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## Cognitive and motor processing in mild spastic cerebral palsy

Hakkarainen, Elina Kristiina

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2017

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Hakkarainen, E. K. (2017). *Cognitive and motor processing in mild spastic cerebral palsy: an event-related potential study*. University of Groningen.

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**ELINA HAKKARAINEN**

**Cognitive and motor processing  
in mild spastic cerebral palsy**  
An event-related potential study



university of  
 groningen

**Cognitive and motor processing  
 in mild spastic cerebral palsy**  
 An event-related potential study

**PhD Study**

to obtain the degree of PhD at the  
 University of Groningen  
 on the authority of the  
 Rector Magnificus Prof. E. Sterken  
 and in accordance with  
 the decision by the College of Deans.

This thesis will be defended in public on

Thursday 18 May 2017 at 12:45 hours.

by

**Elina Kristiina Hakkarainen**

born on 22 January 1976  
 in Jämsä, Finland

**Supervisors**

Prof. J.J. van der Meere  
Prof. J. Hietanen

**Co-supervisor**

Dr. S. Pirila

**Assessment committee**

Prof. K. Hartikainen  
Prof. T.P.S. Ahonen  
Prof. B. Steenbergen  
Prof. A.F. Bos

## Abstract

Cerebral palsy (CP) is a motor disorder often accompanied by cognitive deficits. The spastic subtype is the most common type (66 % - 82 %) of all cases, and abnormalities in attention, working memory, and executive functions are common clinical observations in this group. The present series of event-related potential (ERP) studies investigated cognitive and motor processing in youth with mild spastic cerebral palsy. Attention, working memory, and executive functions were evaluated in an oddball task and in a memory search task.

Study I showed that fundamental attention processes (orientation and evaluation of stimulus novelty) were intact in youth with mild spastic cerebral palsy when measured in a condition requiring no overt reactions.

In Study II, findings indicated an overall slowness and lower performance accuracy in youth with mild spastic cerebral palsy. An event-related potential analysis revealed that the stimulus evaluation processing, indexed by the parietal P300, was intact in the group of patients. Also event preparation and action planning, indexed by the frontal late contingent negative variation and the frontal P2, respectively, were intact in the group of patients. It was concluded that patients' motor slowness reflected poor motor execution processes.

In study III, findings indicated that error responses in youth with mild spastic cerebral palsy were associated with weak motor preparation, as indexed by the amplitude of the late contingent negative variation. However, patients were detecting their errors as indexed by the amplitude of the response-locked negativity and thus improved their performance in next trial. The results suggest that the consequence of error making on future performance is intact in the sample of youth with mild spastic cerebral palsy.

In study IV, it was found that error making was foreshadowed by a decrease in stimulus evaluation in the patient group and in the control group. Further, altered motor preparation for erroneous responses discovered in study III was perceived already in the correct trial directly preceding an error. It was concluded that although the patient group showed intact stimulus and response evaluation capacity, their weaker behavioral outcomes (slower response times and pronounced error rates) in comparison to controls reflected difficulties in motor processes, namely, disturbances in poor motor execution processes and fluctuations in motor presetting.

## SAMENVATTING

Cerebrale parese (CP) is een motorische handicap die dikwijls gepaard gaat met cognitieve tekorten. Dit geldt zeker ook voor het spastische subtype dat het meest voorkomt (66 % - 82 %). Bij hen wijzen klinische observaties in de richting van een zwakke aandachtsspanne, werkgeheugen en executieve functies. De uitgevoerde event –related potential (ERP) studies waren gericht om cognitive en motorische processen die ten grondslag liggen aan overte motorische reacties tijdens de uitvoering van een oddball en een geheugen zoektaak nader te onderzoeken.

De uitkomsten van de eerste studie geven aan dat fundamentele aandachtsprocessen (orientatie en evaluatie van stimulus eigenschappen (novelty) intact zijn wanneer geen overte reactie vereist is bij kinderen met milde CP. De uitkomsten van de tweede studie geven aan dat hun motorische reacties op stimuli traag zijn. Analyse van de bijbehorende event related potentials geeft aan dat het traag reageren veroorzaakt wordt door gebrekkige stimulus evaluatie, geïndiceerd middels de parietale P300. Dit geldt eveneens voor actie - preparative en planning, geïndiceerd middels de frontale late contingentie variatie en de frontale P2. De conclusie van de tweede studie is dat motorische traagheid bij de targetgroep samenhangt met zwakke motorische executieprogramma's.

De uitkomst van studie 3 is dat foute responses bij de doelgroep samenhangen met een zwakke motorische preparatie, zoals geïndiceerd door de amplitude van de late contingentie negatieve variatie (CNV). Echter, de doelgroep was wel in staat eigen fouten te herkennen, zoals geïndiceerd door de amplitude van de response-locked negativiteit. Bovendien verbeterde hun taakgedrag bij de volgende trial. De algemene conclusie van studie 3 is dat het effect van fouten maken op toekomstig gedrag meer dan normaal verloopt bij de doelgroep.

Studie 4 geeft aan dat voorafgaand aan een fout de stimulus evaluatieprocessen bij de norm alsook bij de doelgroep in kwaliteit verminderen. Het grote verschil tussen de norm en doelgroep was dat motorische preparatieprocessen bij de doelgroep verzwakken voordat de fout zich daadwerkelijk aandient. In feite is er sprake van opmerkelijke fluctuaties in motorpreparatie bij de doelgroep: deze is normaal direct na een gemaakte fout, daarna wordt de preparatie zwakker.

De algemene conclusie van de these is dat milde cerebrale parese samenhangt met gebrekkige motorische (voorbereidings en uitvoeringsprocessen. Deze uitkomst kan niemand verbazen. Wat nieuw is dat fundamentele cognitieve processen bij de doelgroep intact verlopen.

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## CHAPTER 1: INTRODUCTION

### 1.1 Cerebral palsy: a group of movement disorders

Although the history of cerebral palsy (CP) carries to the Ancient World, detailed medical descriptions were lacking until the 19<sup>th</sup> century (Panteliadis et al., 2013). William Little was the first to describe the disability in 1840s (Sankar et al., 2005). After him, Sigmund Freud united various infantile motor deficits of brain origin (Kavčič & Vodušek, 2005). In addition, he was the first to highlight also the prenatal origin of the symptoms, which were previously associated with difficult or protracted labor and neonatal asphyxia (Obladen, 2011). More recently, the description of CP is based on clinical symptoms. Today, the term describes a group of disorders of the development of movement and posture, causing activity limitations which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. Compromised movement and posture might be accompanied by disturbances of sensation, cognition, communication, perception, and/ or by a seizure disorders (Bax et al., 2005).

The incidence of CP is approximately 2 per 1000 live births, which makes it the most common motor impairment in children (Reddihough & Collins, 2003). In their systematic review and meta-analysis, Oskui et al. (2013) concluded that the overall prevalence of CP has remained constant in recent years despite increased survival of at-risk preterm infants.

### 1.2 Etiology

#### Multiple causes

Damages occurring during cerebral development can cause cerebral palsy by harming those parts of the brain that control movement and posture. The damage can be congenital or acquired, the latter being notably more infrequent. The neuropathological picture of brain injury depends on the gestational and neonatal age of the infant (Chai & Yin, 2014). Especially the period between the last



trimester of fetal development to the first post-natal months is a vulnerable phase due to rapid development of the brain (Fairhurst, 2012; Panigrahy et al., 2012).

The quality of the brain injury is associated with brain maturation phase when the injury takes place. Consequently, causes of cerebral palsy are often classified into prenatal, perinatal/ neonatal, and postnatal, according to the timing of the injuring event (Griffin et al., 2002), yet the cause may also remain unknown (Shevell et al., 2003). In the next part of the chapter, some major causes of cerebral palsy will be shortly discussed.

Seventy to eighty percent has a prenatal origin (Kriger, 2006), such as maternal infections during the first and second trimesters of pregnancy, vascular events, severe hypoglycaemia, untreated jaundice, and severe neonatal infections. But also problems occurring during labor and delivery can be a cause (McIntyre et al., 2012; Reddihough & Collins, 2003). Sometimes causes are postnatally acquired such as infections and injuries (Reddihough & Collins, 2003).

Periventricular leukomalacia (PVL) (cerebral white matter lesions) is typical in children born before about 34 weeks of gestation (Bax et al., 2006; Panigrahy et al., 2012) and in infants with low birth weight (Shang et al., 2015). In fact, PVL is the most common cause of cerebral palsy (Bax et al., 2006; Shevell et al., 2003). The white matter lesions can be cystic or diffuse by nature (Gibson & Clowry, 2003; Lee et al., 2011).

Intrapartum asphyxia is another common condition causing cerebral palsy. Estimations range from less than 3 to more than 50 %. The discrepancy in percentage is partially due to diverse definitions for both birth asphyxia and cerebral palsy (Ellenberg & Nelson, 2012). Asphyxia can lead to hypoxic-ischemic brain injury, when brain tissue is destroyed in basal-ganglia-thalamus region, subcortical white matter, or in cortex, causing uni- or bilateral lesions (de Vries & Groenendaal, 2010).

Intracranial and intraventricular hemorrhage (IVH), i.e. bleeding in the brain, is seen as a third cause, affecting circa 13 percent of the cases (Shevell et al., 2003). Prematurity is a significant risk for intraventricular hemorrhage (Panigrahy et al., 2012). The prevalence of intracranial hemorrhage in neonates born before the 30<sup>th</sup> week of gestation or with a birth weight less than 1500 grams varies between 20 and 25 % (Schmid et al., 2013). Bolisetty et al. (2014) studied IVH survivors in a cohort study of infants born between 23 and 28 weeks of gestation. Depending on the severity grade of the IVH, the prevalence of CP varied between 10 % and 30 %, whereas in the no-IVH group the prevalence was 6.5 %, illustrating that IVH is a massive risk factor.

Finally, brain structural malformations may also cause cerebral palsy as is estimated to be the case in 9 percent (Bax et al, 2006). Vascular anomalies cover about 10 percent of the cases (Shevell et al., 2003).

### **Risk factors**

Risk factors for cerebral palsy do not necessarily causally lead to the condition but may contribute to its formation. They can be present before and during pregnancy, during labor and birth, and/or shortly after birth (Reddihough & Collins, 2003). It is well-recognized that prematurity and low birth weight belong to the most important risk factors (Sankar et al, 2005; Thorngren-Jerneck & Herbst, 2006). Also multiple pregnancies (associated with prematurity and low birth weight), birth defects and complications during birth are seen as risk factors (Bax et al, 2006; Reddihough & Collins, 2003).

