteristics and results, see **table 8**. Approval for the experiment was obtained from the local Ethical Committee of the Faculty



of Social Science (EC) from the Radboud University Nijmegen (Registration number: 2012/049; NL nr: 39607.091.12). The parents of all participants signed a written informed consent.

**Table 8.1.** Group characteristics

	noDD	DD	Statistics
Age (years; months) (range (years; months))	8; 8 (4; 8-11; 2)	8; 1 (5; 7-12; 11)	8; 1 (5; 7-12; 11)
Gender (male/female)	5/7	10/2	Fisher's Exact Tests: n.s.

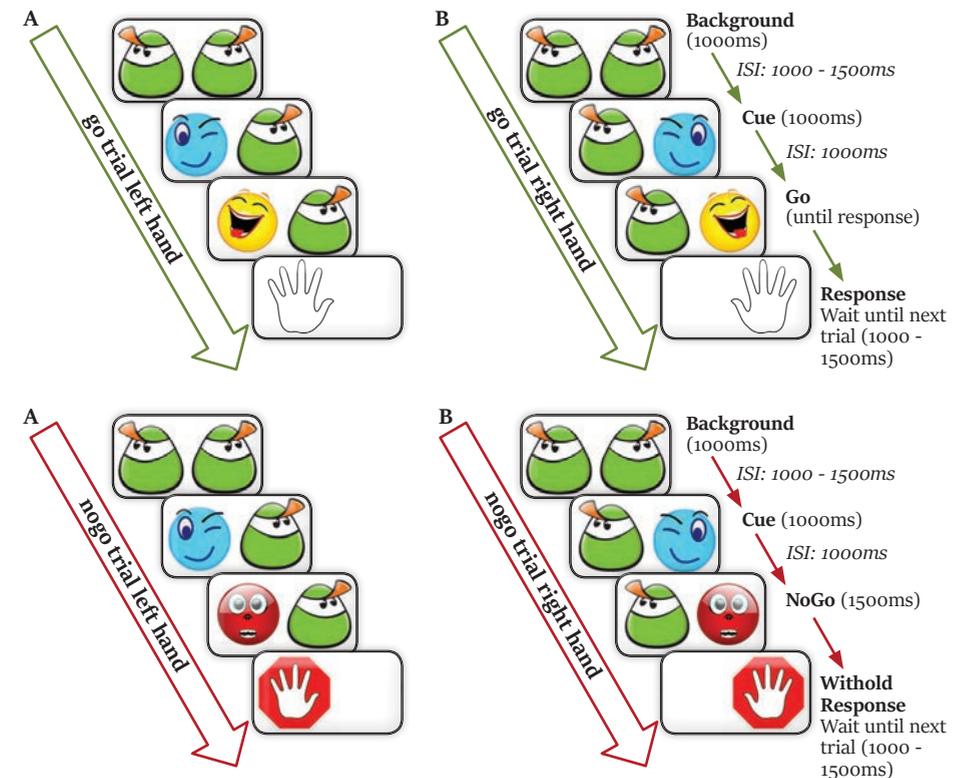
	noDD	DD	Statistics
AS (left/right)	7/5	6/6	Fisher's Exact Tests: n.s.
MACS (range)	1.6 (1-3)	2 (1-3)	Fisher's Exact Tests: n.s.

**Abbreviations:** DD, developmental disregard; AS, affected side; MACS, manual ability classification system; n.s., non-significant

### 8.2.2 Design

In this cross-sectional study a modified go/nogo paradigm (Jonkman, 2006) was used. Visual stimuli consisting of pairs of “smiley” figures against a white background (size of smileys 7×7cm) were presented on a laptop screen approximately 40 cm in front of the child. Background-stimuli consisted of two green smileys. Cue-stimuli consisted of a blue paired with a green smiley. Go-stimuli consisted of a yellow smiley paired with a green smiley. Nogo-stimuli consisted of a red smiley paired with a green smiley. Go- and nogo-stimuli were always presented at the same side as the preceding cue-stimulus. **Figure 8.1.** provides a graphical presentation of the stimuli. Trials consisted of one to three background-stimuli and a cue-stimulus, followed by either a go- or nogo-stimulus.

Thus, four different types of trials were presented: go-trials for the less-AS, go-trials for the AS, nogo-trials for the less-AS and nogo-trials for the AS. Each trial type was presented 20 times. Trials (N = 80) were presented in a random order, demanding regular response switching and response inhibition with respect to both hands. The stimulus duration was 1000 ms for background- and cue-stimuli, 1500 ms for nogo-stimuli, and for go-stimuli until a response



**Figure 8.1.** Trials of go/nogo paradigm. The four different trials of the modified go/nogo paradigm with a left hand go (A) and nogo (C) trial and a right hand go (B) and nogo (D) trial. ISI, inter-stimulus interval.

was made. The inter-stimulus interval (ISI) between cue- and go/nogo-stimuli was kept fixed at 1000 ms. Participants were instructed to respond as quickly as possible to go-stimuli. For this purpose two red buttons (diameter: 9.5cm; height: 5.5cm) were located next to the laptop keyboard, one at the right side and one at the left side. The distance between these buttons was kept at 30 cm to prevent that the wrong hand was used to press the according button. After each correct response to a go-stimulus a short laughing sound was presented. After each correct inhibited response to a nogo-stimulus a short trumpeting sound was presented. Errors were defined as false hits following cue- and nogo-stimuli as well as omissions following go-stimuli (no response within 2000 ms).

### 8.2.3 Electrophysiological recordings

EEG signals were recorded with a 32-channel active electrode system (actiCap MedCaT B.V. Netherlands) and amplified by a 32-channel BrainAmp EEG



amplifier with electrode placement according to the international 10–20 system at Fz, FCz, Cz, Pz, Oz, Fp1/2, F3/4/7/8, FC1/2/5/6, C3/4, T7/8, CP1/2/5/6, P3/4/7/8, O1/2 (Klem, Luders, Jasper, & Elger, 1999). A ground electrode was placed over AFz. The EEG signal was offline re-referenced to linked mastoids and stored on disk for offline analyses. Electrooculography (EOG) was recorded with bipolar channels placed above and below the right eye and on the outer canthi of each eye. Electrode impedance was kept below 5 k $\Omega$ . The signal was digitized at 1000 Hz between 0.016–250 Hz. For each participant an ocular correction was applied (Gratton, Coles, & Donchin, 1983) and segments containing artifacts exceeding  $\pm 150 \mu\text{V}$  were removed. The EEG signal was detrended and off-line filtered between 1–24 Hz. Next, the EEG was segmented from -250 ms to 750 ms related to stimuli and baseline corrected (-250 – 0 ms). Epochs corresponding to incorrect trials were excluded (total of 7.9% of the trials). Segments were averaged per stimulus type (cue vs. go vs. nogo) and hand (AS vs. less-AS).

### 8.2.4 Data analysis

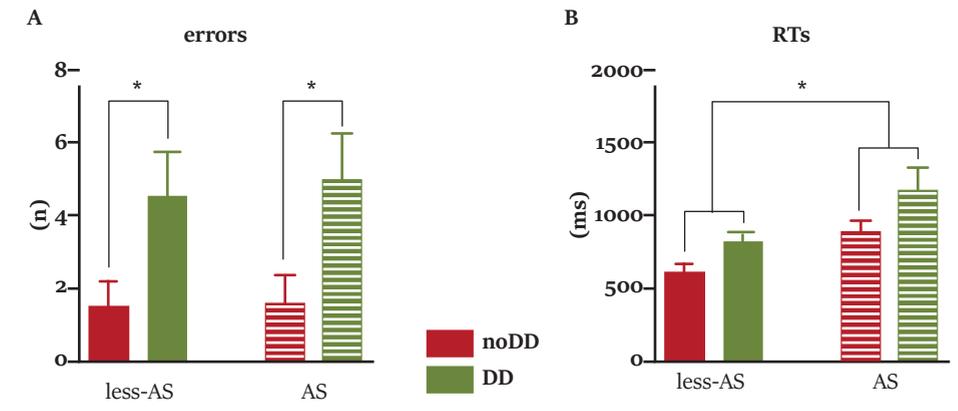
Errors and Reaction Times (RTs) of all correct responses were analyzed using repeated measures general linear model (GLM) analysis with handedness (AS vs. less-AS) as independent within-subject variables and group (control group vs. developmental disregard group) as between-subject factor.

The ERP N1, P2, N2, and P3 component amplitudes at Fz, FCz, and Cz were further analyzed. To allow blind scoring, ERP amplitudes were defined as the averaged value within a fixed latency window: N1 (120–140 ms), P2 (220–240 ms), N2 (320–360 ms), and P3 (500–60 ms). ERP components were analyzed using repeated measures GLM analyses with handedness (AS vs. less-AS) and electrode side (Fz, FCz, and Cz) as independent within-subject variables and group (control group vs. developmental disregard group) as between-subject factor.

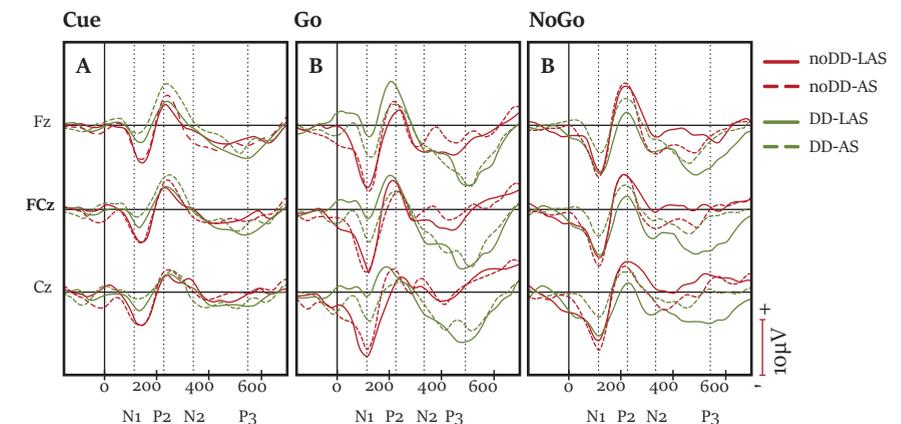
Whenever interaction effects were observed, appropriate T-Tests were performed. To account for multiple testing, a Bonferroni correction was applied. Whenever group differences were observed, multivariate linear regression analyses were applied with age as independent variable. This was done to explore possible developmental changes within the groups that might explain the group differences. For all analyses, the significance level was set at  $\alpha < .05$ .

## 8.3 RESULTS

With respect to the behavioral data, the analyses of errors revealed a significant group effect ( $F(1,22) = 22.83$ ;  $p = .023$ ;  $\eta^2 = .213$ ; 95% CI, .48 to 5.94). Children



**Figure 8.2. Errors (A), and RTs (B).** Depicted are means  $\pm$  SEMs. Red bars show the results of the CP children without developmental disregard; green bars show the results of children with developmental disregard. Filled bars depict the results of the less-AS; striped bars depict the results of the AS. noDD, no developmental disregard; DD, developmental disregard; RTs, reaction times; AS, affected side.



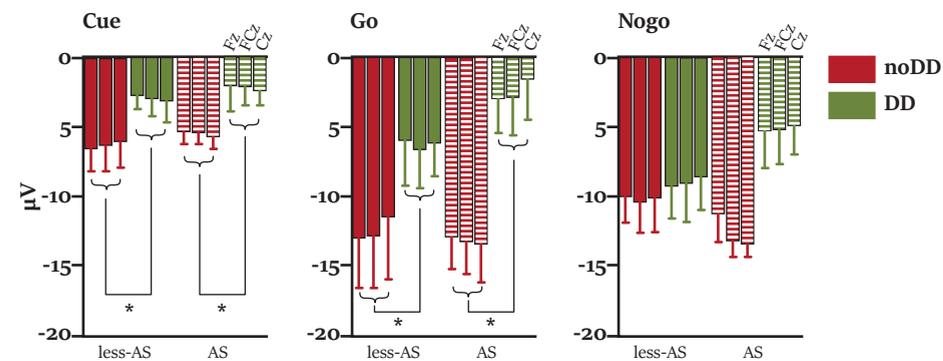
**Figure 8.3. Grand averaged waveforms.** Grand average ERPs following cue- (A), go- (B), and nogo-stimuli (C). ERPs of children with unilateral CP without developmental disregard are depicted in red and for children with developmental disregard in green. ERPs for the less-AS are depicted in solid lines and for the AS in dashed lines. noDD, no developmental disregard; DD, developmental disregard; LAS, less-affected side; AS, affected side.

with developmental disregard made significantly more errors. No interactions were found (see **figure 8.2.A**). The multivariate linear regression analysis with age as independent variable and total errors for both hands as dependent variables did not reveal any predictable value of age for the amount of mistakes for either group.

In addition, the RT data revealed a significant hand effect ( $F(1,22) = 11.24$ ;  $p = .003$ ;  $\eta^2 = .338$ ; 95% CI, 37.91 to 160.93), showing that children across both groups responded significantly slower with their AS. No group effect with respect to the RTs was found (see **figure 8.2.B**).

The grand average ERPs following cue-, go-, and nogo-stimuli contained a clear N1 (mean latency: 130 ms), P2 (mean latency: 230 ms), and N2 (mean latency: 340 ms) component. Instead of a classic P3, a late latency negative wave was observed following go- and nogo-stimuli (mean latency: 550 ms). This fronto-central negative wave in children has earlier been reported to be comparable to the classic P3 wave in adults (Picton, 1992). Grand average ERPs at Fz, FCz, and Cz electrode location following cue-, go-, and nogo-stimuli for both the developmental disregard and control group (CP without developmental disregard) are depicted in **figure 8.3**.