In a systematic review by McIntyre et al. (2012), risk factors for term-born infants were charted. Placental abnormalities, major and minor birth defects, low birth weight, meconium aspiration, instrumental/ emergency Ceasarean delivery, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia, and neonatal infections were considered as statistically significant risk factors for infants born at term.

### **1.3 Subtypes of motor disorder**

Cerebral palsy (CP) is an umbrella term varying from mild to severe impairments. The lesions behind the clinical symptoms vary and are roughly associated with the affected brain areas. There are two major subtypes of CP: spastic and non-spastic (Himpens et al., 2008). The first, the most common one, has a prevalence varying from 65 % to 98 % (Reid et al., 2011). Here, white matter lesions are typical (Bax et al., 2006; Bottcher, 2010; Krägeloh-Mann et al., 2007; Prasad et al. 2011). The type is highly predominant in preterm infants, with the bilateral form more common than the unilateral form (Himpens et al., 2008). There are four spastic sub types. In monoplegia, only one of the lower extremities is affected. In diplegia, lower extremities are affected, commonly associated with white matter injuries (Reid et al., 2013). In hemiplegia, the right or the left side of the body is affected and stiffness is present especially in the upper limb. Here, focal vascular insults are a predominant finding (Bax et al, 2006; Reid et al., 2013). In quadriplegia, all four limbs are affected, and abnormal brain imaging findings are common (93 %), the grey matter injuries being the most frequent ones (Reid et al., 2013).

Non-spastic cerebral palsy is a more common subtype in term-born infants (Himpens et al., 2008). It is classified as ataxic or dyskinetic (Himpens et al., 2008). The proportion ataxic CP is around five percent (Reid et al., 2011; Shevell et al. 2009). In many cases (24-57 %), no abnormalities are reported using MRI (Reid et al., 2013). The dyskinetic form of CP is found in about four to seven percent (Reid et al., 2011; Shevell et al, 2009). Here, grey matter injuries are the most common (Reid et al., 2013).

As is clear from the above, CP has multiple causes. In addition, CP has also multiple outcomes, captured by the motor and cognitive classification, discussed in the next paragraphs.

### Classification by functional abilities

Gross Motor Functional Classification System (GMFCS) (Palisano et al, 1997) has 5-levels describing the gross motor function of children and youth on the basis of their self-initiated movement. Distinctions between the levels are based on functional abilities, the need for assistive technology, and to a much lesser extent, quality of movement. In addition to gross motor function limitations, also manual ability can be affected in children with cerebral palsy. The Manual Ability Classification System (MACS) (Eliasson et al., 2006) describes how these children use their hands to handle objects in daily activities. Also the MACS describes five levels based on children's self-initiated ability to handle objects and their need for assistance or adaptation to perform manual activities in everyday life (Table 1).

Table 1. Descriptions of the levels of the Gross Motor Functional Classification System (GMFCS) and the Manual Ability Classification System (MACS).

Level	GMFCS	MACS
I	Walks without limitations	Handles objects easily and successfully.
II	Walks with limitations	Handles most objects but with somewhat reduced quality and/or speed of achievement.
III	Walks using a hand-held mobility device	Handles objects with difficulty; needs help to prepare and/or modify activities
IV	Self-mobility with limitations; may use powered mobility	Handles a limited selection of easily managed objects in adapted situations.

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V	Transported in a manual wheelchair	Does not handle objects and has severely limited ability to perform even simple actions.
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MACS level and GMFCS level together enable a detailed analysis of the functional level of children with spastic cerebral palsy (Günel et al., 2009), and are important determinants for limitations in activities and restrictions in participation (Beckung & Hagberg, 2002; van Meeteren et al., 2010).

In a nation wide study by Sigurdardottir et al. (2008), 45 % of the Icelandic individuals with CP scored at Level I of the GMFCS, 32 % scored at Levels II or III, and 23 % Levels IV or V. GMFCS levels are associated with the severity of the brain lesions, as indexed by MRI. Reid et al. (2013) found normal imaging results in 17 % of cases with GMFCS level I or II, compared to a percentage of 7 to 8 percent in children functioning at level IV or V. In addition, milder cases were more frequently associated with focal vascular insults, whereas white matter injury was the most frequent finding at all GMFCS levels.

#### 1.4 Cognitive and communication deficits in cerebral palsy

Cognitive disorders are associated with cerebral palsy (Minciu, 2012). Intellectual impairment is one of the most common comorbidity (Krigerger et al., 2006; Shang et al., 2015). An IQ level below 70 has been reported in 40 % (Gabis et al., 2015; Sigurdardottir et al., 2008) to 60 % (Numata et al., 2012) of the cases.

An association between intellectual capacity and level of motor functioning has been reported, suggesting a linkage between the two domains (Smits et al., 2011). In the comprehensive study by Sigurdardottir et al. (2008), 19.4 % of the individuals with spastic hemiplegia had an IQ level below 70. In individuals with spastic diplegia and spastic quadriplegia, the percentages were 28.9 and 64.3, respectively.

In addition to intellectual disability, narrow range cognitive impairments are also part of the clinical picture. Communication impairments and dysarthria occur approximately in half of the children with cerebral palsy (Pirila et al., 2007; Zhang et al., 2015). In dysarthria, motor and

premotor cortex and descending corticospinal and corticobulbar pathways are affected, and it is characterized by slow speaking rate, monopitch and monoloudness (Clark et al., 2014).

Communication problems are often associated with IQ level below the norm (Legault et al., 2011; Parkes et al., 2010; Zhang et al., 2015), and with disturbed facial expression, body movements, gesture and speech (Pennington et al., 2006)

Visual processing deficits are especially pronounced in the spastic forms (Pueyo et al., 2003). For instance, visuoperceptual/visuospatial abilities are compromised in 60 % to 90 % of individuals with bilateral posterior lesions (Pueyo et al., 2009). More specifically, Sigurdardottir et al (2008) found that IQ scores tapping visual perceptual reasoning were significantly lower than verbal reasoning scores in children with bilateral lesions. This disharmonic cognitive profile is especially characteristic in children born preterm (Pagliano et al., 2007).

Sensory and tactile deficits are also very common (Minciu, 2012; Shang et al., 2015). For instance, 40 % of the individuals with spastic quadriplegic CP have hearing problems (Venkateswaran & Shevell, 2008). Also vision problems such as ametropia (79 %) and strabismus (45 %) are common (Lew et al., 2015) and vary with the gross motor function level classified by GMFCS (Ghasia et al., 2008). A retrospective systematic medical record study by Venkateswaran & Shevell (2008) showed visual impairment in 80 % of individuals with spastic quadriplegic CP.

Recently, executive function (EF) has been a target of vivid international research. EF deficits, defined as poor planning, organizing, response inhibition, have been reported in children and youth with cerebral palsy (Pirila et al., 2004; Pirila et al., 2011; Bottcher et al., 2009). The prevalence is 58 to 74 % in bilateral cerebral palsy (Pueyo et al., 2009), especially pronounced in preterm children with bilateral spastic CP (Pirila et al., 2011; White & Christ, 2005). EF deficits might be shown irrespectively of the lesion side, and might be noticed across many domains, such as attention control, cognitive flexibility, goal setting, and information processing, as is reviewed by Bodimeade et al. (2013).

Also, short-term memory deficits might be compromised (Pueyo et al., 2009; Toomela, 2012). More specifically, deficits in imagery and visuospatial abilities (Barca et al., 2012), declarative memory (Pueyo et al., 2009), prefrontally-mediated memory processes (White & Christ, 2005), and verbal memory (Handel et al., 2012) have been reported.

It is obvious that deficits in attention, executive functioning and working memory, as discussed above, may lead to learning difficulties at school-age. And indeed, about half of the children with CP have learning difficulties, as is reviewed by Straub and Obrzut (2009), such as arithmetic

and working memory problems (Jenks et al., 2007). In fact, executive functions and working memory scores at the second grade are predicting third grade arithmetic abilities (Jenks et al, 2009), whereas visual perceptual reasoning and working memory updating predict skills in verbal problem solving and reading (Jenks et al., 2012). Epilepsy occurs in about one half of the cases (Minciu, 2012; Shang et al., 2015; Krigger et al., 2006; Venkateswaran & Shevell, 2008), and might complicate cognitive functioning to a further extent.

Finally, cerebral palsy has a higher prevalence of psychiatric disorders (Goodman & Graham, 1996). This and the severity of the symptomatology are loading on family functioning (Pirila et al, 2010). However, there is some evidence that the earlier discussed comorbidities are determining the quality of life (QoL) to a higher extent in people with CP, compared to the severity of the CP symptomatology itself. For instance, Tessier et al. (2014) reported a strong association between comorbidity and psychosocial QoL, whereas motor symptom severity was not clearly connected with QoL. Parkes et al. (2011) showed that communication impairment, moderate to severe pain, and intellectual impairment were associated with stress in parents, when motor impairment per se was not. These finding justify to underline the importance of management of comorbidities in children with CP (Fairhurst, 2012).

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## CHAPTER 2: THE PRESENT STUDY

The neuromotor disability and communication problems in people with cerebral palsy challenge the use of standard neuropsychological tests as used in the clinic (Beaumont et al. 1996; Fennell & Dikel, 2001; Sabbadini et al., 2001). Put in other words: the handicaps may lead to an over- or under-evaluation of patient's true cognitive abilities (Sabbadini et al., 2001) since standard tests typically require oral, written or pointing answers that may exceed motor speech and verbal expressive – and comprehensive restrictions, seen in many children (Pirila et al, 2007). In their systematic review, Yin Foo et al. (2013) aimed to identify and examine intelligence assessments for children with CP. They concluded that standard assessment lacks (1) reliability data, (2) consensus regarding the validity data, and (3) population-specific norms. From this perspective, Yin Foo and colleagues direct the need for research to establish psychometrics for children with CP and for multiple options to appropriate assessment.

Thus, the availability of alternative assessment measures would provide valuable information about the learning capacity of children with CP. It may lead to positive consequences concerning their quality of life, and, maybe, to more specific cognitive rehabilitation planning and special training. Within this spirit, Byrne, Dywan, and Connolly (1995), Connolly, D'Arcy, Newman, and Kemps (2000), and Connolly and D'Arcy (2000) advocated to utilize event-related potential (ERP) methodology for a neuropsychological assessment of patient groups who might be difficult to evaluate by traditional methods. They have demonstrated in their pilots that ERPs can be used to reliably evaluate reading and speech comprehension abilities and EF capacity independent of behavioral and speech production impediments.

The main advantage in using the ERP methodology is that it offers the possibility to evaluate cognitive abilities apart from motor skills. Consequently, when an individual obtains scores in the lower range of the distribution, it may identify the source of the low score: is it caused by compromised motor system, cognitive deficits or both?

In addition, also the theoretical research on cognition in CP might improve when using ERPs. Now the research which has put forward the popular hypothesized executive function deficit might be inflated since it is mainly based on reaction time tests (see; Pirila et al., 2011; White & Christ 2005). Thus, again, what the CP research on cognition needs is a methodology that is apt to differentiate between cognitive and motor processes, i.e. the event related potential methodology explained in Chapter 2.

To date, there are not many ERP studies available investigating individuals with cerebral palsy, and none of them is focused on attention, working memory or executive functions. The studies focus on motor characteristics of CP. For instance, Van Elk et al. (2010) studied neural correlates of action planning in individuals with hemiparetic cerebral palsy. They found a strong reduction in the amplitude of the P2 component, associated with impaired action selection processes. The authors suggested that compromised anticipatory planning in cerebral palsy could be partly explained by their impaired action selection process. Zielinski et al. (2014) used the ERP methodology in children with unilateral cerebral palsy to test whether movement of the affected hand requires more cognitive load in comparison to the unaffected hand. They found increased N2b between 330 and 380 milliseconds after stimulus onset for movements conducted by the affected hand in children who did not use this hand with its full potential in everyday life.

Important as these ERP findings are, the mission of the present thesis is not to investigate characteristics of the motor impairment but to evaluate whether basic cognitive processes are compromised in individuals with CP. This thesis constitutes of four articles that focus on cognitive and motor processing in children and adolescents with mild spastic cerebral palsy. The first aim was to investigate whether allocation of attention is altered in children with cerebral palsy compared to a control group. (Study I). The second aim was to study stimulus evaluation time, event preparation, and motor action planning of patients with mild spastic cerebral palsy and a control group (Study II). The third study aimed to explore the brain activation state during error making in adolescent with mild spastic cerebral palsy and a control group while carrying out a stimulus recognition task (Study III). Lastly, the fourth study examined patterns of brain activity preceding errors in the patient and control group (Study IV). Processes and methodology are discussed below.

## **2.1 Orientation (Study 1).**

In the first study, we explored whether attention orientation was compromised in youth with mild spastic cerebral palsy in a condition where no motor effort was required. An oddball paradigm was obtained. In the oddball paradigm, a string of standard stimuli is presented together with lower probability deviant stimuli which differ from the standard stimuli in their physical and/or informational characteristics (Harker & Connolly, 2007; Duncan et al., 2009). The N2-P300 component is a crucial component in this paradigm. The paradigm is suitable for clinical groups with motor disturbances, because it does not require an overt response from the participant. By



comparing brain activation for frequently presented standard stimuli with that elicited by infrequent deviant stimuli, attention allocation (orientation) can be examined (Linden, 2005; De Pascalis et al., 2008; Polich & Comerchero, 2003; Strüber & Polich, 2002).

## **2.2 Motor and cognitive components of executive functions (Study 2).**

In Study II, we elaborated on the issue whether poor reaction time performance of individuals with spastic cerebral palsy obtained during executive functioning demands is associated with impaired information processing, motor processes, or both. Stimulus evaluation time, event preparation, and motor action planning was investigated. The stimulus-locked P300, P2, CNV components and reaction times for correct responses in two load conditions were analyzed.

### **2.2.1 Stimulus evaluation and decision making**

The positive P300 (or P3) occurring 300-900 ms after stimulus onset with a maximal distribution over midline scalp sites (Duncan et al., 2009) because it is independent of overt (motor) reaction. P300 is a sensitive measure of the neural activity related to attention allocation and memory processes (Polich et al., 2000), and stimulus evaluation time (De Pascalis et al., 2008; Polich, 2007). That is to say, the latency of the P3 component is sensitive to time pressure (shortens when time pressure increases) and attention allocation (lengthens when attention has to be divided) (Hohnsbein et al., 1995).

The amplitude of the P3 component is sensitive to stimulus probability and effort allocation (Duncan et al., 2009; Polich, 2007). Two phases of information processing can be detected in the P3 component, an earlier peaking P3a which is associated to automatic processes and a later peaking P3b is associated to controlled attention processing (Polich, 2007; Polich & Criado, 2006; Stige et al., 2007).

Since the P300b latency might be considered an index of stimulus evaluation and cognitive decision making, the mean reaction time minus the P300 latency is considered to index of motor preparation and execution.

### **2.2.2 Motor action planning and response preparation**

A positive P2 component with a frontocentral scalp distribution occurs ca. 200 ms after stimulus onset, and it has been shown to reflect motor action planning: the more pronounced the motor action planning, the higher is the P2 amplitude (van Elk et al., 2010).

On the psychophysiological level, motor preparation to anticipated event is indexed by a long lasting negative component called contingent negative variation (CNV). It is a negative component developing few hundred milliseconds before actual response. The typical CNV paradigm consists of a warning stimulus (S1) followed by the imperative stimulus (S2) few second later (Walter et al., 1964). Wild-Wall et al. (2007) showed increased frontal CNV amplitude for older participants (54-64 years) compared to the younger ones (18-25 years). The authors underline the role of the CNV as a neurophysiological indicator for effortful cognitive preparation. They consider CNV as a reflection of a mixture of sensory, cognitive and motor preparation, depending on the type of the task. Gómez et al. (2003) suggest that anterior cingulate cortex (ACC) together with supplementary motor area (SMA) start the motor action preparation process.

The P300 and CNV characteristics have been mainly studied when the stimulus has been correctly identified leading to a correct reaction, but ERPs can also be helpful in exploring cognitive processes when errors are made, discussed in the next section.

#### **2.4 Error processing: response evaluation and performance adjustment (study 3 and 4)**

On the psychophysiological level, errors are often foreshadowed by compromised attention and motor processing. That is, attention lapses may lead to erroneous performance, and they can be perceived in EEG already 20 seconds before an actual error occurs (O'Connell et al., 2009). Also a momentary reduction in target anticipation indicated by an attenuated CNV before an error has been demonstrated (O'Connell et al., 2009). As an index of attention lapses, diminished P3 amplitude before an error has been pointed out (O'Connell et al., 2009; Datta et al., 2007).

Another component involved in error making is the error preceding positivity (EPP). This is a response-locked positive component that peaks during the first 100 ms after the error-preceding response (Ridderinkhof et al., 2003). It has been interpreted in terms of a neural index of occasional deficiencies of the monitoring system prior to actual execution of an error (Allain et al., 2004; Hajcak et al., 2005; Ridderinkhof et al., 2003; Simons, 2010).

When responses are correct, a medial frontal negativity (correct response negativity, CRN) peaks shortly after response execution (Ridderinkhof et al., 2003; Simons, 2010; Vidal et al., 2000). When responses are incorrect, diminished CRN occurs after error making which is associated to response monitoring lapses and decreased executive control (Allain et al. 2004).

During the first hundred milliseconds after an erroneous motor response, a negative brain potential with a fronto-central scalp distribution occurs (Bernstein et al, 1995; Mathalon et al., 2003; Pourtois, 2011). This negative peak is called error-related negativity (ERN) and it is associated with

early, preconscious error detection (O'Connell et al., 2007; Dhar et al., 2011; Wessel, 2012) and subsequent compensatory processes to avoid future errors (Gehring et al., 1993; Maier et al., 2011). Based on his review of error processing studies, Wessel (2012) suggests that ERN is a feed-forward input signal into those systems that are related to more aware processing of errors. ERN has been shown also in children (Arbel & Donchin, 2011), and it has been studied in various clinical groups.

Once the error has been detected, the performance monitoring system seeks to restore the optimal performance level. On behavioral level, reaction times are getting longer to prevent future errors. This phenomenon is called post-error slowing and it is a well-established finding in error making literature (Allain et al., 2009; Eichele et al., 2010; Masaki et al., 2012; Spinelli et al., 2011).

In Study III, brain activation state during error making was evaluated. Response-locked negativities for correct and erroneous responses directly after (< 100 ms) the response were measured as indices of response evaluation efficacy. Central contingent negative variation was measured for correct and incorrect trials to test, whether motor preparation differs between the correct and incorrect trials. Reaction times for correct and incorrect responses and correct responses directly after an error were measured to find out, whether youth with cerebral palsy show compensatory mechanisms after error making to avoid future errors.

In Study IV, brain state before error making was investigated. The main question was whether errors of the patient group were preceded by attention lapses, by weak motor preparation, or both. Reaction times together with ERPs associated with motor preparation (frontal late CNV), attention (parietal P300), and response evaluation (parietal error-preceding positivity) were investigated in three subsequent correct trials preceding an error. The sequence of three successive correct trials was isolated from an original sequence of four correct trials. This was done to ensure that the E-3 trial was not preceded by an erroneous trial.

Reaction times tend to speed before error making (Allain et al., 2009; Eichele et al., 2010; Masaki et al., 2012), and faster reaction times for incorrect trials compared to correct trials have been reported (Allain et al., 2009; Bernstein et al., 1995; Masaki et al., 2012; Simons, 2010; ).

## 2.5 The discrete serial stage model of Saul Sternberg (1969)

In studies II to IV, the ERPs connected with the above-formulated phenomena were studied using the discrete serial stage model of Saul Sternberg (1969). According to this model, the performance implies a sequence of temporally distinct processing stages: stimulus encoding, memory retrieval, decision, and response preparation, and each stage has to be completed before proceeding to the next stage (Figure 1).

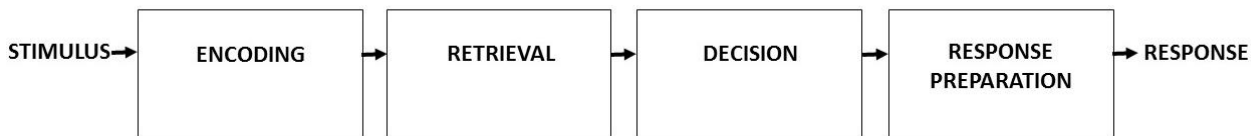


Figure 1. Discrete serial stage model of information processing (Sternberg, 1969).