The analyses of the N1 ERP component revealed a main effect of group following cue- ( $F(1,22) = 7.01$ ;  $p = .015$ ;  $\eta^2 = .242$ ; 95% CI, 0.77 to 6.36) and go-stimuli ( $F(1,22) = 5.36$ ;  $p = .030$ ;  $\eta^2 = .196$ ; 95% CI, 0.89 to 16.10). The N1 component was diminished in the developmental disregard group compared



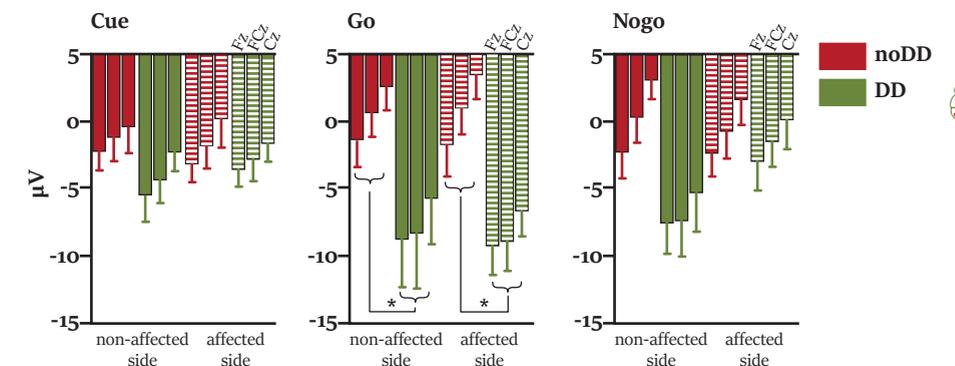
**Figure 8.4.** N1 amplitudes (mean  $\pm$  SEM; Fz, FCz, Cz) to cue-, go-, and nogo-stimuli. Children without developmental disregard are depicted in red bars and children with developmental disregard in green bars. Filled bars depict the results of the less-AS; striped bars depict the results of the AS. noDD, no developmental disregard; DD, developmental disregard; AS, affected side.

to the control group (**figure 8.4**). In addition, a hand\*group interaction was found following nogo-stimuli ( $F(1,22) = 4.78$ ;  $p = .04$ ;  $\eta^2 = .178$ ). However, post-hoc analyses (Independent-Samples T-Test) revealed no significant group or hand effects. Furthermore, for both the cue- and go-stimuli, the multivariate linear regression analyses per group, with age as independent variable, and N1 amplitude at different electrode positions as dependent variables, did not reveal any age effects.

With respect to the P2 component only electrode effects were found following cue- ( $F(2,21) = 6.58$ ;  $p = .006$ ;  $\eta^2 = .385$ ) and go-stimuli ( $F(2,21) = 6.29$ ;  $p = .007$ ;  $\eta^2 = .375$ ). Also, following cue-stimuli a hand\*electrode interaction was found ( $F(2,21) = 3.93$ ;  $p = .036$ ;  $\eta^2 = .272$ ). Post-hoc analyses of this interaction (Paired Samples T-Test) revealed no hand effect at the separate electrode sides.

The analyses of the N2 component also revealed significant electrode effects following go- ( $F(2,21) = 6.14$ ;  $p = .008$ ;  $\eta^2 = .369$ ) and nogo-stimuli ( $F(2,21) = 5.54$ ;  $p = .012$ ;  $\eta^2 = .345$ ). In addition, an electrode\*group interaction was found following go-stimuli ( $F(2,21) = 4.25$ ;  $p = .028$ ;  $\eta^2 = .288$ ). Post-hoc analyses (Independent-Samples T-Test) revealed no differences between groups at the different electrode sides.

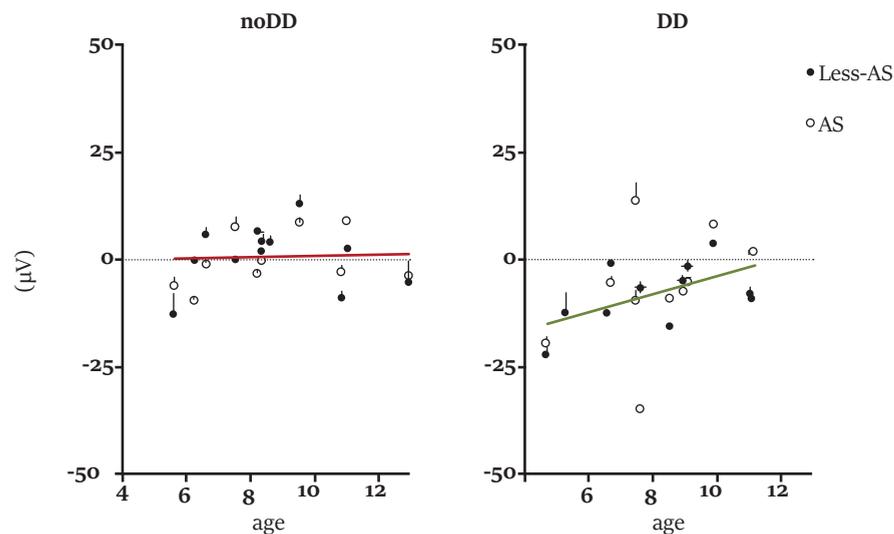
Next to significant electrode effects following cue- ( $F(2,21) = 10.55$ ;  $p = .001$ ;  $\eta^2 = .501$ ), go- ( $F(2,21) = 8.29$ ;  $p = .002$ ;  $\eta^2 = .441$ ), and nogo-stimuli ( $F(2,21) = 8.97$ ;  $p = .002$ ;  $\eta^2 = .452$ ), the analyses of this P3-like ERP component



**Figure 8.5.** P3 amplitudes (mean  $\pm$  SEM; Fz, FCz, Cz) to cue-, go-, and nogo-stimuli. Children without developmental disregard are depicted in red bars and children with developmental disregard in green bars. Filled bars depict the results of the less-AS; striped bars depict the results of the AS.



revealed a main effect of group following go-stimuli only ( $F(1,22) = 9.00$ ;  $p = .007$ ;  $\eta^2 = .290$ ; 95% CI, - 14.72 to - 2.69). Following go-stimuli, the P3 ERP component was enhanced in the developmental disregard group compared to the control group (CP without developmental disregard). No interactions were observed for either stimulus (see figure 8.5.).



**Figure 8.6.** Mean P3 amplitudes with age (mean  $\pm$  SEM of Fz, FCz, Cz per participant) to go-stimuli. Children without developmental disregard are depicted on the left (noDD) and children with developmental disregard on the right (DD). Data of the less-AS are depicted as dots and for the AS as circles. The regression line for children without developmental disregard is depicted in red and for children with developmental disregard in green.

The multivariate linear regression analysis with age as independent variable and P3 amplitude at different electrode positions as dependent variables did reveal significant predictable value of age for the amplitude of the go-P3 component in the developmental disregard group ( $R^2 = .402$ ;  $p = .027$ ). The older the children in the developmental disregard group, the less enhanced the P3 component was. This was not the case in children without developmental disregard (see figure 8.6.).

## 8.4 DISCUSSION

The goal of the current study was to test the hypothesis that children with developmental disregard experience deficits that are directly related to a

developmental delay in executive functions (EFs) involved in goal-directed motor behavior, also known as motor EFs. Under the assumption that developmental disregard might be associated with a delay in motor-skill development (Deluca et al., 2006; Houwink et al., 2011) as well as a broader delay in the development of motor EFs (Houwink et al., 2011; Zielinski et al., 2014), we expected that children with developmental disregard would demonstrate impaired performance during a modified go/nogo task. Next to evaluating the overt responses measured in terms of response accuracy, covert cognitive processes involved in attentional control related to response selection and response preparation as well as in response switching, and response inhibition were registered using Event-Related Potentials (ERPs) extracted from the ongoing EEG. We expected children with developmental disregard to (1) make more errors and to (2) show enhanced late latency N2 and P3 ERP components as these components have been reported to reflect covert cognitive control processes when elicited in a go/nogo task (Liu et al., 2011; Luck, 2005). We furthermore expected that (3) if developmental disregard is related to a developmental delay in motor EFs, these effects would diminish with age.

With respect to the first hypothesis, our behavioral results indeed showed that children with developmental disregard, compared to children without developmental disregard, made more errors during the modified go/nogo-task. Therefore, our first hypothesis was confirmed. This increase was however not restricted to an increase in false hits (i.e. diminished response inhibition), or misses (i.e. diminished response switching), but rather reflected in the total amount of errors. Thus, children with developmental disregard do not seem to experience any specific difficulties related to response inhibition or response switching, but seem to experience general difficulties when completing the modified go/nogo-task. These general difficulties did however not seem to be determined by developmental aspects, as age in neither group did predict the number of errors. With respect to our behavioral findings, our third hypothesis was therefore not confirmed.

To examine the underlying cognitive factors that might have contributed to this increase of errors, the ERPs following the different stimuli were inspected. Our ERP data of the late latency N2 and P3 components showed a similar pattern of results as the behavioral data. Our second hypothesis was partly confirmed: Although no group differences with respect to the N2 and P3 components following nogo-stimuli were observed, children with developmental disregard showed an enhanced fronto-central P3 component following go-stimuli. Nogo-N2 and nogo-P3 amplitudes are respectively correlated with response inhibition and inhibition control processes (Liu et al., 2011; Spronk et al., 2008). As there were no differences between groups regarding these components, it



seems that children with developmental disregard do not experience any specific difficulties in response inhibition processes compared to children with unilateral CP without developmental disregard. This is in line with the behavioral findings, as the increased errors were not restricted to false hits following nogo-stimuli.

The go-P3 component, which was found to be enhanced in the developmental disregard group, is known to reflect executive control processes preceding the motor response (Liu et al., 2011). In this respect it has often been reported that the go-P3 is affected by the mental effort that the participant devotes to the task, so that increased mental effort is accompanied by an increase in the P3 amplitude (Liu et al., 2011; Luck, 2005; Zielinski et al., 2014). As such, the current finding of an enhanced P3 following go-stimuli in children with developmental disregard might reflect increased mental effort serving executive or cognitive control mechanisms involved in goal directed behavior. With respect to the go-P3, it was furthermore found that only in the developmental disregard group, age had a predictable value on the P3 amplitude. With respect to the go-P3 component our third hypothesis was therefore confirmed. As children with developmental disregard got older, the enhancement of the go-P3 amplitude was reduced. It might therefore be concluded that the differences between the two groups might be best explained by a developmental delay of executive control mechanisms involved in goal directed motor behavior in children with developmental disregard.

In all, our findings add to the accumulating evidence that the performance difficulties observed in children with developmental disregard might be related to a disproportional amount of attentional control needed during motor performance (Houwink et al., 2011; Zielinski et al., 2014). Indeed, in our previous ERP study we also observed that children with developmental disregard allocated more mental effort when preparing a response with the AS during a bimanual cued-target paradigm (Zielinski et al., 2014). Furthermore, the finding that for children with developmental disregard age is significantly related to the amount of cognitive control involved in response preparation is in line with the assumption that developmental factors play an important role in the development and persistence of developmental disregard (Boyd et al., 2010; Deluca et al., 2006; Eliasson et al., 2003; Houwink et al., 2011; Taub et al., 2004; Zielinski et al., 2014). However, as the total amount of errors in our current study was not related to age in either group, there seemed to be additional cognitive factors, next to the developmental related cognitive control processes, contributing to the observed performance deficits in the developmental disregard group. One possible explanation was given by the additional ERP findings of the mid-latency N1 component of the current study.

Next to the differences between groups in the total amount of errors and the late-latency go-P3 component, the electrophysiological results of the

current study revealed distinctive effects on the mid-latency N1 ERP component. Following both cue- and go-stimuli, the N1 component was decreased in children with developmental disregard compared to children without developmental disregard. However, there was no relation with age observed in either group related to the N1 amplitude.

The N1 ERP component, a negative going wave occurring at approximately 120 ms after presentation of a visual stimulus, is known to be particularly modulated by early orienting and spatial attention processes (Di Russo, Martinez, & Hillyard, 2003; Eason, 1981; Eimer & Driver, 2001; Luck, Heinze, Mangun, & Hillyard, 1990; Näätänen & Picton, 1987). The visual N1 component in particular, reflecting the activity within the intraparietal sulcus (IPS) in the dorsal parieto-occipital cortex, has been stated to reflect bottom-up stimulus processing at a level dealing with spatial attention and visuomotor control (Di Russo, Aprile, Spironi, & Spinelli, 2008; Key et al., 2005). Interestingly, the N1 component following cue- and target-stimuli has already been found to be diminished in patients with a post-stroke neglect syndrome (Di Russo et al., 2008; Verleger, Heide, Butt, Wascher, & Kompf, 1996). From the current finding of a diminished N1 component in children with developmental disregard, it may therefore be concluded that these children experience difficulties in stimulus processing at a level dealing with spatial attention and visuomotor control similar to that observed in post-stroke neglect. In line with this conclusion, Sutcliffe, Logan and Fehlings (Sutcliffe et al., 2009) indeed stated that the clinical symptoms of developmental disregard can be conceived of as a phenomenon similar to post-stroke neglect syndrome leading to an underuse of one side of the body unrelated to the impaired movement capacity (Chatterjee, 2002; Freeman, 2001).

As stated above, there was no relation observed between age and the N1 amplitude. This finding suggests that development does not influence these deficits in spatial attention and visuomotor control in children with developmental disregard. This might be explained by the premotor theory of Rizzolatti and Carmada (1987). In this theory it is stated that motor deficits observed in motor neglect patients can be explained by an underlying injury to neural networks of spatial attention as these neural networks are substantially connected with areas that are responsible for motor planning and preparation (Rizzolatti & Carmada, 1987)]. This theory, in combination with our current findings, leads to the suggestion that in children with developmental disregard neural networks involved in spatial attention seem to be affected. This would mean that in children with developmental disregard, next to their developmental delay in cognitive control processes related to motor behavior, different neural networks seemed to be affected than in children with unilateral CP but without developmental disregard. In future studies, this question could be addressed



using neuroimaging techniques that are able to look at these specific neural networks.