In “Sternberg Memory Search Task” (Sternberg, 1966), a set of letters (memory set) is presented to be temporally memorized. After a short delay, a new set (display set) is presented, and the participant has to recall whether one letter (a positive trial) or no letter (a negative trial) of the memory set is present in the display set by pressing “yes” or “no” button. Memory load is manipulated by adding letters to the memory set. The task is probably the most used test in clinical, developmental, and psychophysiological research (Donkin & Nosofsky, 2012).

By using electroencephalography ERP methodology, each information processing stage in the Sternberg memory search task can be perceived in scalp-recorded brain activation during the task performance. Figure 2 shows the task characteristics.

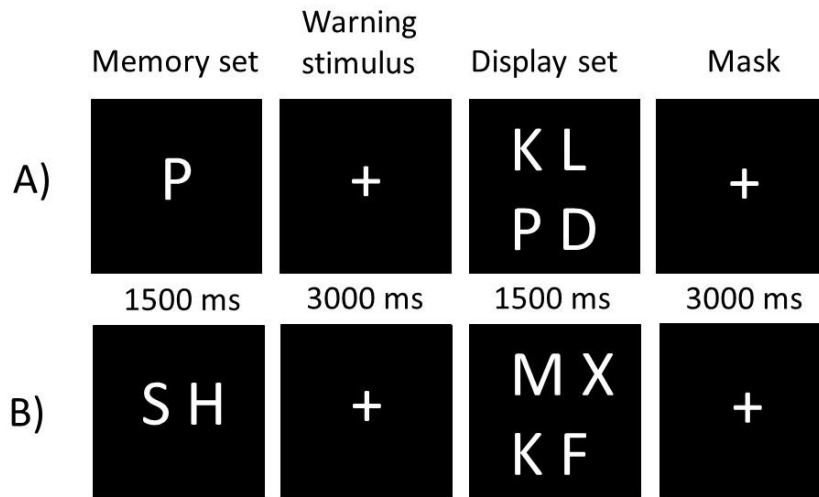


Figure 2. Time sequence of a positive trial in load condition 1 x 4 (A) and a negative trial in load condition 2 x 4 (B).

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## **CHAPTER 3: Visual attention study in youth with spastic cerebral palsy using the event-related potential method**

E. Hakkarainen<sup>1</sup>, S. Pirilä<sup>1,2</sup>, J. Kaartinen<sup>3</sup>, K. Eriksson<sup>2</sup>, J. J. van der Meere<sup>4</sup>

<sup>1</sup>Department of Psychology, University of Tampere, Tampere, Finland

<sup>2</sup>Department of Pediatrics, Tampere University Hospital, Tampere, Finland

<sup>3</sup>Department of Psychology, University of Jyväskylä, Jyväskylä, Finland

<sup>4</sup>Department of Clinical and Developmental Neuropsychology, University of Groningen, Groningen, The Netherlands

Journal of Child Neurology (2011), 26, 1525-1528

## **Abstract**

Youth with mild spastic cerebral palsy ( $n = 14$ ) and a peer control group were compared on an oddball paradigm. Here, visual stimuli were presented with low and high probability and participants were instructed to count in silence the number of rare stimuli. The infrequent stimulus typically elicits an enhanced frontal central N2 and a centroparietal P300 event-related brain potential, reflecting orientation and evaluation of stimulus novelty. No differences in latency and amplitude of the N2–P300 complex were found between the 2 groups, indicating that some fundamental attention processes are intact in youth with mild spastic cerebral palsy.

## **Introduction**

Cerebral palsy is a permanent, nonprogressive motor disorder with a prevalence rate of 2 per 1000 live births.<sup>1</sup> The disorder is often associated with other disturbances, such as poor attention. As reviewed,<sup>2</sup> youth with cerebral palsy have low scores on tests tapping disengagement of attention, redirection of attention, reduced attention requirements of postural control, and response inhibition. A recent study showed that half of the participating sample of youth with spastic cerebral palsy had attention problems in the clinical domain, especially those with diplegia compared with those with hemiplegia.<sup>3</sup> However, the attention studies carried out so far were limited to overt performance indices, reaction time latency, and error profile (errors of omission and commission). It is well recognized that overt performance indices reflect cognitive processes in combination with motor-related processes. Consequently, poor performance of youth with cerebral palsy on neuropsychological tests might be determined, at least partly, by their variety of motor limitations.

The present study tests individuals with spastic cerebral palsy on the oddball paradigm, which does not require an overt motor response. In this paradigm, visual stimuli are presented with low and high probability, and the participant is instructed to attend to the rare (low probability) stimuli by counting them. In recording the electroencephalogram during task performance, the frontal central N2 and the centroparietal P300 event-related potentials were extracted. The infrequent stimulus typically elicits an enhanced frontal central N2 and a centroparietal P300 event-related brain potential, reflecting fundamental attention processes.<sup>4</sup> It is expected that the N2–P300 complex in youth with cerebral palsy is less pronounced when poor attention is associated with the phenotype of cerebral palsy.

To our knowledge, this is the first investigation of cognitive event-related brain potentials in youth with cerebral palsy while they perform the oddball paradigm. The validity for the oddball paradigm has been determined among others from documented differences in the N2–P300 complex between

patients after sustained traumatic brain injury and age-matched normal individuals.<sup>5-7</sup> Studies reported both a longer latency and reduced P300 amplitude in the patient group, indicating compromised perception and discrimination of stimulus features and evaluation.

### **Methods Study Population**

Fourteen patients with cerebral palsy (6 girls, 8 boys; age range, 9-18 years; mean, 14 years and 0 months) participated in the experiment. All were diagnosed with spastic cerebral palsy when they were between the ages of 1 and 3 years. Brain magnetic resonance imaging (MRI) (1.5 T; Siemens Erlangen, Erlangen, Germany) data during the first year of life or later were used to check the lesion site. Patients were recruited through the Department of Pediatric Neurology at Tampere University Hospital in Finland. All patients had experienced perinatal complications. Five patients were prematurely born (with a birth weight <1500 g) but none had severe visual or hearing impairments or epilepsy. One child was diagnosed as having attention-deficit/hyperactivity disorder (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV]). One child had hydrocephalus. Three children had pervasive learning difficulties on the basis of the verbal intelligence index; however, all except 2 children were joining mainstream education. Functional motor and fine motor abilities were measured using the Gross Motor Function Classification System<sup>8</sup> and the Manual Ability Classification System.<sup>9</sup> Table 1 provides clinical characteristics of the group of participants with spastic cerebral palsy.

Table 1. Group Characteristics

Patient	FIQ	VIQ	PIQ	GMFCS	MACS	Diagnosis	Lesion Site	Prematurity
1	64	75	53	2	1	Diplegia	Bilateral	–
2	61	71	52	1	1	Diplegia	Bilateral	–
3	94	103	85	3	2	Diplegia	Bilateral	–
4	117	133	100	1	1	Hemiplegia	Bilateral	þ
5	65	80	50	3	2	Hemiplegia	Unilateral	–
6	87	103	73	1	1	Hemiplegia	Bilateral	–
7	82	99	65	2	1	Hemiplegia	Bilateral	þ
8	83	89	78	1	1	Diplegia	Bilateral	–
9	77	79	77	1	1	Hemiplegia	Unilateral	–
10	108	100	118	1	3	Hemiplegia	Unilateral	–
11	101	109	93	1	2	Hemiplegia	Unilateral	þ
12	62	68	56	3	1	Diplegia	Bilateral	þ
13	83	100	68	3	2	Diplegia	Bilateral	–
14	72	80	64	1	1	Diplegia	Bilateral	þ

FIQ, Full-Scale Intelligence Quotient; GMFCS, Gross Motor Function Classification System (score 1 = ambulatory, score 2 = some limitations in walking, score 3 = some assistive devices); MACS, Manual Ability Classification System (score 1 = average fine motor functionality, score 2 = some limitations, score 3 = pronounced limitations); PIQ, Performance Intelligence Quotient; VIQ, Verbal Intelligence Quotient. Intelligence was estimated using the Wechsler Intelligence Scale for Children–Third Edition.

To recruit the control group, contact was made with a primary and a secondary mainstream school in the direct neighborhood of the laboratory in the city of Tampere. Both schools were willing to participate with the experiment. Of the school populations, 14 age- and gender-matched control children and adolescents (6 girls, 8 boys; age range, 10-18 years; mean, 14 years and 7 months) were selected. Informed consent was obtained from all participants and their parents. A movie ticket was offered to every control child and adolescent for participation. Ethical approval was obtained from Tampere University Hospital Ethics Committee.

## Study Design

A white plus sign on a black background was used as standard stimulus ( $n = 200$ ) and a white letter O on a black background as deviant stimulus ( $n = 50$ ). Each stimulus was presented for 200 milliseconds. The interstimulus interval was 500 milliseconds. The stimuli were presented pseudo-randomly so that 2 deviant stimuli were never presented successively and there was always at least 1 standard stimulus between the deviant stimuli.

## Procedure

The participants were seated in front of a monitor, about 80 cm from the screen. They were asked to monitor the unpredictable and infrequent stimuli and count them silently without any overt response. The task duration was 3 minutes. A short training session was given before the experiment started.

## Electrophysiological Measures

Electroencephalograms (EEGs) were recorded using Ag/AgCl-electrodes at 9 electrode sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4). The reference electrodes were placed on mastoids. Four additional tin electrodes were attached for a bipolar recording of the vertical electrooculogram from above and below the left eye and for horizontal electrooculogram from the outer canthi of both eyes. Impedances were kept below 5 k $\Omega$  at all electrodes. Digital data together with triggers marking specific events were stored on hard disk for later analysis. Data were first re-referenced to linked mastoids and band pass filtered from 0.1 to 30 Hz at 12 dB per octave. Epochs contaminated with artifacts (threshold for artifact rejection was +100  $\mu$ V in all channels) were rejected, and EEG was segmented into 600-millisecond epochs beginning at the stimulus onset. The EEG was averaged separately for deviants ( $n = 50$ ) and standards preceding the deviants ( $n = 50$ ). Waveforms were then aligned to a baseline between the stimulus-onset to 30 milliseconds after stimulus. The amplitude of the P300 was defined as the most positive peak in the 250- to 550-millisecond interval after the stimulus onset. The amplitude of the N2 was defined as the most negative peak in the 250- to 400-millisecond interval after the stimulus onset. P300 and N2 latencies were defined as the time interval between stimulus onset and maximal positive or negative amplitude, respectively.

## Statistical Analysis

Repeated-measures analysis of variance (ANOVA) with group (cerebral palsy vs control) as between-subject factor and stimulus type (standard vs deviant) as within-subject factor were

performed for latencies and amplitudes of N2 and P300 components. A level of  $P < .05$  was accepted as significant.