Interestingly, in the current study all observed effects (enhancement of errors; enhanced go-P3; decreased cue- and go-N1) were not restricted to the affected side. This finding might be explained by the neurocognitive perspective on developmental disregard proposed by Houwink and colleagues (2011). They proposed that developmental disregard can be explained by the high attentional demands associated with the use of the affected upper limb (Houwink et al., 2011). The attentional demands of the go/nogo-task used in the current study were higher than in a simple cued-target paradigm, as has been used in earlier studies (Di Russo et al., 2008; Zielinski et al., 2014). It might therefore be concluded that this enhancement of attentional demands led to a general decrease in stimulus processing and response preparation within the developmental disregard group.

Study limitations of the current study include the heterogeneity of the studied group concerning their etiology as well as the underlying differences in brain injury. This limitation is however inherent to the participant population, as unilateral CP comprises a very heterogeneous group of movement disorders (Odding et al., 2006; Rosenbaum et al., 2007). Further limitations of the current study relate to the limited data on the cognitive and perceptual information of the individual child. For future studies it should be considered to add a short screening procedure to gain some quantitative information on the cognitive functioning as well as the perceptual processing.

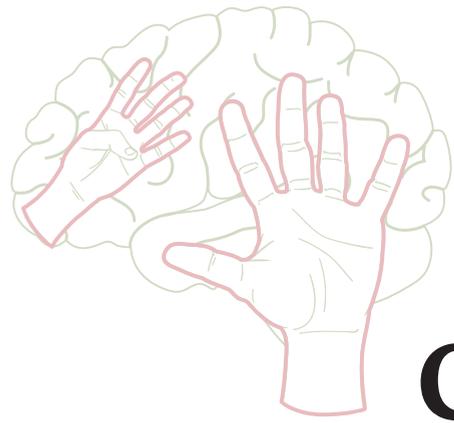
#### 8.4.1 Conclusion

The current study shows that next to difficulties in motor EFs that diminish with age, children with developmental disregard show neglect like symptoms that do not seem to resolve during development. This implies that therapies aimed at reducing motor neglect could be a promising addition to existing therapies for developmental disregard. Rather than only counter-conditioning learned non-use, as in Constraint Induced Movement Therapy (CIMT) (Aarts, Jongerius, Geerdink, van Limbeek, & Geurts, 2010; Taub, Uswatte, & Pidikiti, 1999), or automating bimanual performance, as in bimanual training therapies (BiT) (Aarts, Jongerius, Geerdink, van Limbeek, & Geurts, 2011), therapies aiming at reducing developmental disregard should also account for possible spatial attention deficits. To our knowledge, there are no therapies for children with unilateral CP directly aiming at reducing motor neglect. Future research should therefore be directed at studying the efficacy of therapies that are based on training children with developmental disregard to attend voluntarily to their contralesional space. This is for example done in limb activation training (LAT) that is already applied to adult neglect patients (Neill & McMillan, 2004).

## 8.5 ACKNOWLEDGEMENTS

We want to thank all the children and their families who took part at this study. This work was part of a doctoral dissertation that was supported by grants from (in alphabetical order): Hersenstichting Nederland, Johanna KinderFonds, Stichting Rotterdams Kinderrevalidatie Fonds Adraanstichting, Phelps Stichting voor Spastici, and Revalidatiefonds.





# CHAPTER IX

General Discussion



Due to the tremendous amount of research on unilateral CP that was conducted during the last decades, our knowledge on this neurodevelopmental movement disorder has been greatly enhanced. Not only do we now know a lot more about its epidemiology, etiology, and clinical presentation (Odding, Roebroek, & Stam, 2006; Speth, 2014), research has also improved our insight on the efficacy of different treatment programs (Novak et al., 2013). However, some phenomena related to unilateral CP can still not be fully explained, potentially hindering successful treatment. One of these phenomena is developmental disregard, observed in 50% to 90% of all children with unilateral CP (Deluca, Echols, Law, & Ramey, 2006; Houwink, Aarts, Geurts, & Steenbergen, 2011; Liu, Chen, Wang, & Shieh, 2016). Children with developmental disregard seem to underuse their preserved upper limb capacity. When performing typical bimanual tasks, these children show a preference for unimanual performance, even if recruiting the affected side (AS) would result in a more effective and/or efficient performance. Understanding this phenomenon to ultimately find solutions for treatment is important as these children's ability to independently perform daily routines is potentially harmed. Although these children may manage to perform typical bimanual tasks with only one hand (employing strategies such as using the teeth or stabilizing objects against the body), time for task completion is commonly prolonged (Van Zelst, Miller, Russo, Murchland, & Crotty, 2006). This might in turn lead children to seek assistance of others, or even to avoid certain activities, eventually leading to reduced participation in physical and social activities (Skold, Josephsson, & Eliasson, 2004).

The focus of the current dissertation was to understand developmental disregard in children with unilateral CP. We attempted to identify different factors that potentially contribute to developmental disregard based on two explanatory frameworks:

1. The operant conditioning framework; explains developmental disregard as a “learned” phenomenon and directly compares it to the phenomenon of learned non-use originally observed in adult stroke patients (Taub et al., 1994; Taub et al., 2007)
2. The information processing framework; states that developmental disregard might be best explained by a delayed or deficient development of information processing mechanisms relevant for successful goal directed motor behavior (Deluca et al., 2006; Houwink et al., 2011)

Although not mutually exclusive, each theoretical framework leads to different approaches for treating developmental disregard. Based on the operant conditioning framework, treatment would have to focus on overcoming the learned non-use. The focus would be on re-learning the use of the affected upper limb, thus solely focussing on improving the AS movements (e.g. by applying

mCIMT programs). Based on the information processing theory, therapy should rather focus on the automation of daily motor activities, while taking into account potentially delayed or deficient cognitive processes (e.g. attentional processes). The focus of this approach would thus not only be on improving the unimanual capacity, but rather on improving the actual (bi)manual performance. For a more detailed description of treatment recommendations (also directly related to our study results), we refer to **part 9.2.1** of the current chapter (“Clinical implication for rehabilitation”).

The aim of the current dissertation was to formulate and validate different hypothesis resulting from either the operant conditioning or information processing framework. These hypothesis were tested via a combination of behavioral and electrophysiological studies. In this final chapter, the results of these studies will be summarized and it will be discussed how these findings contribute to understanding the phenomenon of developmental disregard in children with unilateral CP. Additionally, possible clinical implications for rehabilitation will be given and future perspectives will be outlined. For an overview of the summarized results of each tested hypothesis, please see **figure 9.1**.

## 9.1 SUMMARY OF THE FINDINGS AND RELATED CONCLUSIONS

### 9.1.1 Prefix: Novel tools and procedures to study aspects of developmental disregard

In the prefix of the current dissertation we present two novel research methods. These methods were developed to study different hypothesis that might explain the phenomenon of developmental disregard in children with unilateral CP. In **chapter 2**, a quantitative tool to measure the amount of so-called mirror movements in children with unilateral CP is introduced: the “Windmill-task”. This tool was developed to answer the question whether children with developmental disregard do indeed show enhanced mirror movements, possibly explaining the non-use of the affected upper limb. This hypothesis was tested in **chapter 5** of the current dissertation. In addition to giving the opportunity to test this hypothesis, the results from **chapter 2** imply that it should be generally advised to apply the Windmill-task for future studies on mirror movements in children with unilateral CP. This is, because this task was shown to have many advantages compared to the commonly used Woods and Teuber scale (Woods & Teuber, 1978).

In **chapter 3**, an Event-Related Potential (ERP) protocol is introduced. This protocol was developed to study potential differences of information processing



mechanisms between children with and without developmental disregard when performing tasks that demand a motor response of the hands. Next to applying this method for the current study aim (which was done in **chapter 7** and **8**), the presented protocol opens opportunities for the broad implementation of research on cognitive aspects of different movement disorders in children. The ERP technique enables to study covert cognitive processes, while the child friendly task protocol allows the broad application of this method even in young children.

### 9.1.2 Part 1: The operant conditioning framework: developmental disregard as a “learned” phenomenon

One of the first theoretical frameworks that was used to understand developmental disregard in children with unilateral CP was based on the concept of behavioral reinforcement, derived from the operant conditioning theory (Taub, Ramey, DeLuca, & Echols, 2004). This framework suggests that the observed symptoms of non-use develop due to both negative reinforcement processes (i.e. the unsuccessful use of AS) and simultaneous positive reinforcement processes (i.e. the successful use of the less-AS). The resulting phenomenon is called learned non-use and has originally been reported in adult stroke patients (Taub, Uswatte, Mark, & Morris, 2006). In children with unilateral CP a similar phenomenon has been referred to as “special case” of learned non-use, as developmental aspects play an important additional role (as compared to adult stroke patients) (Taub et al., 2004). Principally, these children never had the experience of using their AS without difficulties. The phenomenon of non-use in children with unilateral CP has thus more appropriately been referred to as developmental disregard (DeLuca et al., 2006).

Following this line of reasoning, the non-use of the AS observed in developmental disregard is explained by a learned suppression of movement and related developmental delay processes. In **part 1** of the current dissertation (**chapter 4** & **5**) we focussed on testing hypotheses underlying the operant conditioning framework to explain developmental disregard.

#### 9.1.2.1 Developmental disregard in obstetric brachial plexus palsy vs. unilateral CP

In **chapter 4**, we compared two groups of pediatric patients: 1. children with unilateral CP and 2. children with obstetric brachial plexus palsy (OBPP). OBPP is characterized by a reduced unimanual capacity caused by a lesion of the peripheral brachial plexus nerve. In contrast to children with unilateral CP, children with OBPP do thus not have a central nervous system lesion. Still, impairment of the affected upper limb and thus the impact on learned suppression of movement

should be comparable to unilateral CP. To test if developmental disregard can be satisfactorily explained by these underlying reinforcement mechanisms, children with OBPP therefore yield the suitable control group. We studied the impact on spontaneous bimanual performance of a therapy program (mCIMT-BiT) aiming at overcoming developmental disregard. It was argued that if developmental disregard can be satisfactorily explained by behavioral reinforcement and related developmental delay processes, the impact of this therapy on spontaneous bimanual performance (typically reduced in developmental disregard) should be the similar for both groups, i.e. unilateral CP and OBPP.

Our results showed improvements on bimanual performance and spontaneous affected upper limb use following the mCIMT-BiT program in both groups of children (unilateral CP & OBPP). These results are confirming the frequently reported positive effects of mCIMT-BiT on upper limb functioning in general, independent of the etiology (Aarts, Jongerius, Geerdink, van Limbeek, & Geurts, 2011; Gordon et al., 2011). However, spontaneous use of the affected upper limb further improved after therapy in children with OBPP but not in children with uCP. These results indicate that children with OBPP have indeed effectively overcome their learned non-use. The finding that children with unilateral CP did not further improve on spontaneous use of the AS, but seemed to keep disregarding this AS suggests that, apart from learned non-use, additional mechanisms not targeted in the mCIMT-BiT program may underlie the developmental disregard in this group.

- mCIMT-BiT may help to effectively overcome developmental disregard in OBPP, but less so in unilateral CP
- Learned suppression of movement and related developmental delay processes (comparable between both patient groups, i.e. unilateral CP & OBPP) may not sufficiently explain the non-use of spontaneous affected upper limb in children with unilateral CP (i.e. developmental disregard)

#### 9.1.2.2 Developmental disregard and mirror movements

Within the operant conditioning framework that states that developmental disregard results from learning mechanisms it has additionally been proposed that so called mirror movements (frequently observed in children with unilateral CP) enhance the learned suppression of using the AS (Hoare, Wasiak, Imms, & Carey, 2007; Kuhtz-Buschbeck, Sundholm, Eliasson, & Forssberg, 2000; Woods & Teuber, 1978). It has been argued that mirror movements appearing in the less-AS (e.g. during bimanual activities) cause a reduction in independent control of the preferred hand, and mirror movements appearing in the AS result in a reduction of the typical stabilizing function of the AS. Based on the operant conditioning theory, both these experiences would ultimately cause a non-use of the AS.



In **chapter 5** we tested if children with developmental disregard showed enhanced mirror movements when compared to children with unilateral CP but without developmental disregard. Although our results showed a direct association between enhanced mirror movements and reduced (bi)manual functioning (Adler, Berweck, Lidzba, Becher, & Staudt, 2015; Klingels et al., 2015; Kuhtz-Buschbeck et al., 2000), no relation between mirror movements and developmental disregard was observed. Thus, the proposed learned suppression of AS movement following mirror movements does not necessarily lead to a developmental disregard in children with unilateral CP. Next to the important clinical implications of these findings (that will be discussed later), these results are in line with the claim of **chapter 4**, that apart from behavioral reinforcement processes, additional factors may contribute to developmental disregard in children with unilateral CP.

- Severity of mirror movements is not related to the presence of developmental disregard in unilateral CP
- Apart from behavioral reinforcement processes additional mechanisms appear to be involved in developmental disregard in unilateral CP

### 9.1.3 Part 2: The information processing framework: developmental disregard as a phenomenon of a deficient and/or delayed development of cognitive processes involved in movement control

An alternative theoretical framework potentially explaining developmental disregard in children with unilateral CP is the information processing theory that focuses on cognitive aspects involved in developmental disregard (Deluca et al., 2006; Houwink et al., 2011). This framework states that developmental disregard is explained by deficient or immature information processing mechanisms relevant for successful goal directed motor behavior. Based on this framework in the current dissertation three hypotheses were addressed. To be able to study the cognitive aspects of movement behavior that are potentially altered in children with developmental disregard, Electro-encephalography (EEG) measurements were applied.

#### 9.1.3.1 Developmental disregard and the delayed or deficient development of neuronal circuits of motor control

Related to the information processing theory it has been proposed that a delayed or deficient development of top-down cognitive control mechanisms typically involved in voluntary movement may underlie developmental disregard (Deluca et al., 2006; Grefkes, Eickhoff, Nowak, Dafotakis, & Fink, 2008). This delayed or deficient development was proposed to be directly related to a lack of movement input, as brain circuits involved in manual motor control only develop when

spontaneous hand movement occur (Deluca et al., 2006; Sanes & Donoghue, 2000). Research on sensitive periods for motor development furthermore suggest that these spontaneous movements are especially important during early developmental periods (between 6 months and 3 years; Roeber, Gunnar, & Pollak, 2014; Watanabe, Savion-Lemieux, & Penhune, 2007).