## Results

Both groups were able to detect the 50 infrequent stimuli. This was checked directly after the experiment. Figure 1 presents the difference wave (produced by subtracting the event-related waves generated by the standard stimuli from the event-related potentials for the deviant condition) of the 2 groups.

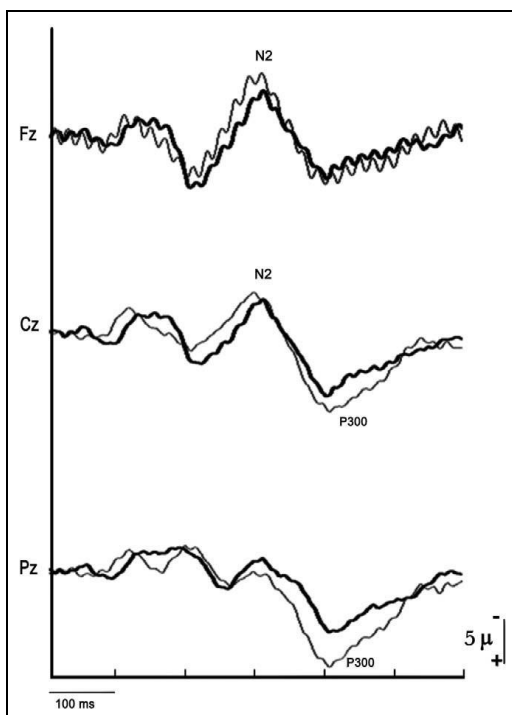


Figure 1. Grand-averaged difference waves in the group with cerebral palsy (thick line) and the control group (thin line) at the midline electrode positions.

The figure illustrates that the oddball manipulation produced the expected effects on the amplitude and latency of the N2–P300 complex: the N2 was maximally recorded around 300 milliseconds at Fz and Cz, with the P300 recorded around 450 milliseconds at Cz and Pz. The visual impression obtained from the figure (no group differences with respect to the N2–P300 complex) was confirmed by ANOVA, depicted in Table 2.

Table 2. Analyses of Variance Concerning the N2–P300 Complex Differentiation of Standard and Deviant Stimuli Between Patients With Cerebral Palsy and Controls



Channel	Component	Measure	Group Differences
Fz	N2	Amplitude	$F_{1,26} = 0.023, P = .88$
		Latency	$F_{1,26} = 0.608, P = .44$
Cz	N2	Amplitude	$F_{1,26} = 0.292, P = .59$
		Latency	$F_{1,26} = 0.546, P = .47$
Cz	P300	Amplitude	$F_{1,26} = 0.784, P = .39$
		Latency	$F_{1,26} = 0.814, P = .38$
Pz	P300	Amplitude	$F_{1,26} = 1.981, P = .17$
		Latency	$F_{1,26} = 0.595, P = .45$

The group main effects remained nonsignificant after exclusion of 4 patients with spastic hemiplegia from the analyses.

## Discussion

Impaired N2–P300 generation is one of the most robust indices of attention difficulties.<sup>10</sup> The outcome of the present study shows no significant differences in the N2–P300 complex between youth with spastic cerebral palsy (4 with spastic hemiplegia and 10 with spastic diplegia) and a peer control group. This finding likely reflects that fundamental attention processes (orientation and evaluation of stimulus novelty) are intact in the patient group measured in a condition when no overt reaction is required. So far, 2 other event-related potential studies have been carried out on youth with cerebral palsy. In the first study, an anticipatory planning task was used in which participants were required to grasp and rotate a hexagonal knob over different angles. At a neural level, individuals with right hemiparetic cerebral palsy showed a strong reduction in the amplitude of the P2 component, likely reflecting an impaired process of action selection.<sup>11</sup> In the second study, participants were required to judge the laterality of hand pictures (motor imagery). The same reduction of the P2 component was found in patients with right hemiparetic cerebral palsy.<sup>12</sup>

In sum, the present study and the 2 motor studies indicated that in a subset of youth with mild spastic cerebral palsy, the stimulus input and central information processing system are intact together with a compromised motor action system. Future studies on the N2–P300 complex of youth with spastic cerebral palsy are underway to pinpoint more precisely the complex interplay between processing of more complex stimuli and the timing of initiating an overt motor response. Better definition of functional brain–behavior relationships in youth with cerebral palsy would allow us to

better understand how to develop more specific educational, psychological, and vocational interventions to enhance or maximize outcome in youth with cerebral palsy.<sup>2</sup>

### **Limitation of the Study**

The sample was small and cannot be seen to represent the population of youth with spastic cerebral palsy. In addition, this study used a limited but standardized brain imaging technique apt to diagnose unilateral and bilateral spastic cerebral palsy when children were in the age range of 1 to 3 years. More detailed studies with quantitative assessment of brain images may be useful in future studies in executive functions to examine detailed correlations between specific anatomic lesions and various aspects of executive functioning.

### **Conclusion**

The outcome of the present study shows that patients with spastic cerebral palsy have intact orientation and evaluation of stimulus novelty in a condition when no overt reaction was required.

### **Acknowledgments**

The study was done at Tampere University Hospital, Department of Pediatric Neurology, Tampere, Finland, and at the Human Information Processing Laboratory, Tampere, Finland. The authors thank the parents and children participating in this study.

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## **CHAPTER 4: Stimulus Evaluation, Event Preparation and Motor Action Planning in Young Patients With Mild Spastic Cerebral Palsy: An Event-Related Brain Potential Study**

E. Hakkarainen<sup>1</sup>, S. Pirilä<sup>1,2</sup>, J. Kaartinen<sup>3</sup>, J. J. van der Meere<sup>4</sup>

<sup>1</sup>Department of Psychology, University of Tampere, Tampere, Finland

<sup>2</sup>Department of Pediatrics, Tampere University Hospital, Tampere, Finland

<sup>3</sup>Department of Psychology, University of Jyväskylä, Jyväskylä, Finland

<sup>4</sup>Department of Clinical and Developmental Neuropsychology, University of Groningen, Groningen, The Netherlands

Journal of Child Neurology (2011), 27, 465-470

## **Abstract**

The study investigated stimulus evaluation time, event preparation, and motor action planning of patients with mild spastic cerebral palsy and a peer control group in the age range of 9 to 18 years. To this end, participants were carrying out a stimulus recognition task. Findings indicated an overall slowness and inaccurate reaction time performance of the patient group. An event-related potential analysis revealed that the stimulus evaluation processing, indexed by the parietal P300, was intact in the group of patients. Also event preparation and action planning, indexed by respectively the frontal late contingent negative variation and the frontal P2, were intact in the group of patients. It was concluded that patients' motor slowness reflected poor motor execution processes.

## **Introduction**

With a prevalence estimate of 2 per 1000 live births,<sup>1</sup> cerebral palsy is considered a motor disorder associated with, among others, cognitive executive dysfunctions. And indeed, as recently reviewed,<sup>2,3</sup> patients show poor performance on a variety of executive function tasks with mean reaction times and errors as the main dependent variables. However, given patients' weak motor skills, the key question remains whether poor reaction time performance on executive function tasks truly reflects compromised executive functions in this group of patients. For instance, recently, a parietal P300 event-related potential study demonstrated that individuals with spastic cerebral palsy are not compromised in fundamental attention executive skills, orientation and evaluation of stimulus novelty, when no overt motor response was required.<sup>4</sup>

The aim of the present study is to elaborate on the issue whether poor reaction time performance of individuals with spastic cerebral palsy obtained during executive functioning demands is associated with impaired information processing, motor processes, or both. To this end, a group of patients will be compared with a peer control group on a cognitive task that differentiates between cognitive and motor-related aspects: the stimulus recognition task originally developed by Sternberg.<sup>5</sup>

In this task, participants are required to compare a set of items (memory set) with a second set of items (display set) that is displayed on a monitor after a brief interval. If one of the items of the memory set matches one of the items of a display set, a positive ("yes") response is required. Otherwise, a negative ("no") response is required. The positive and negative responses are given by touching, respectively, the left and right button with the dominant hand.

Increasing the cognitive load (increasing the number of items in the memory set) results in a linear increase in mean reaction times. This so-called load effect on mean reaction times reflects the stimulus evaluation time. The residual is considered an index of motor processing.<sup>5</sup> Using the stimulus recognition task, we hypothesize that if impaired stimulus evaluation is essential to cerebral palsy, the load effect on the performance measures should be more pronounced in this group than in controls. In statistical terms, the 2-way interaction group with load should be significant. However, if impaired motor processes, but not impaired stimulus evaluation, is essential to cerebral palsy, it is expected that slowness in this group should be found independently of the cognitive load. In statistical terms, the group main effect should be significant, not the interaction group by load.

Admittedly, the reaction time is a robust measure. Registering electroencephalograms while the participants are carrying out the Sternberg task and deriving evoked potentials connected with stimulus evaluation and motor processes from it may provide more detailed information about the efficiency of information processing compared to evaluating reaction times alone. The present study focuses on 3 event-related potentials. The first is the contingent negative variation, also called as the readiness potential. This wave develops in the period between the offset of the memory set and the onset of the display set. In particular, the late part of the wave reflects motor preparation toward an approaching predictable event. More specifically, the more preparation takes place, the faster is the response.<sup>6</sup> A few hundred milliseconds after the onset of the display set, motor action planning takes place, indexed by the frontal positive P2. The more pronounced the motor action planning, the higher is the P2 amplitude.<sup>7</sup> The next positive peak, the P300, measured at the parietal lead, reflects the stimulus evaluation time and decision making. It is well recognized that the latency of this wave increases and the amplitude decreases as a function of cognitive load. After the maximization of the P300, motor execution processing takes place, resulting in the overt reaction time.<sup>8</sup>

In sum, exploring overt measures (reaction times and number of errors) in tandem with characteristics of the late contingent negative variation, the P2, and the P300, it is tested whether mild spastic cerebral palsy is associated with poor stimulus evaluation, poor motor-related processes, or both. If mild cerebral palsy is associated with poor stimulus evaluation, then the effects of load on the latency and amplitude of the P300 will be more pronounced compared to the control group. If, on the other hand, cerebral palsy is associated with poor motor organization processes, it is expected that the late frontal contingent negative variation and frontal P2 should be reduced. Finally, if patients' slow responding is not associated with poor stimulus evaluation and poor motor organization processes, then the slowness is apparently related solely to poor motor execution processes.

## Methods Study Population

Thirteen patients with cerebral palsy (5 girls, 8 boys; M = 14 years 6 months, SD = 3 years 6 months, min-max = 9-18 years) participated in the experiment. All were diagnosed with spastic cerebral palsy when they were between the ages of 1 and 3 years. Brain magnetic resonance imaging (MRI) (Siemens Erlangen, 1.5 T) data during the first year of life or later were used to check the lesion side. Patients were recruited through the Department of Pediatric Neurology at Tampere University Hospital in Finland. All had experienced peri/ neonatal complications. Four patients were born preterm (birth weight <1500 g) but none had severe visual or hearing impairments, or epilepsy. One child had hydrocephalus. The clinical characteristics of the patient group are shown in Table 1.

Table 1. Group Characteristics

Patient	FIQ	VIQ	PIQ	GMFCS	MACS	Diagnosis	Lesion site	Prema
1	64	75	53	2	1	Diplegia	Bilateral	-
2	61	71	52	1	1	Diplegia	Bilateral	-
3	94	103	85	3	2	Diplegia	Bilateral	-
4	117	133	100	1	1	Hemiplegia	Bilateral	þ
5	65	80	50	3	2	Hemiplegia	Unilateral	-
6	87	103	73	1	1	Hemiplegia	Bilateral	-
7	82	99	65	2	1	Hemiplegia	Bilateral	þ
8	83	89	78	1	1	Diplegia	Bilateral	-
9	77	79	77	1	1	Hemiplegia	Unilateral	-
10	108	100	118	1	3	Hemiplegia	Unilateral	-
11	62	68	56	3	1	Diplegia	Bilateral	þ
12	83	100	68	3	2	Diplegia	Bilateral	-
13	72	80	64	1	1	Diplegia	Bilateral	þ

Abbreviations: FIQ = Full-Scale Intelligence Quotient, VIQ = Verbal Intelligence Quotient, PIQ = Performance Intelligence Quotient, GMFCS = Gross Motor Function Classification System (score 1 = ambulatory, score 2 = some limitations in walking, score 3 = some assistive devices), MACS = Manual Ability Classification System (score 1 = average fine motor functionality, score 2 = some limitations, score 3 = pronounced limitations). Note: Intelligence was estimated using the Wechsler Intelligence Scale for Children–Third Edition.

Fourteen control children and adolescents (7 girls, 7 boys; M = 14 years 4 months, SD = 2 years 5 months, min-max = 10-18 years) were recruited from mainstream elementary schools and upper secondary schools in the same city. The control group and the group of patients did not differ

significantly with respect to age,  $t(24) = 0.51$ ,  $P = .07$ . Informed consent was obtained from all participants. Ethical approval was obtained from Tampere University Hospital Ethics Committee.

### Study Design

The participants were seated in front of a monitor, about 80 cm from the screen. All stimuli were white letters (consonants only) measuring 1.5 cm on a black background. On each trial, a memory set was presented of 1 or 2 target letters, which were to be memorized temporarily. These letters were simultaneously shown on a single row in the centre of the screen. Subsequently, a new set of letters was presented, making up a square of 8 x 8 cm. The number of letters in this display set was held constant (4) and either 1 member of the memory set or none was presented in this set. A varied mapping procedure was followed: targets and distracters were randomly intermixed over trials.

Per trial, participants placed their dominant hand between 2 response buttons. When the target was present in the display set (positive set), subjects were pressing the left “yes” button with their dominant hand. When the target was not present (negative set), subjects were pressing the right “no” button with their dominant hand. The probability that the target was present in the display set was 0.5. Task characteristics are depicted in Figure 1.

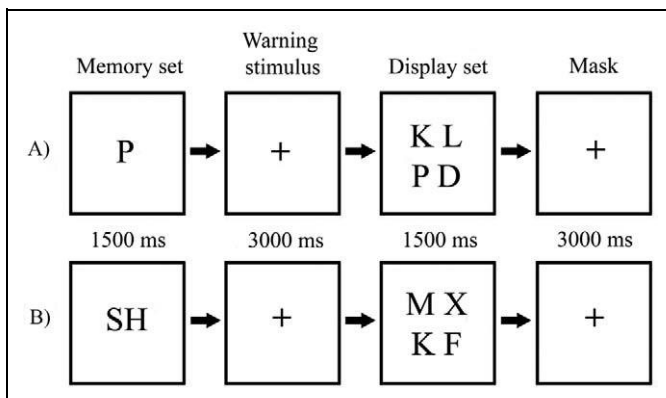


Figure 1. Time sequence of a positive trial in load condition 1 X 4 (A) and a negative trial in load condition 2 X 4 (B).

The letters in each trial were randomly selected with the restriction that no letter occurred as a target in 2 consecutive trials and that no more than 3 consecutive positive or negative trials occurred in sequence. In addition, it was ascertained that the frequencies were approximately equal for the target appearing in 1 of the 4 positions of the display set (left up, right up, left down, right down). All participants were presented the same random sequence of memory and display sets.



Starting from the appearance of the display set, participants had 4500 ms to respond. For each response, the interval between onset of the display set and button press was measured as the reaction time. The accuracy of the target identification was also recorded, including incorrect responses (button press errors) and failure to press a button within 4500 ms (time out). Precipitate responses (reaction time <200 ms) were excluded from the analysis. Based on cognitive load (memory set items x display set items), the task was divided into 2 conditions, always presented in the same sequence: first load 4 (1 x 4) and then load 8 (2 x 4). Within each condition, 60 trials were performed. Participants were given a short practice period, which generally lasted about 2 minutes, until they completely understood the task. A short break was introduced between the 2 conditions. The experiment, including instruction and practice, lasted about 15 minutes. During the test, the researcher sat out of sight of the child, and no interaction was allowed.

### **Electrophysiological Measures**

Electroencephalograms (EEGs) were recorded by Neuroscan using Ag/AgCl electrodes at nine electrode sites (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4). The reference electrodes were placed on mastoids.

Four additional tin electrodes were attached for a bipolar recording of the vertical electro-oculogram from above and below the left eye and for horizontal electro-oculogram from the outer canthi of both eyes. Impedances were kept below 5 k $\Omega$  at all electrodes. Digital data together with triggers marking specific events were stored on hard disk for later analysis. Data were first digitally filtered with a highpass filters of 1.59 Hz and a low-pass filter of 30 Hz at 12 dB/Octave for the P2 and P300 components. For contingent negative variation, a high-pass filter of 0.01 Hz and a low-pass filter of 30 Hz at 12 dB/ Octave were employed. Epochs contaminated with artifacts (threshold for artifact rejection was +100  $\mu$ V in all channels) were rejected.

P300 and P2. Only EEG associated with correctly identified trials (positive/negative) was analyzed. Signals were epoched offline with a window from 100 ms before to 1200 ms after the onset of the display set. The EEG from individual trials was visually inspected and corrected for horizontal and vertical eye movements using the Gratton, Coles, and Donchin algorithm,<sup>9</sup> before averaging the epochs. All ERPs were aligned to a prestimulus baseline of -100 to 0 ms before the onset of the display set. ERPs were sorted and averaged separately according to load (4 or 8) and the type of trial (positive or negative).

After averaging, components were scored in the ERPs based on inspection of the grand-average waveforms. P300 components were identified at Pz and P2 components at Fz for each subject. The

peak amplitude and latency of the P300 component were determined over a time interval of 350 to 900 ms post stimulus. For the P2 component, the peak amplitude and latency were determined in a time window of 150 to 250 ms.

Contingent negative variation. Data were epoched into 6000 ms segments starting 500 ms before the onset of the memory set. Possible artifacts (such as eye movements and body movement artifacts) were taken into account by visually inspecting the segments one by one and excluding the bad segments from the further analyses. To investigate a change of the wave across the time, a baseline was set at 2500 to 2600 ms and an average window was created at 4400 to 4500 ms (100-ms period before the onset of the display set).

### **Statistical Analysis**

Behavioral data. The performance efficiency was expressed in terms of mean reaction time and response accuracy (percentage of button press errors and time-out). Only trials with correct responses were included in the mean reaction time for each subject. These performance measurements were analyzed using a MANOVA with repeated measures, with Group (cerebral palsy and control) as the between-subject factor and load (4 and 8) and trial (positive and negative) as the within-subject factors. An alpha level of .05 (2-tailed) was used for all statistical tests.

Evoked response potentials. The amplitude and latency of the P300 component at Pz and P2 component at Fz were analyzed using a MANOVA with repeated measures, with Group (cerebral palsy and control) as the between-subject factor and load (4 and 8) and trial (positive and negative) as the within-subject factors. In addition, separate ANOVAs with repeated measures were performed for positive and negative trials, with Group as the between-subject factor and load as the within-subject factor. An alpha level of .05 (2-tailed) was used for all statistical tests.

### **Results**

No group differences were found with respect to positive and negative responses at mean reaction time, accuracy level, and at the electrophysiological level. To save space, the average mean reaction times and related P300 latencies of both response types for both groups are depicted in Figure 2.

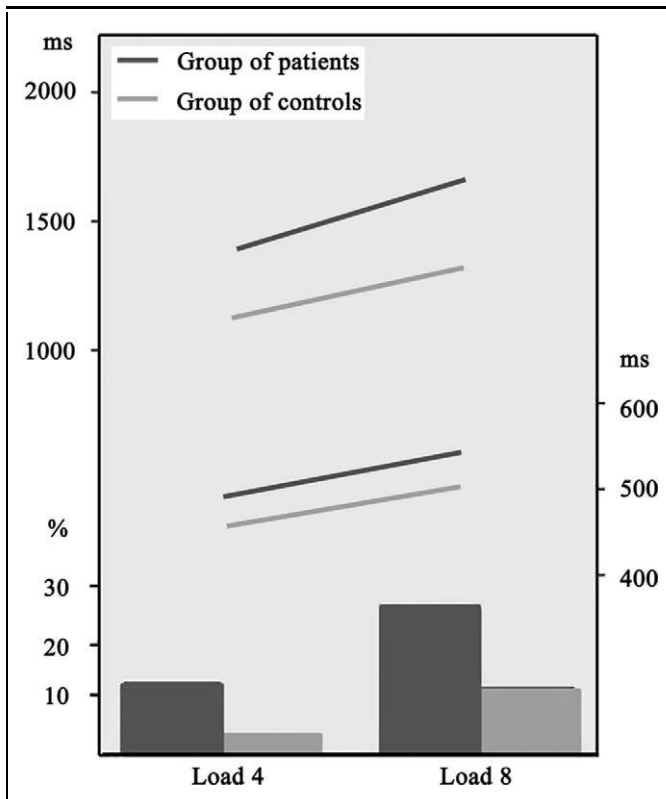


Figure 2. Mean reaction times (upper left scale), P3 latencies (right scale), and the percentage of errors (lower left scale) in the 2 groups for the 2 load conditions.