In our study reported in **chapter 6**, we tested the hypothesis that developmental disregards results from the delayed maturation or damaged neural circuits involved in motor control. This was done by monitoring the EEG mu-rhythm during voluntary hand movements in children with and without developmental disregard. The restoration of the mu-rhythm after voluntary movements is of special interest when studying top-down cognitive control mechanisms of motor behavior, as this mu-restoration plays an important role in preparing the functional neural circuit to perform new motor tasks (Klimesch, Sauseng, & Hanslmayr, 2007).

Study results show that while a typical mu-restoration after voluntary hand movements of either hand was observed in children with unilateral CP but without developmental disregard, no restoration of mu during rest was observed in children with developmental disregard. This lack of cortical synchronization during rest suggests a lack of integrity of the complex functional system typically involved in preparing voluntary hand movements in children with developmental disregard, but not universally in unilateral CP (as it was earlier suggested (Daly et al., 2014)). These findings indicate that the observed clinical symptoms of non-use might be best explained by a lack of “neural preparedness” or readiness to perform a new motor task. Unexpectedly, this lack of preparedness was apparent for movements of both hands, the AS as well as the less-AS.

- Children with developmental disregard show a lack of cortical synchronization typically involved in preparing voluntary manual movements, suggesting a lack of integrity of neural circuits involved in motor control
- Children with developmental disregard might lack a sufficient readiness to perform a new motor task (with both hands) potentially explaining the clinical symptoms of non-use

#### 9.1.3.2 Developmental disregard and enhanced cognitive effort

Another hypothesis related to the information processing theory proposes that developmental disregard in children with unilateral CP might be best explained based on the widely accepted model of motor learning of Fitts and Posner (Fitts & Posner, 1967; Houwink et al., 2011; see **figure 1.2.**). Based on this model it is suggested that the observed discrepancy between sufficient unimanual capacity but inadequate bimanual performance may be related to the fact that these



children have never automated certain bimanual movements (Houwink et al., 2011). Typical bimanual activities are therefore suggested to be accompanied by an enhanced cognitive effort, as motor tasks that are not yet automated are cognitively more demanding (Fitts & Posner, 1967). This enhanced cognitive effort might explain the non-use of the affected upper limb during daily activities in children with developmental disregard. This is because many daily activities demand most of the cognitive resources (e.g. playing, listening, walking), so that insufficient resources are available for using the affected upper limb in activities that are not yet automated.

In **chapter 7** we tested the hypothesis that children with developmental disregard show enhanced cognitive effort when moving their AS during bimanual tasks compared to the same movements within unimanual task settings. This was tested by comparing Event-Related Potentials (ERPs) of response preparation processes between two cued target response tasks: an unimanual (capacity) and a bimanual (performance) task. It was hypothesized that if AS-use in bimanual settings in children with developmental disregard is indeed related to an enhanced cognitive effort, these children should show alterations in their ERP components when selecting a response with their AS during the bimanual task. It was indeed observed that the ERP N2b component was affected indicating a diminished cognitive control of response-related processes (Folstein & Van Petten, 2008). It was concluded that children with developmental disregard experience an enhanced cognitive effort when including their affected upper limb during a bimanual task setting that cannot be explained by a general increase of cognitive load when simply executing AS movements in an unimanual task.

As a follow up on these findings, we aimed to find out if the increased cognitive effort was due to a delayed maturation of goal-directed motor development (**chapter 8**). It was hypothesized that if children with developmental disregard do experience a general delay of motor development, this would be especially reflected by an immaturity of executive functions (EFs) related to goal-directed motor behavior. Diminished EFs are commonly observed with a delayed maturation. To study EFs of goal-directed motor behavior, a bimanual go/nogo task was used while recording ERPs. Children with developmental disregard made more mistakes on the go/nogo task and showed an enhanced late latency P3 ERP component following the go-stimuli. This go-P3 ERP component is known to reflect executive control processes preceding a motor response (thus comparable to the late latency N2b component reported in **chapter 7**) (Liu, Xiao, Shi, & Zhao, 2011). Furthermore, this effect diminished with age, suggesting a delayed maturation of these executive control processes preceding a manual response.

In line with the unexpected findings reported in **chapter 6**, in this study enhanced cognitive effort was generally observed for the response preparation

of both the hands, the AS as well as the less-AS. These findings were explained by the enhanced cognitive demands of the go/nogo task (as compared to the more simple bimanual cued-target response task that was used in the **chapter 7**). It was concluded that increased cognitive demands of a task lead to a general reduction of successful manual response preparation in children with developmental disregard, also affecting the less-AS. In combination with the “bilateral” finding of **chapter 6**, this might indicate a certain “bimanual” involvement in children with unilateral CP and developmental disregard.

- Developmental disregard is related to enhanced cognitive effort of response preparation of the affected upper limb during bimanual tasks, but not during unimanual tasks (**chapter 7**)
- This enhanced cognitive effort appears to decline with age, indicating that a delayed maturation indeed underlies developmental disregard (**chapter 8**)
- The enhanced cognitive effort generalizes to response preparation of both the hands when enhancing task difficulty, indicating a certain “bimanual” involvement in developmental disregard (**chapter 8**)

### 9.1.3.3 Developmental disregard and motor neglect

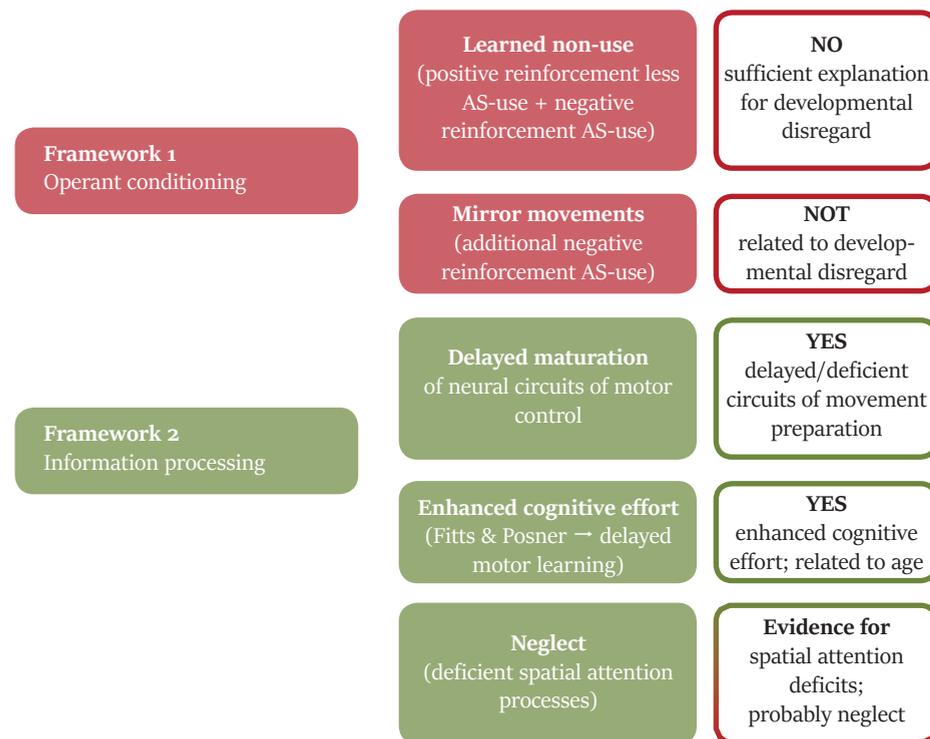
A different hypothesis based on the information processing theory compares developmental disregard to the phenomenon of post-stroke motor neglect (Sutcliffe, Logan, & Fehlings, 2009). As in children with developmental disregard, stroke patients with motor neglect appear to forget to use their AS during common, bimanual daily activities (Gurd, Kischka, & Marshall, 2010; Saevarsson, 2013). These comparable symptoms may be related to the same cause, i.e. an injury of brain circuits responsible for spatial attention processes involved in voluntary motor behavior (Sutcliffe et al., 2009).

In **chapter 8** differences between children with and without developmental disregard were found when examining their ERPs. Children with developmental disregard showed a decreased mid-latency N1 ERP component following both cue- and go-stimuli. This N1 component is known to reflect bottom-up stimulus processing at a level dealing with spatial attention and visuomotor control (Di Russo, Aprile, Spitoni, & Spinelli, 2008; Key, Dove, & Maguire, 2005). These additional results suggest that children with developmental disregard experience difficulties related to spatial attention. In comparison: diminished N1 ERPs have also been reported in patients with a post-stroke neglect syndrome (Di Russo et al., 2008). These results thus indicate that children with developmental disregard may experience comparable deficits as stroke patients with motor neglect. If children with developmental disregard do indeed experience neglect like symptoms, attention might not be automatically directed to the affected upper limb, leading to the observed disregard of the



existing motor capacities in developmental disregard. This hypothesis does however request future study.

- Children with developmental disregard appear to experience difficulties in spatial attention processes potentially explaining clinical symptoms of non-use
- The reduces spatial attention processes might be comparable to those observed in post stroke neglect patients (this hypothesis requests future validation)



**Figure 9.1. Schematic overview of the results related to the different hypotheses of the two frameworks explaining developmental disregard.** Depicted are the two frameworks (operant conditioning: red; information processing: green) and the related hypothesis that are aiming to explain the observed symptoms of non-use in children with unilateral CP and developmental disregard (middle column). The summarised related findings of the current dissertation are depicted on the right side of the figure. The red frame is indicating that the hypothesis was not confirmed, the green frame is indicating that the hypothesis was confirmed, the red & green frame is indicating that evidence for the hypothesis was found that do however request further validation.

## 9.2 DISCUSSION OF THE FINDINGS

While behavioral reinforcement processes as proposed by the operant conditioning framework certainly contribute to a diminished use of the AS in children with unilateral CP, the results summarized above indicate that this behavioral reinforcement cannot sufficiently explain the phenomenon of developmental disregard. Our cumulative study results presented in this dissertation strongly support the information processing framework for explaining developmental disregard in children with unilateral CP. It is thus suggested that developmental disregard is indeed related to a delayed and/or deficient development of different cognitive processes underlying voluntary hand movements. Each of our findings related to these deficient or immature cognitive processes in children with developmental disregard have important clinical implications that will be discussed below.

Unexpectedly, several studies presented in the current dissertation indicate that the altered cognitive processes of motor behavior involved in developmental disregard, might not be limited to the affected upper limb alone, but to a certain degree also affect the less-affected limb (**chapter 6 and 8**). These findings suggest a certain “bimanual” involvement of the deficient or immature cognitive processes observed in developmental disregard. In other words, these results indicate that developmental disregard might be related to a more general cognitive disorder, not limited to cognitive processes of movement behavior of the AS. Based on this line of reasoning we suggest that children with developmental disregard might not only experience the typical first order motor disability that is specific to unilateral CP, but furthermore experience a higher order motor disability generally affecting manual movement behavior. As opposed to the typical first order motor disorder affecting one upper limb as a direct result of a certain brain lesion, the proposed higher order motor disability is suggested to be an indirect result of the cortical lesion by altered learning experiences (operant conditioning theory) and particularly by an altered development of different cognitive processes underlying voluntary hand movements (information processing theory).

In line with this hypothesis of a higher order “bimanual” involvement to underlie developmental disregard, it has previously been reported that some children with unilateral CP actually experience subtle bimanual disabilities with an additional diminished movement capacity of the less-AS (Arnould, Bleyenheuft, & Thonnard, 2014; Tomhave, Van Heest, Bagley, & James, 2015). Some children were showing reduced strength and dexterity of their less-AS (Tomhave et al., 2015) as well as signs of coordination disorders of this less-AS during bimanual situations (Skold et al., 2004). Based on our findings indicating a higher order



motor disability affecting the movement control of both hands in children with developmental disregard, it might thus be speculated that developmental disregard is related to a comparable “bimanual” involvement. Future studies should focus on this hypothesis of a possible bimanual involvement underlying developmental disregard by also studying the motor behavior of the less-AS (during unimanual and bimanual conditions). Furthermore, future research should focus on more cognitive assessments in children with unilateral CP to unravel possible higher order cognitive processes related to movement behavior (e.g. planning, attention, automation) potentially underlying developmental disregard.

An alternative explanation for the proposed higher order motor disability affecting movement processes of the hands, next to being an indirect result of the primary cortical lesion might be given by the primary brain injury (as direct result of the cortical lesion). The primary cortical injury might have directly affected brain areas involved in cognitive processes relevant for successful motor control in children with developmental disregard (e.g. planning, attention, automation). One famous example of specific brain injury affecting cognitive processes that are important for goal directed behavior, is post stroke (motor) neglect. These patients show lesions of the parietal lobe which directly affects their automatic attentional processing, causing a non-use of the contralateral arm and hand (Laplane & Degos, 1983; Laurent-Vannier, Pradat-Diehl, Chevignard, Abada, & De Agostini, 2003). Although the non-use is often viewed as a motor disability it is in fact more related to an attentional disorder. In line with the hypothesis that developmental disregard might be a direct result of the primary brain injury, it has earlier been reported that in unilateral CP the type and extent of the brain lesion correlate to a large degree with the severity of the upper limb disability (Gordon, Bleyenheuft, & Steenbergen, 2013; Mackey, Stinear, Stott, & Byblow, 2014). It might therefore be speculated that the type and/or extent of the primary brain lesion might also affect higher order motor processes, possibly causing symptoms of non-use. Future research on this topic is warranted, investigating the possibility of the type and/or extent of the primary cortical injury to cause developmental disregard.

### 9.2.1 Clinical implication for rehabilitation

Rehabilitation of the reduced upper limb functioning in children with unilateral CP mostly focuses on three different training principles:

1. Training the AS in isolation (e.g. mCIMT) (Taub, Uswatte, & Pidikiti, 1999),
2. Training both hands using bimanual training (e.g. BiT) (Gordon, J. A. Schneider, A. Chinnan, & J. R. Charles, 2007; Green et al., 2013),
3. Training of unimanual strategies with the less-AS (Adler, Rauchenzauner, Staudt, & Berweck, 2014; Staudt, 2016).

For a detailed description of these training principles, and possible combinations of the different programs we refer to the introduction of the current dissertation (page 17; 1.1.2 “Treatment of upper limb functioning in unilateral CP”).

Originally, in order to counteract the learned non-use, mCIMT was the training of first choice in the rehabilitation of developmental disregard (Taub et al., 2004). It was proposed that this mCIMT would enhance the spontaneous use of the affected upper limb through processes of repetitive training and shaping, thus reversing the proposed negative behavioral reinforcement processes (Taub et al., 1994). The results presented in the current dissertation have however shown that behavioral reinforcement processes do not offer a sufficient explanation to understand, nor treat, developmental disregard in children with unilateral CP. It should thus be critically inspected if isolated mCIMT approaches are suitable for children with unilateral CP and developmental disregard.

More recently, it was argued that mCIMT should ideally be combined with BiT when treating developmental disregard (Aarts et al., 2010; Aarts et al., 2011; Charles & Gordon, 2005; Gordon, Schneider, Chinnan, & Charles, 2007; Hoare et al., 2007). Such a combined training schedule was proposed to be necessary to train bimanual coordination and possibly facilitate the maturation of the motor circuits in the brain. Indeed, findings of the current dissertation suggest a deficient or immature development of higher order motor functions affecting both hands in children with developmental disregard. Thus, a bimanual training approach appears most appropriate to specifically promote these bimanual skills and higher cognitive functions involved in controlling bimanual activities. However, as mCIMT approaches have been proven to effectively increase the unimanual capacity of the AS (Novak et al., 2013), we suggest that therapy approaches focusing on reducing developmental disregard in unilateral CP should include both mCIMT and BiT approaches with an enhanced focus on bimanual training.

Next to specifically training uni- and/or bimanual motor skills, our reported findings suggest that interventions should take into account possible spatial attention deficits, similar to neglect disorders, in children with developmental disregard. We argue that if potential spatial attention deficits are not targeted during treatment, the effects of a standard BiT training might be limited. Next to assessing developmental disregard, it would thus be favorable to assess if children do also experience spatial attention deficits. If this is the case, therapy should incorporate a training focusing on voluntarily attending to the contralesional space. However, to date, no such training has been described for children with unilateral CP. Future therapies could therefore implement elements of the so called limb activation training (LAT) used in adult neglect patients to treat

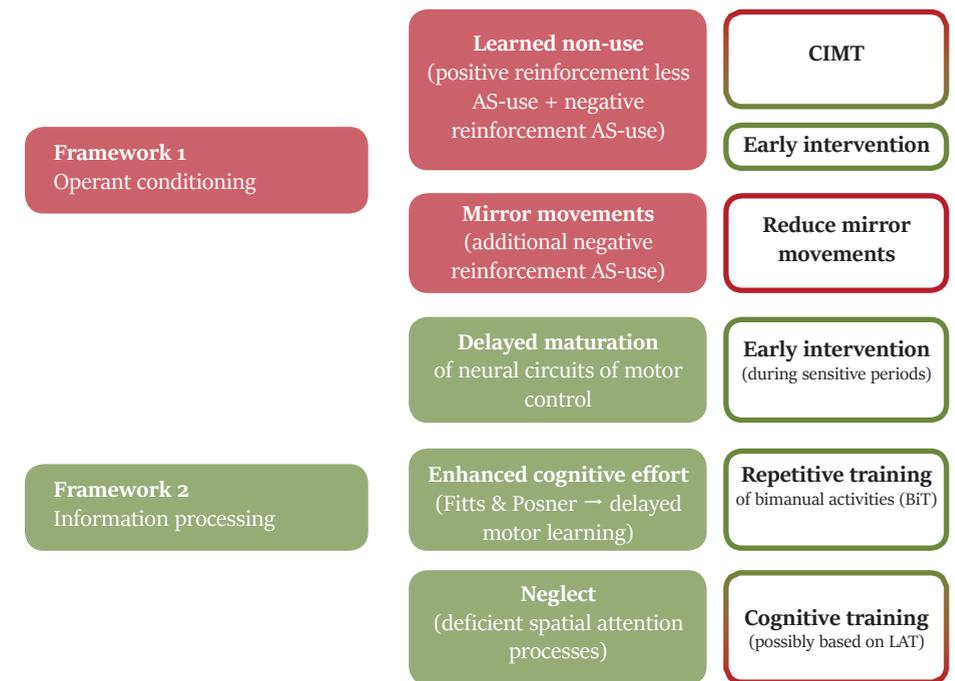


potential deficits of visuo- motor control (Pitteri, Arcara, Passarini, Meneghello, & Priftis, 2013). The efficiency of this proposed additional training in children with unilateral CP and additional spatial attention deficits does however warrant future research.

In addition to the recommendations on the content of therapies, our findings indicating a delayed maturation of motor circuits in developmental disregard suggest a need for implementing early interventions. These early intervention programs could potentially promote a more typical maturation of the neural circuits involved in motor behavior, preventing the observed immaturity of development (Morgan et al., 2016). Furthermore, early intervention programs would potentially also prevent a learned suppression of movement, therefore reducing the possibility of operant conditioning processes to cause symptoms of non-use. In line, initial results on the effects of early intervention programs on upper limb functioning in unilateral CP are promising (Morgan et al., 2016). Based on our findings we argue that especially symptoms of non-use might be prevented when training the inclusion of the AS during early sensitive periods. An additional clinical implication is based on our finding that developmental disregard does not appear to be related to mirror movements. In particular, this means that when mirror movements are observed in children with unilateral CP, this does not automatically mean that interventions should be focused on treating developmental disregard (Staudt, 2016). Both phenomena should be separately assessed and treated as separate phenomena. How to effectively treat mirror movements in children with unilateral CP is however still under debate with potential disadvantages being related to both mCIMT and BiT programs (Hoare et al., 2007; Staudt, 2016). For children with severe mirror movements a training including unimanual compensation strategies using only the less-AS may be favorable.

It should generally be concluded that therapy programs aiming at enhancing upper limb functioning in children with unilateral CP should be individualized. First, developmental disregard should be assessed, which is not done consistently across countries and hospitals. The results presented in the current dissertation repetitively show that children with unilateral CP and developmental disregard differ from children with unilateral CP but without developmental disregard. Knowledge of developmental disregard could thus lead to more individualized therapy recommendation. Next, different cognitive assessments to unravel possible higher order cognitive processes possibly underlying developmental disregard are recommended. Specifically, our study results suggest that children with unilateral CP should also be screened for signs of motor and/or visual neglect. Finally, our results suggest a potential “bimanual” involvement in developmental disregard as a direct result of affected higher order movement processes affecting

both hands do furthermore encourage more cognitive assessments for these children. It might also be encouraged to assess the children’s less-AS functioning during unimanual and bimanual situations to target a potential additional involvement of this less-AS. For an overview of the recommended treatment approaches related to both frameworks of developmental disregard and related hypothesis, please see **figure 9.2**.



**Figure 9.2. Schematic overview of different therapy recommendations related to the different hypotheses of the two frameworks explaining developmental disregard.** Depicted are the two frameworks (operant conditioning: red; information processing: green) and the related hypothesis that are aiming to explain the observed symptoms of non-use in children with unilateral CP and developmental disregard (middle column). The related therapy recommendations are depicted on the right side of the figure. The red frame is indicating that there is no motive of applying this therapy to treat developmental disregard, the green frame is indicating that this therapy is recommended to be applied when treating developmental disregard, the red & green frame is indicating that this therapy might be added to an existing program if the related hypothesis is confirmed for the individual child (neglect or learned non-use). mCIMT might be added to specifically train the children’s unimanual capacity.



- Training aimed at reducing developmental disregard should focus on bimanual training (e.g. BiT) with possible additional mCIMT to simultaneously provoke enhanced unimanual capacity
- Therapy should incorporate a training focusing on voluntarily attending to the contralesional space to treat potential spatial attention deficits in children with developmental disregard
- Early intervention programs during sensitive developmental periods may facilitate maturation of the motor circuits in children with developmental disregard and prevent a learned suppression of movement
- Mirror movement and their effects on upper limb functioning should be assessed and treated independently of developmental disregard
- Developmental disregard should generally be assessed in children with unilateral CP when selecting suitable therapy programs; additional assessments of both spatial attention (i.e. neglect), higher order cognitive deficits, and less-AS functioning should be considered.

### 9.2.2 Future directions

Based on the results presented in the current dissertation, future research on developmental disregard in children with unilateral CP should first of all focus on the question if the suggested therapy approaches are indeed reducing developmental disregard. In this respect it should be tested whether or not a bimanual therapy program (i.e. BiT) does indeed reduce symptoms of developmental disregard to a greater extent than therapy focussing on unimanual capacity and overcoming learned non-use (i.e. mCIMT). Additionally, future therapies should implement elements of the so called limb activation training (LAT) used in adult neglect patients to treat potential deficits of visuo- motor control in children with unilateral CP (Pitteri, Arcara, Passarini, Meneghello, & Priftis, 2013). The efficiency of this additional training for children with additional spatial attention deficits should then be focused on. Furthermore, studies applying early intervention programs should include the assessment of developmental disregard as a dependent variable when assessing the children on a follow up. These results should then be compared to the prevalence of developmental disregard in children that did not receive early intervention. If less children show symptoms of developmental disregard after participating at an early intervention program, this would encourage early intervention programs to all children at risk of-, or with unilateral CP (Morgan et al., 2016). To conclude, our findings give clear suggestions for treatment. However the question “What help best?” needs to be answered by future studies.

Next to evaluating the effects of therapy programs that potentially reduce or even prevent developmental disregard, some hypothesis based on incidental

findings of the current dissertation warrants further study. First, the hypothesis needs to be confirmed that developmental disregard is indeed related to a certain “bimanual” involvement due to a more general cognitive disorder, not limited to cognitive processes of movement behavior of the AS. This could be done by also focusing on the children’s less-affected upper limb functioning within both unimanual and bimanual tasks, or by directly assessing certain cognitive processes related to manual movement behavior (e.g. planning, attention, automation). If it can indeed be confirmed that children with developmental disregard actually experience a higher order “bimanual” movement disorder, this would strongly support the recommendation of applying bimanual training with an additional focus on the potential affected cognitive processes.

Furthermore, our observation of reduced spatial attention in developmental disregard needs to be further investigated. The question remains if this finding indicates that children with developmental disregard experience similar symptoms as post stroke neglect patients. This would imply that these children do not automatically attend to their contralesional space caused by a lesion to brain network responsible for these typically automated processes (Laplaine & Degos, 1983). Alternatively, the observed findings might indicate that children with developmental disregard experience a more generalized visuo-spatial attention deficit that is not restricted to their contralesional space, thus substantially different to the phenomenon of unilateral post stroke neglect. To answer this question, existing neuropsychological test batteries typically used in neglect diagnostic might be of potential value. For children with unilateral CP the so-called Teddy Bear Cancellation Test has earlier been used to screen for neglect symptoms (Laurent-Vannier, Chevignard, Pradat-Diehl, Abada, & De Agostini, 2006). We propose a future study to apply this test to children with and without developmental disregard to test if children with developmental disregard do indeed experience spatial attention deficits comparable to those of post stroke neglect patients.

Finally, future studies need to investigate the possibility of primary injury to specific neural circuits underlying developmental disregard. Differences in etiology of the brain lesions in children with and without developmental disregard could potentially further explain cognitive aspects of developmental disregard.

Even though we were able to support our results by statistical significance, additional replication of our findings are warranted, especially due to the small amount of children tested. Furthermore, future research should try to differentiate between different types of unilateral CP (e.g. spastic vs. dystonic), side of the AS, or manual ability level (e.g. MACS) when studying the phenomenon of developmental disregard. Within the current dissertation this was not done



related to the small amount of children included for the studies. Research with children with unilateral CP would benefit tremendously from studies with larger sample sizes, also when studying underlying processes related to clinical symptoms as in developmental disregard. Furthermore, longitudinal studies following the children for several years would have enormous benefits, not only to study different therapy effects, but also to directly study different factors that influence the development or possible disappearance of developmental disregard in children with unilateral CP.

### 9.3 GENERAL CONCLUSION

The results presented in the current dissertation reveal that developmental disregard in children with unilateral CP can most likely not solely be explained by processes of operant conditioning. Developmental disregard appears to be related to a delayed or deficient development of cognitive processes involved in upper limb motor control. Unexpectedly, several results presented in the current dissertation suggest that the delay of upper limb movement development might not be restricted to the affected upper limb, but seems more generic with respect to higher order cognitive control of manual ability, therefore affecting both hands. Even though this latter hypothesis also needs further validation, cumulative findings suggest that training aimed at reducing developmental disregard should mainly focus on bimanual training. Additionally, early intervention programs are advised to potentially prevent this observed developmental delay as well as a potential learned suppression of movements. Future studies should focus on the effects of the suggested interventions, preferably including large sample sizes that are followed longitudinally. Furthermore, the suggested higher order “bimanual” involvement underlying developmental disregard and the comparison between developmental disregard and post stroke neglect need further confirmation.