Figure 2 shows that the patient group was slower than the control group: the main effect of group on mean reaction time was significant,  $F(1, 25) = 5.71, P < .05$ . In addition, the patient group made more errors compared to the control group: the main effect of group on number of errors was  $F(1, 25) = 10.83, P = .003$ . Reaction times increased as a function of cognitive load: the main effect of load was  $F(1, 25) = 37.09, P < .000$ , reflecting the extra time to evaluate the stimuli. Also the number of errors increased as a function of cognitive load: the main effect of load was  $F(1, 25) = 56.27, P < .000$ . The load effect on mean reaction time and errors was similar in the 2 groups: the interaction group by load for mean reaction time was  $F(1, 25) = 1.05, P = .32$ , and for accuracy  $F(1, 25) = 2.36, P = .14$ . The nonsignificant interactions between cognitive load and the overt performance measures (mean reaction time and error percentage) indicate no difference in stimulus evaluation time between the 2 groups. Put in other words, poor performance of the patient group was not associated with poor stimulus evaluation. This suggestion was supported by analyzing the parietal P300 event-related potential. As expected, the P300 latency increased significantly with increasing load (see Figure 2): the main effect of load was  $F(1, 25) = 4.26, P < .05$ , reflecting the extra time needed to evaluate the number of stimuli. Groups did not differ with respect to the stimulus evaluation time: the main effect

of group was  $F(1, 25) = 0.85, P = .37$ , and the 2-way interaction between load and group was  $F(1, 25) = 0.00, P = .97$ . Note: the P300 amplitude was insensitive for the cognitive load manipulation; the cognitive load effect was  $F(1, 25) = 0.60, P = .45$ . Also the groups did not differ with respect to their P300 amplitude; the group main effect was  $F(1, 25) = 0.27, P = .61$ . To save space, Figure 3 shows the P300 characteristics of both groups registered in the load 8 condition only.

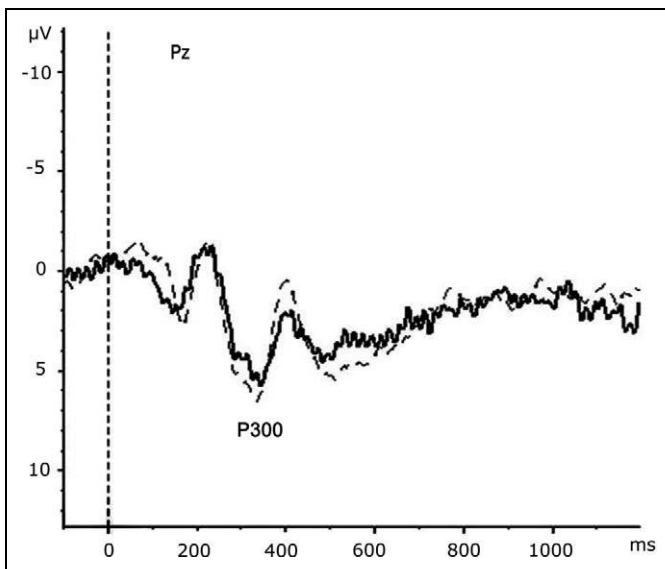


Figure 3. Parietal grand averages for correct responses for the patient group (solid line) and the control group (dashed line) in the load 8 condition. The component is calculated using correct responses only.

In a subsequent analysis, we explored whether the inefficient reaction time performance of the patient group was associated with impaired motor presetting, reflected by the contingent negative variation. Note: Because of measurement artifacts, data of 4 children (2 patients and 2 controls) were excluded from the analysis. Nevertheless, groups remained comparable with respect to the age factor,  $t(20) = 0.65, P = .53$ . The analysis focused on the final 100 ms of the contingent negative variation that was in our study most pronounced at Fz: the main effect of channel was  $F(2, 40) = 16.90, P = .000$ . The more pronounced the wave, the faster the reaction times ( $r = .23, P < .03$ ), reflecting motor presetting. Groups did not differ with respect to motor presetting: the group main effect was  $F(1, 20) = 0, P = 1.00$ . To save space, Figure 4 shows the contingent negative variation of the 2 groups in the load 8 condition only.

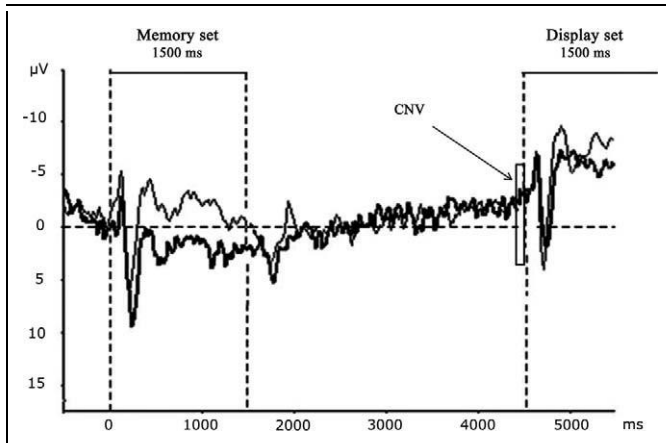


Figure 4. Grand-averaged frontal contingent negative variation (CNV) of the patient group (thick line), and the control group (thin line) in the load 8 condition. The wave is measured in the period of 3 seconds between the offset of the memory set and the onset of the display set (baseline at 2500-2600 ms).

In a subsequent analysis, we explored whether the inefficient reaction time performance of the patient group was associated with impaired motor action planning, reflected by the frontal P2. The Pearson correlation between the latency and amplitude of the P2 with the mean reaction time was respectively  $r = .22$ ,  $P < .02$ , and  $r = -.06$ ,  $P < .53$ , indicating that motor action planning was reflected by the P2 latency, not its amplitude. Groups did not differ with respect to anticipatory action planning: the group main effect for latency was  $F(1,25) = 2.75$ ,  $P = .11$ . To save space, Figure 5 presents the frontal P2, reflecting motor action planning of the 2 groups in the load 8 condition only.

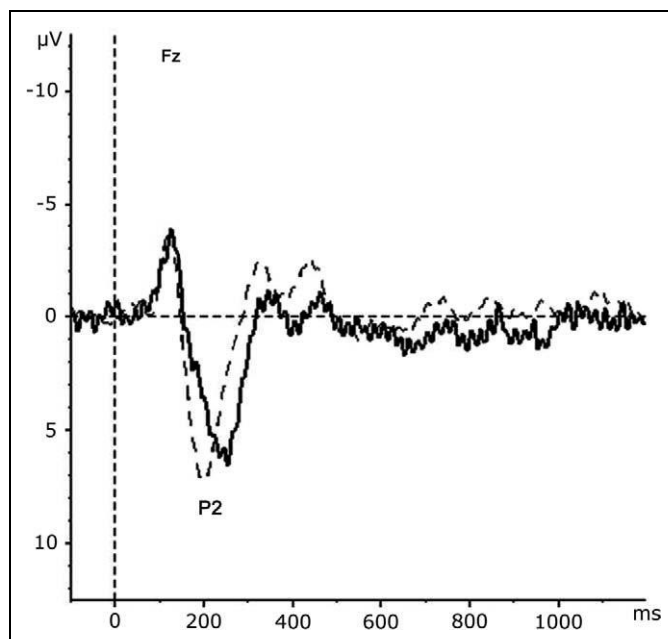


Figure 5. Sum of frontal grand averages in the patient group (solid line) and in the control group (dashed line) in the load 8 condition. The component is calculated using correct responses only.

## Discussion

An enduring problem in cognitive neuroscience is that of explaining the duration and variability of reaction times. The general view is that the measure is determined by formally distinct stages of processing: stimulus input, evaluation, and a residual time to initiate the movement. But questions remain as to whether the transformations between stages are discrete or continuous. Discrete models of information processing predicts that after event preparation, indexed by the late contingent negative variation, and action planning, indexed by the P2, evidence about the stimulus characteristics build up, reaching a criterion (reflected by the parietal P300 amplitude and latency) that is then translated in a motor command.<sup>10</sup> Along the lines of discrete models, the main findings of the present study are that individuals with mild spastic cerebral palsy are slower and more inaccurate in reacting toward stimuli than the control group. However, this slowness is not caused by the speed of evaluating the nature of stimuli. In fact, this cognitive process is intact, given the effects of cognitive load on overt indices (the mean reaction time, error percentages) and covert indices (latency and amplitude of the P300). Exploring 2 motor components, the late contingent negative variation and the P2 amplitude, indicated that patients' inefficient performance was also not related to weak motor presetting and motor planning. Apparently, the motor execution system itself caused slow and inaccurate performance in them. To confirm this statement, other motor measures are needed to implement in future studies to investigate in more detail at what particular moment the motor execution process is initiated. The lateralized readiness potential could be a good candidate.<sup>11,12</sup> In the current study, it was not possible to measure this potential because the participants were using their dominant hand to respond, instead of 2, which is needed to estimate the potential.

In an earlier study,<sup>4</sup> using the event-related potential methodology, we reported that patients with spastic cerebral palsy are not compromised in fundamental attention executive skills, orientation and evaluation of stimulus novelty, when no overt motor response was required. The present findings suggest that when a simple overt motor response is required, patients with mild spastic cerebral palsy are slower but able to evaluate stimuli adequately. This finding needs replication using a higher number of participants.

## Acknowledgments

The study was done in Tampere University Hospital, Department of Pediatric Neurology, Tampere Finland, and in the Human Information Processing Laboratory, University of Tampere, Finland. The authors thank the parents of the children participating in this study. In addition, the authors thank M.S. Anne Salminen and M.S. Paula Vaara-tinen for developing and testing the methodology.