# APPENDIX

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References

List of Abbreviations

English summary

Nederlandse samenvatting

Deutsche Zusammenfassung

List of Publications & Presentations

Acknowledgements

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## LIST OF ABBREVIATIONS

<b>ACC</b>	Anterior cingulate cortex
<b>AS</b>	Affected side
<b>AHA</b>	Assisting Hand Assessment
<b>BiT</b>	Bimanual intensive therapy/ training
<b>CCC<sub>max</sub></b>	Maximum cross-correlation coefficient
<b>(m)CIMT</b>	(modified) Constraint-induced movement therapy
<b>COPM</b>	Canadian Occupational Performance Measure
<b>CP</b>	Cerebral palsy
<b>CVA</b>	Cerebrovasculair accident
<b>EEG</b>	Electroencephalography
<b>EFs</b>	Executive functions
<b>EOG</b>	Electrooculography
<b>ERP</b>	Event-Related potential
<b>GLM</b>	Generalized linear model
<b>IES</b>	Inverse efficiency scores
<b>IQR</b>	Interquartile range
<b>LAS</b>	Less-affected side
<b>LAT</b>	Limb activation training
<b>MACS</b>	Manual Ability Classification System
<b>MMs</b>	Mirror movements
<b>MVC</b>	Maximal voluntary contraction
<b>N.s.</b>	Non-significant
<b>OBPP</b>	Obstetric brachial plexus palsy
<b>OTCPDD</b>	Observatory Test of Capacity, Performance, and Developmental Disregard
<b>RT</b>	Reaction time
<b>VOAA-DDD-R</b>	Video-Observation Aarts and Aarts module: Determine Developmental Disregard
<b>W&amp;T</b>	Woods and Teuber scale

## ENGLISH SUMMARY

Cerebral palsy (CP) is the most common cause of movement disability in childhood, with an incidence of 1.5 – 3 per 1000 live births within western countries. It is caused by injury to brain regions involved in movement processes. This injury occurs before, during, or shortly after birth, causing movement deficits that are present from birth on (or appear shortly after). Even though being not progressive, CP is associated with lifelong movement impairments. Mostly, these movement impairments are characterized by spasticity of the involved muscle groups.

Unilateral, or “one-sided” CP is among the most common subtypes, affecting 21-40% of the children with CP. These children experience substantially greater movement deficits on one side of their body, with their arm and hand frequently being most affected. In addition to these unilateral impairments, many of these children experience difficulties to include their affected side (AS) for typical bimanual activities (e.g. shoveling, as demonstrated by the boy on the cover of this dissertation). Even if their remaining AS capacity would allow them to assist the other “good” hand, many tasks are still performed one-handed, or are even completely avoided. This “non-use” of the remaining hand capacity in unilateral CP is referred to as **developmental disregard**.

The goal of the current dissertation was to understand this phenomenon of developmental disregard that is potentially causing reduced participation of children with unilateral CP in daily activities. To unravel different underlying mechanisms that are likely contributors to developmental disregard, we applied different behavioral and electrophysiological methods (i.e. EEG methods).

In the **prefix** of this dissertation we introduced two novel methods specifically developed to study potential underlying mechanisms of developmental disregard. In **chapter 2**, a novel tool is presented to assess so-called mirror movements. These mirror movements were earlier suggested to possibly cause developmental disregard. In **chapter 3**, an Event-Related Potential (ERP) protocol is reported. This protocol was developed to study cognitive processes involved in voluntary hand movements possibly affected in developmental disregard. Both methods were applied in **part 1** and **2** of this dissertation to answer related research question.

**Part 1** of the current dissertation focuses on developmental disregard as a learned or “conditioned” phenomenon. This conditioning approach suggests that developmental disregard develops due to negative (unsuccessful use of AS) and simultaneous positive (successful use of the other hand) reinforcement processes.

**Chapter 4** presents the results of a study comparing therapy effects between two groups of pediatric patients: children with unilateral CP and children with

obstetric brachial plexus palsy (OBPP). As opposed to children with unilateral CP, children with OBPP do not have a brain injury. However, the actual hand capacity deficits are comparable to those in unilateral CP (caused by injury to peripheral nerves). It was hypothesized that if developmental disregard can be fully explained by a learned suppression of movement, then symptoms of developmental disregard should be comparable between both patient groups. The results indicate that a therapy program aiming at overcoming developmental disregard (a so-called mCIMT-BiT program) only seems to effectively help overcoming developmental disregard in children with OBPP, but not in children with unilateral CP. This suggests that a learned suppression of movement may not sufficiently explain the symptoms of developmental disregard in children with unilateral CP.

Within this operant conditioning framework, so-called mirror movements have been hypothesized to play a central role. These are involuntary movements that mirror voluntary movements of the opposite side of the body. The involuntary movements of one hand while voluntarily moving the other hand is frequently observed in unilateral CP. It was hypothesized that due to these involuntary movements children learn to rather not include the AS for bimanual actions. This is, as this hand would be of no additional value when simply mirroring the movements of the other hand, or even worse, would cause a loss of control of the “good” hand, when actively moving the AS. In **chapter 5** we empirically tested the hypothesis that children with developmental disregard show enhanced mirror movements (using the method introduced in chapter 2). The results indicate that mirror movements are not related to developmental disregard. This gives an initial indication that next to the suggested behavioral reinforcement processes, additional mechanisms may underlie developmental disregard in unilateral CP.

Next to the framework focussing on behavioral reinforcement processes, another framework to explain developmental disregard focuses on potential underlying cognitive mechanisms. **Part 2** of the dissertation reflects on developmental disregard as a potential phenomenon of impaired information processing mechanisms. To study this, we applied Electro-encephalography (EEG) measurements to directly examine cognitive mechanisms related to voluntary hand movements.

In **chapter 6**, we focused on a neurodevelopmental perspective to explain developmental disregard. We studied if children with developmental disregard might experience a delayed or deficient development of neural circuits typically involved in motor control. This was done by monitoring the so-called “EEG mu-rhythm” during voluntary hand movements. It was found that while a typical mu-pattern was observed in children with unilateral CP but without developmental

disregard, this was not the case for children with developmental disregard. These findings indicate that developmental disregard might be best explained by a lack of preparedness or readiness to perform a new motor task, related to a deficient or delayed development of underlying neural circuits. Unexpectedly, this lack of preparedness was observed for both the hands, indicating a certain “bimanual” involvement.

In **chapter 7** it is studied if children with developmental disregard need enhanced cognitive effort when moving their AS during bimanual tasks. To study this, an ERP protocol was used based on the protocol introduced in chapter 3. It was indeed found that children with developmental disregard, compared to children with unilateral CP but without developmental disregard, experience enhanced cognitive effort when including their AS for bimanual tasks. This could however not be explained by a general increased cognitive effort when simply moving the AS, as there were no differences between groups when children were performing a unimanual task with their AS.

As a direct follow-up (again using an ERP protocol based on chapter 3), **chapter 8** focuses on the question if the observed increased cognitive effort may be best explained by a delayed movement development. Next to replicating the finding of an enhanced cognitive effort during bimanual tasks, this effect was now also shown to diminish with age. These results indeed strongly suggest developmental delay processes to underlie developmental disregard. In line with the unexpected “bimanual” findings of chapter 6, it was found that when enhancing the task difficulty, the enhanced cognitive effort generalizes to movements of both the hands.

In **chapter 8** additional differences between children with and without developmental disregard were found when examining their ERPs. These findings indicate that children with developmental disregard experience difficulties related to spatial attention processes. It was proposed that these difficulties might be comparable to those observed in post-stroke neglect patients. Following this hypothesis, attention might never automatically be directed to the affected upper limb, possibly causing the observed non-use in developmental disregard.

To conclude, the results presented in the current dissertation reveal that developmental disregard in children with unilateral CP appears to be related to a developmental delay of motor control, especially affecting bimanual performance. Interventions aiming at reducing developmental disregard should therefore focus on bimanual practice. The developmental delay was suggested to be explained by a lack of use of the AS during sensitive developmental periods of early childhood. Early intervention programs might therefore furthermore be of special interest to potentially prevent this developmental delay as well as target a potential learned suppression of movement. Future studies should focus

on the potential effects of these interventions. Furthermore, the hypotheses of a potential “bimanual” involvement underlying developmental disregard, or rather a higher order motor disability affecting cognitive processes of both hands’ movements need further investigation and validation. Also, the comparison between developmental disregard and post stroke neglect should be focused on in future research.

## NEDERLANDSE SAMENVATTING

Cerebrale Parese (CP) is de meest voorkomende oorzaak van lichamelijke beperking bij kinderen. In Westerse landen heeft CP een incidentie van 1.5 – 3 per 1000 levend geboren. De lichamelijke beperkingen worden veroorzaakt door een letsel aan delen van de hersenen die betrokken zijn bij bewegingsprocessen. Dit letsel ontstaat voor, tijdens, of vlak na de geboorte. Dit veroorzaakt beperkingen die vanaf de geboorte (of kort erna) aanwezig zijn. Hoewel deze bewegingsbeperkingen niet progressief zijn, gaat CP gepaard met levenslange beperkingen. Meestal worden deze bewegingsbeperkingen gekarakteriseerd door een spasticiteit van de betrokken spieren.

Unilaterale, of eenzijdige CP is één van de meest voorkomende vormen en komt voor bij 21-40% van de kinderen met CP. Deze kinderen ervaren substantieel meer bewegingsbeperkingen aan één kant van hun lichaam, waarbij hun hand en arm meestal het meest aangedaan zijn. Naast deze eenzijdige beperkingen, laten veel van deze kinderen problemen zien als ze hun aangedane hand in zetten voor tweehandige activiteiten (bijv. scheppen, zoals gedemonstreerd door het jongetje op de voorkant van dit proefschrift). Ook als de bewegingscapaciteit van hun aangedane hand het niet verhindert om hun andere, “goede” hand te assisteren, worden er veel taken alsnog eenhandig uitgevoerd, of wordt de activiteit zelfs compleet vermeden. Dit “niet-gebruiken” van de aanwezige hand capaciteit bij kinderen met unilaterale CP wordt *developmental disregard* genoemd.

Het doel van dit proefschrift was om het fenomeen van *developmental disregard* beter te begrijpen, omdat het kan leiden tot een verminderde participatie van kinderen met unilaterale CP tijdens allerlei dagelijkse activiteiten. Om verschillende onderliggende factoren te bestuderen die mogelijk betrokken zijn bij **developmental disregard**, hebben wij verschillende gedrags- en elektrofysiologische (i.e. EEG) methoden toegepast.

Aan het begin van de proefschrift (**prefix**) worden twee nieuwe methoden geïntroduceerd die specifiek zijn ontwikkeld om mogelijke onderliggende factoren van *developmental disregard* te bestuderen. In **hoofdstuk 2** wordt een meetinstrument geïntroduceerd om zogenoemde spiegelbewegingen te meten. Eerder onderzoek heeft gesteld dat duidelijk aanwezige spiegelbewegingen mogelijk leiden tot *developmental disregard*. In **hoofdstuk 3** wordt een Event-Related Potential (ERP) protocol geïntroduceerd. Dit protocol is ontwikkeld om cognitieve processen van willekeurige handbewegingen in kaart te kunnen brengen, die mogelijk aangedaan zijn bij kinderen met *developmental disregard*.

**Deel 1** van het huidige proefschrift richt zich op *developmental disregard* als een aangeleerd of “geconditioneerd” fenomeen. Deze benadering suggereert dat kinderen *developmental disregard* ontwikkelen door negatieve (mislukt

gebruik van de aangedane hand) en gelijktijdige positieve (succesvol gebruik van de andere hand) versterkingsprocessen.

In **hoofdstuk 4** wordt een studie gerapporteerd waarin therapie-effecten vergeleken worden tussen twee patiëntengroepen: kinderen met unilaterale CP en kinderen met obstetrische plexus brachialis parese (OPBP). In tegenstelling tot kinderen met een unilaterale CP, hebben kinderen met OPBP geen hersenletsel. Hun eenzijdige verminderde handcapaciteit (veroorzaakt door een letsel aan perifere zenuwen) is echter vergelijkbaar met die van kinderen met een unilaterale CP. De hypothese was dat als developmental disregard volledig verklaard kan worden door aangeleerde processen, de symptomen van developmental disregard vergelijkbaar zouden moeten zijn tussen beide patiëntengroepen. De studieresultaten laten zien dat een therapieprogramma dat als doel heeft developmental disregard te verminderen (een zogenoemde mCIMT-BiT programma) alleen bij kinderen met OPBP tot een overwinning van developmental disregard leidt, maar niet bij kinderen met unilaterale CP. Dit suggereert dat developmental disregard bij kinderen met unilaterale CP niet volledig verklaard kan worden door aangeleerde processen.

Er is eerder gesuggereerd dat ook zogenoemde spiegelbewegingen een centrale rol spelen bij de bovengenoemde conditioneringsprocessen. Spiegelbewegingen zijn onwillekeurige bewegingen die de willekeurige bewegingen van het tegenoverliggende lichaamsdeel spiegelen. Het onwillekeurig meebewegen van een hand tijdens het willekeurig bewegen van de andere hand wordt vaak geobserveerd bij kinderen met unilaterale CP. Er werd eerder gesteld dat op grond van dit onwillekeurig (en ongecontroleerde) meebewegen deze kinderen leren om hun aangedane hand liever niet meer te gebruiken voor tweehandige activiteiten. De aangedane hand zou namelijk geen extra hulp kunnen bieden als hij simpelweg meebeweegt, en erger nog, als de aangedane hand willekeurig wordt bewogen, zou dit zelfs leiden tot een controleverlies van de andere, “goede” hand. In **hoofdstuk 5** hebben wij de hypothese getoetst dat kinderen met developmental disregard meer spiegelbewegingen laten zien in vergelijking met kinderen met unilaterale CP maar zonder developmental disregard (door gebruik te maken van de methoden geïntroduceerd in hoofdstuk 2). De resultaten laten zien dat spiegelbewegingen niet samenhangen met developmental disregard. In combinatie met de bevindingen van hoofdstuk 4 geven deze resultaten een indicatie dat naast de veronderstelde gedragsmatige versterkingsprocessen andere factoren mogelijk betrokken zijn bij de ontwikkeling van developmental disregard bij unilaterale CP.

Naast de conditionerings-benadering die developmental disregard beschouwd als een aangeleerd fenomeen, focust een andere benadering op potentiële cognitieve factoren die mogelijk ten grondslag liggen aan

developmental disregard. **Deel 2** van dit proefschrift richt zich op mogelijk aangedane informatie verwerkingsprocessen onderliggend aan developmental disregard. Om deze cognitieve processen direct te kunnen bestuderen, hebben wij gebruik gemaakt van Elektro-encefalografie (EEG) metingen.

In **hoofdstuk 6** hebben wij de mogelijke oorzaak van developmental disregard vanuit een neurologisch ontwikkelingsperspectief benaderd. Wij hebben onderzocht of kinderen met developmental disregard mogelijk een vertraagde of afwijkende ontwikkeling van de neurale circuits laten zien die verantwoordelijk zijn voor de cognitieve controle van de bewegingen van hun aangedane hand. Dit hebben wij gedaan door het zogenoemde “EEG mu-ritme” tijdens willekeurige handbewegingen te bestuderen. De resultaten laten zien dat kinderen met unilaterale CP zonder developmental disregard een typisch mu-patroon vertonen. Dit was echter niet het geval bij kinderen met developmental disregard. Deze resultaten suggereren dat developmental disregard wellicht verklaard kan worden door een vertraagde of afwijkende ontwikkeling van onderliggende neurale circuits die normaal betrokken zijn bij de cognitieve processen van bewegingsvoorbereidingen. Hierdoor staan deze kinderen nooit echt paraat voor het uitvoeren van een nieuwe beweging. In tegenstelling tot de hypothese is dit gevonden voor bewegingen van beide handen, de aangedane, maar ook de andere hand. Dit suggereert dat er bij kinderen met developmental disregard mogelijk ook sprake is van een verminderde capaciteit van hun “goede” hand.

Naast de theorie van een vertraagde of afwijkende ontwikkeling van de neurale circuits is er eerder gesteld dat developmental disregard mogelijk samenhangt met het feit dat tweehandige activiteiten (nog) niet geautomatiseerd zijn. Dit zou leiden tot een verhoogde cognitieve inspanning tijdens het bewegen van de aangedane hand bij tweehandige taken. In **hoofdstuk 7** is deze hypothese getoetst. Om dit te onderzoeken werd een ERP protocol gebruikt, gebaseerd op het protocol geïntroduceerd in hoofdstuk 3. Er werd gevonden dat kinderen met developmental disregard inderdaad een verhoogde cognitieve inspanning laten zien wanneer zij hun aangedane hand inzetten voor tweehandige taken, vergeleken met kinderen met unilaterale CP maar zonder developmental disregard. Dit was echter niet te verklaren door een algemeen verhoogd cognitieve inspanning voor bewegingen met de aangedane hand, omdat er geen verschillen gevonden werden tussen de groepen als de kinderen alleen hun aangedane hand moesten bewegen.

Als een vervolg op deze studie (wederom door gebruik te maken van een ERP protocol gebaseerd op hoofdstuk 3) richt **hoofdstuk 8** zich op de vraag of de geconstateerde verhoogde cognitieve inspanning wellicht het beste verklaard kan worden door een vertraagde bewegingsontwikkeling. Naast de replicatie van

de bevindingen van de verhoogde cognitieve inspanning tijdens tweehandige taken, werd in deze studie verder gevonden dat dit beschreven effect minder werd wanneer kinderen ouder werden. Deze resultaten geven een duidelijke aanwijzing dat ontwikkelingsaspecten een rol spelen bij developmental disregard. In overeenstemming met de onverwachte resultaten gerapporteerd in hoofdstuk 6 werd er verder gevonden dat er bij deze complexere tweehandige taak (vergeleken met de wat simpelere taak gebruikt in hoofdstuk 6), de bewegingen van alle twee de handen samengaat met een verhoogde cognitieve inspanning. Dit suggereert weer dat mogelijk ook de bewegingen van de “goede” hand beïnvloed worden door de vertraagde bewegingsontwikkeling.

In **hoofdstuk 8** zijn er bij het bestuderen van de ERP componenten nog andere verschillen gevonden tussen kinderen met en zonder developmental disregard. Deze bevinding geeft een aanwijzing dat kinderen met developmental disregard moeilijkheden ervaren met betrekking tot ruimtelijke aandachtsprocessen. Er werd gesuggereerd dat deze moeilijkheden mogelijk vergelijkbaar zijn met de moeilijkheden die patiënten met een zogenoemde “neglect” ervaren, een stoornis van geautomatiseerde aandachtsprocessen die vaak optreedt na een hersenbloeding. Uitgaande van deze hypothese wordt de aandacht van kinderen met developmental disregard mogelijk nooit automatisch naar hun aangedane zijde gericht, wat het niet-gebruiken van de aangedane hand zou kunnen verklaren.

De resultaten van de huidige proefschrift laten zien dat developmental disregard bij kinderen met unilateraal CP waarschijnlijk samenhangt met een ontwikkelingsvertraging van processen die belangrijk zijn voor het controleren van bewegingen. De resultaten suggereren dat deze vertraging vooral invloed heeft op tweehandige activiteiten. Therapieën die als doel hebben om developmental disregard te verminderen, zouden zich dus vooral moeten richten op het oefenen van tweehandige activiteiten. Er wordt verondersteld dat de beschreven ontwikkelingsvertraging vooral wordt veroorzaakt door een bewegingsgebrek van de aangedane hand tijdens sensitieve perioden van de vroege ontwikkeling. Interventies die al vroeg worden toegepast (zogenoemde “early interventions”) zijn dus vooral relevant om deze vertraagde ontwikkeling tegen te gaan en mogelijk zelfs te voorkomen. Vervolgstudies zouden zich vooral moeten richten op potentiële positieve effecten van de gesuggereerde interventies om developmental disregard te verminderen. Verder moet getoetst worden of er bij kinderen met unilaterale CP en developmental disregard mogelijk sprake is van een hogere orde aandoening die de succesvolle beweging van alle twee de handen beïnvloed (ipv alleen de aangedane hand) en of developmental disregard inderdaad vergeleken kan worden met een “neglect” zoals het vaak optreedt na een hersenbloeding.

## DEUTSCHE ZUSAMMENFASSUNG

Cerebralparese (CP; oder auch Zerebralparese) ist die häufigste Ursache von körperlichen Behinderungen in der Kindheit. In westlichen Ländern sind 1,5 bis 3 von 1000 Neugeborenen hiervon betroffen. Die körperlichen Behinderungen werden durch eine Beschädigung an Teilen des Gehirns verursacht, die verantwortlich sind für Bewegungsabläufe. Diese Beschädigung entsteht vor, während oder kurz nach der Geburt, wodurch die hieraus folgenden Bewegungsstörungen bereits ab der Geburt (oder kurz danach) auftreten. Obwohl diese Bewegungsstörungen nicht progressiv sind, bestehen sie lebenslang und äußern sich meistens durch Spastizität der betroffenen Muskelgruppen.

Unilaterale, oder einseitige CP ist eine der häufigsten Formen der CP und betrifft 21-40% der Patienten. Kinder mit einer unilateralen CP leiden an einer substantiell stärkeren Bewegungsstörung auf einer Seite ihres Körpers, wobei die Hand und der Arm häufig am meisten beeinträchtigt sind. Neben dieser einseitigen Bewegungsstörung zeigen viele dieser Kinder deutliche Probleme bei der Ausführung von typischen „zweihändigen“ Tätigkeiten (z.B. beim Schaufeln, so, wie es bei dem Jungen auf dem Titelblatt dieser Dissertation demonstriert wird). Auch wenn die Bewegungskapazität der beeinträchtigten Hand es ermöglichen würde der anderen „guten“ Hand zu assistieren, werden viele dieser typischen zweihändigen Aktivitäten trotzdem einhändig ausgeführt, oder sogar komplett vermieden. Dieses „nicht Gebrauchen“ der noch vorhandenen Bewegungskapazität der beeinträchtigten Hand bei Kindern mit CP wird *developmental disregard* genannt (dies heißt soviel wie „Entwicklungsbezogene Vernachlässigung“).

Das Ziel dieser Dissertation war es dieses Phänomen von *developmental disregard* besser zu verstehen, vor Allem da diese Vernachlässigung der Hand häufig zu einer geringeren Teilnahme des Kindes am täglichen Leben führt. Um unterschiedliche Erklärungsmodelle von **developmental disregard** untersuchen zu können, haben wir verschiedene Verhaltensstudien wie auch elektrophysiologische (i.e. EEG) Messungen durchgeführt.

Zu Beginn dieser Dissertation (**Präfix**) werden zwei neue Methoden vorgestellt, die speziell entwickelt wurden um Faktoren zu untersuchen, die möglicherweise bei *developmental disregard* eine Rolle spielen. In **Kapitel 2** wird ein Messinstrument vorgestellt, das entwickelt wurde um sogenannte Spiegelbewegungen zu messen. Frühere Studien haben die Hypothese aufgestellt, dass deutliche Spiegelbewegungen möglicherweise *developmental disregard* verursachen. In **Kapitel 3** stellen wir ein Messprotokoll vor, wobei Event-Related Potentials (ERPs) während Handbewegungen gemessen werden. Dieses Protokoll wurde entwickelt um kognitive Prozesse von zielgerichteten Handbewegungen

messen zu können, die möglicherweise bei Kindern mit developmental disregard betroffen sind.

**Teil 1** von dieser Dissertation beschäftigt sich mit dem Erklärungsmodell, dass developmental disregard ein erlerntes oder „konditioniertes“ Phänomen ist. Diese Herangehensweise suggeriert, dass Kinder developmental disregard durch negative (erfolgloser Gebrauch der beeinträchtigten Hand) und gleichzeitige positive (erfolgreicher Gebrauch von der anderen Hand) Verstärkungsprozesse entwickeln.

In **Kapitel 4** werden Therapieeffekte zwischen zwei unterschiedlichen Patientengruppen verglichen: Kinder mit unilateraler CP und Kinder mit einer Plexus brachialis Verletzung. Im Gegensatz zu Kindern mit unilateraler CP, haben Kinder mit einer Plexus brachialis Verletzung keine Gehirnverletzung. Die einseitige Bewegungsstörung der Hand (die verursacht wurde durch eine Verletzung vom peripheren Plexus brachialis Nervenbündel) ist jedoch vergleichbar mit der von Kindern mit unilateraler CP. In dieser Studie haben wir die Hypothese aufgestellt, dass, falls developmental disregard vollständig erklärt werden kann durch Konditionierungsprozesse, die Symptome von developmental disregard vergleichbar sein müssten zwischen diesen beiden Patientengruppen. Die Resultate dieser Studie zeigen, dass ein gezieltes Therapieprogramm gegen developmental disregard (ein sogenanntes mCIMT-BiT Program) nur bei Kindern mit einer Plexus brachialis Verletzung zu einer Überwindung von developmental disregard führt, jedoch nicht bei Kindern mit unilateraler CP. Diese Resultate suggerieren, dass developmental disregard bei Kindern mit unilateraler CP nicht vollständig erklärt werden können durch Konditionierungsprozesse.

Frühere Studien haben die Hypothese aufgestellt, dass auch sogenannte Spiegelbewegungen eine zentrale Rolle spielen bei den hier oben beschriebenen Konditionierungsprozessen. Spiegelbewegungen sind unfreiwillige Bewegungen, die freiwillige Bewegungen von der gegenüberliegenden Körperhälfte spiegeln. Das unfreiwillige „Mit-bewegen“ von einer Hand ist ein häufiges Phänomen bei Kindern mit unilateraler CP. In früheren Studien wurde suggeriert, dass auf Grund dieses unfreiwilligen (und unkontrollierten) Mit-bewegens, Kinder lernen ihre beeinträchtigte Hand nicht mehr für typische zweihändige Aktivitäten zu gebrauchen. Die beeinträchtigte Hand würde nämlich keine Hilfe darstellen wenn sie einfach nur mit der anderen Hand mitbewegt, und schlimmer noch, bei zielgerichteten Bewegungen der beeinträchtigten Hand, würden die Kinder sogar die Kontrolle über Ihre „gute“ Hand verlieren. In **Kapitel 5** haben wir die Hypothese getestet, ob Kinder mit developmental disregard mehr Spiegelbewegungen haben als Kinder mit unilateraler CP aber ohne developmental disregard (durch Gebrauch des Messinstruments von Kapitel 2). Die Resultate dieser Studie zeigen, dass Spiegelbewegungen nicht mit

developmental disregard zusammenhängen. In Kombination mit den Resultaten von Kapitel 4, gibt dies Grund zur Annahme, dass neben der beschriebenen positiven und negativen Konditionierungsprozessen weitere Faktoren bei der Entwicklung von developmental disregard bei Kindern mit unilateraler CP eine Rolle spielen.

Neben dem beschriebenen Erklärungsmodell der Konditionierungsprozesse, das developmental disregard als ein erlerntes Phänomen sieht, fokussiert sich ein anderes Erklärungsmodell auf potentielle kognitive Faktoren die möglicherweise den Grundstein für die Entwicklung von developmental disregard legen. **Teil 2** dieser Dissertation beschäftigt sich mit potentiellen beeinträchtigten Informationsverarbeitungsprozessen die developmental disregard möglicherweise zugrunde liegen. Um diese kognitiven Prozesse direkt untersuchen zu können, haben wir Elektroenzephalographie (EEG) Messungen durchgeführt.

In **Kapitel 6** haben wir uns der potentiellen Ursache von developmental disregard aus einer neulogischen Entwicklungsperspektive genährt. Wir haben hierbei untersucht, ob Kinder mit developmental disregard möglicherweise eine verspätete oder abweichende Entwicklung von neuronalen Kreisläufen vorweisen, die verantwortlich sind für die kognitive Steuerung von Bewegungen der beeinträchtigten Hand. Dies haben wir mit sogenannte „EEG Mu-Rhythmus“ Messungen während zielgerichteter Handbewegungen getan. Die Resultate dieser Studie zeigen, dass Kinder mit unilateraler CP ohne developmental disregard ein typisches Muster des Mu- Rhythmus bei Bewegungen vorweisen. Dies war jedoch nicht der Fall bei Kindern mit developmental disregard. Diese Resultate suggerieren, dass developmental disregard möglicherweise durch eine verspätete oder abweichende Entwicklung von neuronalen Kreisläufen erklärt werden kann, die normalerweise aktiviert werden bei kognitiven Prozessen der Bewegungsvorbereitung. Hierdurch sind diese Kinder niemals wirklich bereit um eine neue Bewegung durchzuführen. Im Gegensatz zu unserer ursprünglichen Hypothese wurde dies jedoch für Bewegungen von beiden Händen gefunden, der beeinträchtigten, aber auch der anderen, „guten“ Hand. Dies suggeriert, dass Kindern mit developmental disregard möglicherweise auch eine verringerte Kapazität der nicht betroffenen Hand vorweisen.

Neben der Theorie von einer verspäteten oder abweichenden Entwicklung neuronaler Kreisläufe, wurde schon früher die Hypothese aufgestellt, dass developmental disregard möglicherweise mit der Tatsache zusammenhängt, dass zweihändige Aktivitäten (noch) nicht automatisiert sind. Dies würde eine erhöhte kognitive Anstrengung verursachen sobald die beeinträchtigte Hand für zweihändige Aktivitäten eingesetzt wird. In **Kapitel 7** wurde diese Hypothese getestet. Hierfür wurde ein ERP Protokoll angewandt das auf dem Protokoll

von Kapitel 3 beruht. Es wurde gefunden, dass Kinder mit developmental disregard in der Tat eine erhöhte kognitive Anstrengung vorweisen, wenn sie ihre beeinträchtigte Hand während zweihändiger Aktivitäten einsetzen. Diese Resultate konnten jedoch nicht durch eine allgemeine erhöhte kognitive Anstrengung für Bewegungen mit der beeinträchtigten Hand erklärt werden, da keine Unterschiede zwischen den Gruppen Kindern gefunden wurden als sie lediglich ihre nicht betroffene Hand bewegen mussten.

Aufbauend auf diese Studie (wiederum beruhend auf das ERP Protokoll von Kapitel 3), hat die Studie, beschrieben in **Kapitel 8**, sich mit der Frage beschäftigt, ob die festgestellte erhöhte kognitive Anstrengung möglicherweise am Besten durch eine verspätete Bewegungsentwicklung dieser Kinder erklärt werden kann. Neben der Replikation der Resultate einer erhöhten kognitiven Anstrengung während zweihändigen Bewegungen, wurde in dieser Studie auch gefunden, dass dieser Effekt weniger wird je älter die Kinder werden. Diese Resultate suggerieren stark, dass Entwicklungsaspekte bei developmental disregard eine Rolle spielen. Im Einklang mit den unerwarteten Resultaten die in Kapitel 6 beschrieben werden, wurde nun wiederholt gefunden, dass bei diesen komplexeren zweihändigen Aktivitäten (verglichen mit der Bewegungsaktivität von Kapitel 7), die Bewegungen von beiden Händen mit einer erhöhten kognitiven Anstrengung zusammenhängt. Dies suggeriert zum wiederholten Male, dass möglicherweise auch Bewegungsprozesse der nicht betroffenen Hand durch die verspätetete Bewegungsentwicklung beeinträchtigt sind.

In **Kapitel 8** haben wir beim Inspizieren der ERP Komponenten noch einen weiteren Unterschied zwischen Kindern mit und ohne developmental disregard festgestellt. Dieser Befund suggeriert, dass Kinder mit developmental disregard Schwierigkeiten mit räumlichen Aufmerksamkeitsprozessen haben. Diese Schwierigkeiten sind möglicherweise vergleichbar mit denen von Patienten mit einem sogenannten Neglect, einem Störungsbild von automatisierten Aufmerksamkeitsprozessen, dass häufig nach einem Schlaganfall auftritt. Von dieser Hypothese ausgehend, würde die Aufmerksamkeit von Kindern mit developmental disregard nie automatisch zu deren beeinträchtigten Seite gelenkt werden, wodurch das „Nicht-gebrauchen“ dieser Hand erklärt werden könnte.

Die kumulativen Resultate dieser Dissertation zeigen, dass developmental disregard bei Kindern mit unilateraler CP wahrscheinlich mit einem Entwicklungsverzug von Prozessen zusammenhängt, die eine wichtige Rolle bei der Bewegungskontrolle spielen. Des Weiteren zeigen die Resultate, dass dieser Verzug vor Allem zweihändige Aktivitäten beeinflusst. Therapien, die als Ziel haben developmental disregard zu verringern, sollten sich daher vor Allem auf ein Training von zweihändigen Aktivitäten konzentrieren. Wir gehen davon aus, dass die beschriebenen Entwicklungsverspätungen vor Allem durch

einen Bewegungsmangel während sensibler Perioden der frühen Entwicklung verursacht werden. Therapeutische Interventionen die schon früh angewandt werden (sogenannte „early interventions“) scheinen daher besonders relevant zu sein um dieser Entwicklungsverspätung entgegenzuwirken oder diese sogar zu vermeiden. Weitere Studien sollten sich insbesondere mit der Thematik der potentiellen Effekte dieser Interventionsmöglichkeiten auf developmental disregard beschäftigen. Des Weiteren sollte untersucht werden, ob bei Kindern mit developmental disregard möglicherweise Sprache ist von einer höher geordneten kognitiven Beeinträchtigung, welche die erfolgreiche Bewegungen beider Hände beeinflusst (anstatt nur der beeinträchtigten Hand), wie auch ob developmental disregard in der Tat verglichen werden kann mit einem Neglect, der häufig nach einem Schlaganfall auftritt.

## LIST OF PUBLICATIONS & PRESENTATIONS

### Publications

- Zielinski, I.M.**, Jongsma, M.L.A., Baas, C.M., Aarts, P.B.M., & Steenbergen, B. (2014). Unravelling developmental disregard in children with unilateral cerebral palsy by measuring event related potentials during a simple and complex task. *BMC Neurol*, *14*(6). doi: 10.1186/1471-2377-14-6.
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- Zielinski, I.M.**, Steenbergen, B., Baas, C.M., Aarts, P.B.M., & Jongsma, M.L.A. (2016). Event-related potentials during target-response tasks to study cognitive processes of upper limb use in children with unilateral Cerebral Palsy. *J Vis Exp* (107), e53420. doi: 10.3791/53420.
- Rudisch, J., Butler, J., Izadi, H., **Zielinski, I.M.**, Aarts, P., Birltes, D., & Green, D. (2016). Kinematic Parameters of Hand Movement during a Disparate Bimanual Movement Task in Children with Unilateral Cerebral Palsy. *Hum Mov Sci*, *46*, 239-50. doi: 10.1016/j.humov.2016.01.010.
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- Zielinski, I.M.**, Van Delft, R., Voorman, J., Geurts, A.C.H., Steenbergen, B. & Aarts, P.B.M. The effects of modified constraint-induced movement therapy combined with intensive bimanual training (mCIMT-BiT) in children with obstetric brachial plexus palsy (re-submitted).
- Zielinski, I.M.**, Steenbergen, B., Schmidt, A., Klingels, K., Simon-Martinez, C., De Water, P., & Brian, H. A new quantitative and objective assessment for mirror movements in unilateral cerebral palsy: introduction of the Windmill-task and concurrent validity. *Arch Phys Med Rehabil* (under review).
- Zielinski, I.M.**, Steenbergen, B., Aarts, P.B.M., Green, D., & Jongsma, M.L.A. Developmental Disregard in unilateral Cerebral Palsy: no EEG mu-restoration following hand movements. *Adv Cogn Psychol* (submitted).
- Weinstein, M., Green, D., Rudisch, J., **Zielinski, I.M.**, Benthem-Munuz, M., Jongsma, M.L.A., McClelland, V.M., Steenbergen, B., Shiran, S., Ben Bashat, D., & Barker, G.J. Understanding the relationship between brain and upper limb function in children with unilateral motor impairments: A multimodal approach. *Eur J Paediatr Neurol* (submitted).

### Conference presentations

- Zielinski, I.M.**, Steenbergen, B. Baas C. M., Aarts P. B. M., Jongsma, M.L.A. (2013). Developmental Disregard in children with unilateral Cerebral Palsy: An Event-Related Potential study. Oral presentation: 11th Motor control and human skill conference, Melbourne, AUS.

- Zielinski, I.M.**, Jongsma, M.L.A., Steenbergen, B. (2013). Unravelling 'Developmental Disregard' in children with unilateral Cerebral Palsy - An EEG approach. Oral presentation: Paclab International colloquium, Leeds, UK.
- Zielinski, I.M.**, Steenbergen, B. Baas C. M., Aarts P. B. M., Jongsma, M.L.A. (2014). Developmental Disregard in children with unilateral Cerebral Palsy - A spatial attention deficit? Oral presentation: NEURONUS 2015 IBRO & IRUN Neuroscience Forum, Krakow, PL.
- Zielinski, I.M.**, Steenbergen, B. Baas C. M., Aarts P. B. M., Jongsma, M.L.A. (2014). Spatial attention deficits as possible explanation for developmental disregard in unilateral cerebral palsy. Oral presentation: 26<sup>th</sup> Annual EACD Meeting, Vienna, AUT.
- Zielinski, I.M.**, Jongsma, M.L.A., Rudisch, J., Green, D., Aarts, P., Steenbergen, B. (2015). Strategic use of mirror movements to control the affected hand in children with unilateral Cerebral Palsy. Oral presentation: 27<sup>th</sup> Annual EACD Meeting, Copenhagen, DK.
- Zielinski, I.M.** (2015). Unraveling Developmental Disregard in unilateral Cerebral Palsy by means of Electrophysiological and Behavioral measurements. Invited speaker: ETH Zürich, CH.
- Zielinski, I.M.**, Jongsma, M.L.A., Rudisch, J., Green, D., Aarts, P., Steenbergen, B. (2015). *Strategic use of Mirror Movements in unilateral Cerebral Palsy*. Poster presentation: Johanna KinderFonds, Arnhem, NL.
- Zielinski, I.M.**, Steenbergen, B., Aarts, P., Green, D., & Jongsma, M.L.A. (2016). Absence of movement related mu de-synchronization in children with unilateral Cerebral Palsy and Developmental Disregard. Oral presentation: AusACPDM, Adelaide, AUS.
- Zielinski, I.M.**, Steenbergen, B., Aarts, P., Green, D., & Jongsma, M.L.A. (2016). Absence of movement related mu de-synchronization in children with unilateral Cerebral Palsy and Developmental Disregard. Oral presentation: 28<sup>th</sup> Annual EACD Meeting, Stockholm, SE.
- Zielinski, I.M.**, Steenbergen, B., Schmidt, A., Klingels, K., Simon-Martinez, C., De Water, P., & Brian, H. (2016). A new quantitative and objective assessment for mirror movements in unilateral cerebral palsy. Oral presentation: BSI day, Nijmegen, NL.
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- Zielinski, I.M.**, van Delft, R., Voorman, J.M., Geurts, A.C.H., Steenbergen, B., & Aarts, P.B.M. (2017). The effects of modified constraint-induced movement therapy combined with intensive bimanual training (mCIMT-BiT) in children with obstetric brachial plexus palsy: a retrospective data base study. Oral presentation: 29th Annual EACD Meeting, Amsterdam, NL.
- Zielinski, I.M.**, Steenbergen, B., Simon-Martinez, C., Klingels, K., Staudt, M., Adler, C., & Jaspers, E. (2017). Mirror movements or not: should we care? Mini symposium: 29<sup>th</sup> Annual EACD Meeting, Amsterdam, NL.

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And now (as it is late at night and I have to get up very early to get to my new job), I have to make this come to an end.

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Van harte bedankt iedereen,  
Vielen Dank ihr Lieben!**



## ABOUT THE AUTHOR

Ingar Marie Zielinski was born on the 18th of March in 1988 in Haltern, Germany. She attended secondary education (pre-university education) at the Gesamtschule Wulfen in Germany, where she received her diploma in 2007. After one year of “work and travel” in Australia, she went to study at the Radboud University in Nijmegen, the Netherlands, where she obtained her Bachelor’s degree in Psychology in 2011. Subsequently, she applied for and was accepted for the Master program of Neuropsychology at Utrecht University. During her masters, she performed her research internship at the Donders institute of the Radboud University Nijmegen. Here she studied test-retest effects on neuroplasticity of a physical therapy in healthy participants by means of EEG, to eventually apply this therapy to patients with a complex regional pain syndrome. This work was performed under the supervision of Dr. Tineke van Rijn (Radboud University, Nijmegen) and Dr. Chris Dijkerman (Utrecht University). During her masters, Ingar also did a clinical internship at the department of neuropsychology of the MediClin Fachklinik Rhein/Ruhr in Essen, Germany. Here she was responsible for the clinical assessment of a client’s needs, abilities, and behavior using a variety of methods. In 2012, she graduated cum laude for her Masters Degree ‘Neuropsychology’ at Utrecht University. Furthermore, she received the basic certificate of psychodiagnostics (“Basisaantekening Psychodiagnostiek”, NIP). In the same year, she started her PhD project at the Behavioural Science Institute (BSI) of the Radboud University Nijmegen, being supervised by Prof. Bert Steenbergen (Radboud University, Nijmegen), Dr. Marijtje Jongsma (Radboud University, Nijmegen), and Dr. Pauline Aarts (Sint Maartenskliniek, Nijmegen). The

main goal of her project was to unravel the phenomenon of developmental disregard in children with unilateral cerebral palsy. The results of her work are described in this dissertation, and most of the research has been published in international scientific journals. During her PhD project, she presented the results of her research at many national and international conferences and furthermore collaborated with many national and international institutes. In 2015 she also organized her own international symposium on “Promoting participation in children with unilateral cerebral palsy”. Next to her research activities, she taught several courses and gave lectures at the department of Psychology of the Radboud University. After finishing her PhD project in 2016, Ingar started working at the department of Child and Adolescent Psychiatry and Psychotherapy of the RWTH University hospital in Aachen, Germany.

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