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## **CHAPTER 5: Error detection and response adjustment in youth with mild spastic cerebral palsy: An event-related brain potential study**

E. Hakkarainen<sup>1</sup>, S. Pirilä<sup>2</sup>, J. Kaartinen<sup>3</sup>, J. J. van der Meere<sup>4</sup>

<sup>1</sup>Finnish Cerebral Palsy Association, Helsinki; Finland

<sup>2</sup>Department of Pediatrics, Tampere University Hospital, Tampere, Finland

<sup>3</sup>Department of Psychology, University of Jyväskylä, Jyväskylä, Finland

<sup>4</sup>Department of Clinical and Developmental Neuropsychology, University of Groningen, Groningen, The Netherlands

Journal of Child Neurology (2012), 28, 749-754



## **Abstract**

This study evaluated the brain activation state during error making in youth with mild spastic cerebral palsy and a peer control group while carrying out a stimulus recognition task. The key question was whether patients were detecting their own errors and subsequently improving their performance in a future trial. Findings indicated that error responses of the group with cerebral palsy were associated with weak motor preparation, as indexed by the amplitude of the late contingent negative variation. However, patients were detecting their errors as indexed by the amplitude of the response-locked negativity and thus improved their performance in a future trial. Findings suggest that the consequence of error making on future performance is intact in a sample of youth with mild spastic cerebral palsy. Because the study group is small, the present findings need replication using a larger sample.

## **Introduction**

Cerebral palsy is a group of disorders of movement and posture attributed to disturbances in the developing fetal or infant brain, causing activity limitations.<sup>1</sup> A large proportion of cerebral palsy disorders is caused by periventricular leukomalacia, intraventricular/periventricular hemorrhages, or infarcts contributing to lesions of gray matter and white matter tracts. The latter lesions are in particular associated with executive dysfunctions,<sup>2</sup> and indeed, youth with cerebral palsy are slower and make statistically more reaction time errors than peer controls on a variety of executive function tasks, as is recently reviewed.<sup>3,4</sup>

The present study examined whether youth with mild spastic cerebral palsy were aware of their own errors while carrying out an executive function task. Rabbitt and Rodgers'<sup>5</sup> pioneering research on error processing showed that error detection results in reaction time improvement in a future trial. This phenomenon is now widely used as a marker for cognitive control in developmental<sup>6</sup> and clinical studies on, for instance, attention deficit hyperactivity disorder.<sup>7</sup>

Neurocognitive studies using the event-related brain potential methodology have shown that weak motor preparation before error making occurs, as indexed by the amplitude of the late contingent negative variation.<sup>8</sup> Error detection and its fine-grained adjustments in performance may be indexed by response-locked error-related negativity. The latter brain potential reaches its negative maximum just after an erroneous response, is substantially larger following errors than following correct trials, and originates in the anterior cingulate cortex, insula, and orbitofrontal cortex.<sup>9-11</sup>

Using the event-related potential methodology, brain activity just before, during, and after error making was compared between a sample of youth with mild spastic cerebral palsy and a peer control group during the execution of a stimulus recognition task. It was tested whether the group of patients was aware of their own error making and thus shows compensatory mechanisms to prevent future errors. The argument for studying error processing in youth with mild spastic cerebral palsy is that identification of error making and strategic response adjustments after error making are keys in learning.

### **Methods Study Population**

Eleven patients (4 girls) with cerebral palsy (mean, 14 years 3 months; standard deviation [SD], 3 years 9 months; range, 9-18 years) participated in the study. All were diagnosed with mild spastic cerebral palsy when they were between the ages of 1 and 3 years. Brain magnetic resonance imaging data during the first year of life or later were used to check the lesion site. Patients were recruited through the Department of Pediatric Neurology at Tampere University Hospital in Finland. All had experienced perinatal/neonatal complications. Four patients were born preterm (birth weight <1500 g). None had severe visual or hearing impairments or epilepsy. One child had hydrocephalus. The clinical characteristics of the patient group are shown in Table 1.

Table 1. Group Characteristics.

Patient	FIQ	VIQ	PIQ	GMFCS	MACS	Diagnosis	Lesion site	Prematurity
1	64	75	53	2	1	Diplegia	Bilateral	–
2	61	71	52	1	1	Diplegia	Bilateral	–
3	94	103	85	3	2	Diplegia	Bilateral	–
4	117	133	100	1	1	Hemiplegia	Bilateral	+
5	65	80	50	3	2	Hemiplegia	Unilateral	–
6	82	99	65	2	1	Hemiplegia	Bilateral	+
7	83	89	78	1	1	Diplegia	Bilateral	–
8	77	79	77	1	1	Hemiplegia	Unilateral	–
9	108	100	118	1	3	Hemiplegia	Unilateral	–
10	83	100	68	3	2	Diplegia	Bilateral	–
11	72	80	64	1	1	Diplegia	Bilateral	+

Intelligence was estimated using the Wechsler Intelligence Scale for Children–Third Edition. FIQ, Full-Scale intelligence quotient; VIQ, Verbal intelligence quotient; PIQ, Performance intelligence quotient; GMFCS, Gross Motor Function Classification System (score 1 = ambulatory, score 2 = some limitations in walking, score 3 = some assistive devices); MACS, Manual Ability Classification System (score 1 = average fine motor functionality, score 2 = some limitations, score 3 = pronounced limitations).

Twelve control children (6 girls) and adolescents (mean, 14 years 3 months; SD, 2 years 8 months; range, 10-18 years) participated in the study. They were recruited from mainstream elementary schools and upper secondary schools in the same city.

Several of the children with mild spastic cerebral palsy had intelligence quotients in the range of learning disabilities. None of these children were diagnosed as mentally retarded because their activities of daily living were intact. For instance, children were joining mainstream education, and part-time special education was provided if necessary. The 2 groups did not differ significantly with respect to age ( $t_2 = -0.04$ ,  $P = .96$ ). Informed consent was obtained from all participants. Ethical approval was obtained from the Tampere University Hospital Ethics Committee.

### Study Design

The participants were seated in front of a monitor, about 80 cm from the screen. All stimuli were white letters (consonants only), measuring 1.5 cm on a black background. A memory set was presented of 2 target letters, which were to be memorized temporarily. These letters were simultaneously shown on a single row in the center of the screen.

Subsequently, a new set of 4 letters was presented, making up a square of 8 X 8 cm. One of the letters of the memory set or neither was presented in this set. A varied mapping procedure was followed: targets and distracters were randomly mixed over trials.

Participants placed their dominant hand between 2 response buttons. When the target was present in the display set (positive set), patients were to press the left “yes” button with their dominant hand. When the target was not present (negative set), patients were to press the right “no” button with their dominant hand. The probability that the target was present in the display set was .5.

The letters in each trial were randomly selected with the restriction that no letter occurred as a target in 2 consecutive trials and that no more than 3 consecutive positive or negative trials occurred in sequence. In addition, it was ascertained that the frequencies were approximately equal for the target appearing in 1 of the 4 positions of the display set (left up, right up, left down, right down). All participants were presented the same random sequence of memory and display sets.

Starting from the appearance of the display set, participants had 4500 milliseconds to respond. For each response, the interval between onset of the display set and button press was measured as the reaction time. The study focused on correct and incorrect responses (button press errors). Failure to press a button within 4500 milliseconds (error of omission) and precipitate responses (reaction time <200 milliseconds) were excluded from the analysis. Participants were given a short practice period, which generally lasted about 2 minutes, until they completely understood the task. The experiment, including instruction and practice, lasted about 15 minutes. During the test, the researcher sat out of sight of the participant, and no interaction was allowed.

### **Behavioral Measures**

Three response types were defined: correct reaction times, incorrect reaction times, and correct reaction times directly after an error.

### **Electrophysiological Measures**

Electroencephalograms were recorded by using Ag/AgCl electrodes at 9 electrode sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4). The reference electrodes were placed on mastoids. Four additional tin electrodes were attached for a bipolar recording of the vertical electrooculogram from above and below the left eye and of the horizontal electro-oculogram from the outer canthi of both eyes. Impedances were kept below 5 k $\Omega$  at all electrodes. Digital data, together with triggers marking specific events, were stored on a hard disk for later analysis.

Data were first digitally filtered with a high-pass filter of 1.59 Hz and a low-pass filter of 30 Hz at 12 dB per octave for the resposerelated negativities. For the contingent negative variation, a highpass filter of 0.01 Hz and a low-pass filter of 30 Hz at 12 dB per octave were employed. Epochs contaminated with artifacts (threshold for artifact rejection was +100  $\mu$ V in all channels) were rejected. Electroencephalograms from individual trials were visually inspected and corrected for horizontal and vertical eye movements.

### Contingent Negative Variation

Data were epoched into 5200-millisecond segments starting 500 milliseconds before the onset of the memory set. Possible artifacts (such as eye movements and body movements) were taken into account by visually inspecting the segments one by one and excluding the invalid segments from the further analyses. In order to investigate a change of the wave across the time, a baseline was set at 2500 to 2600 milliseconds, and an average time window was created at 4000 to 4500 milliseconds (500-millisecond period before the onset of the display set).

### Response-Locked Negativity

The negative polarity potential with a frontocentral scalp distribution was measured as the most negative peak during the first 100 milliseconds after correct and incorrect responses separately. Figure 1 shows an overview of the time windows of the event-related potentials under study and essential task parameters and illustrates that the brain potentials studied do not overlap in time.

Stimuli	SH	+	MX K F	+
Section	Memory set	Warning stimulus		Mask
Duration	1500 ms	3000 ms		3000 ms
Component			CNV	Response-locked components

Figure 1. Time windows used to calculate the event-related potentials.

### Statistical Analyses

Mean reaction times of correct and error responses, together with the response-locked negativities and the contingent negative variation, were analyzed using a MANOVA with repeated measures. Group (cerebral palsy vs control) was the between-patient factor. Response type (error vs correct response) was the within-patient factor. In the reaction time adjustment analysis, response type (error vs correct response directly after an error) was used as the within-patient factor, and group (cerebral

palsy vs control) was used as the between-patient factor. An a level of .05 (2-tailed) was used for all statistical tests.

## Results

The control group made 88% correct responses and 9% error responses (patients were indicating that the target was present, whereas that was not the case, or vice versa). The patient group made 78% correct responses and 12% incorrect responses. Groups slightly differed in their performance efficiency ( $t = -2.1$ ,  $P < .07$ ). The mean reaction times of the error and correct responses ranged between 1250 and 1600 milliseconds. The group of patients tended to react slower than the control group: the group main effect was  $F_{1,21} = 3.32$ ,  $P = .08$ . In addition, error responses tended to be slower than correct responses: the main effect of response type was  $F_{1,21} = 3.24$ ,  $P = .09$ . This effect was the same in both groups: the interaction group by response type did not yield a significance level ( $F_{1,21} = 0.69$ ,  $P = .42$ ). Motor preparation for correct and error responses is presented in Figure 2.

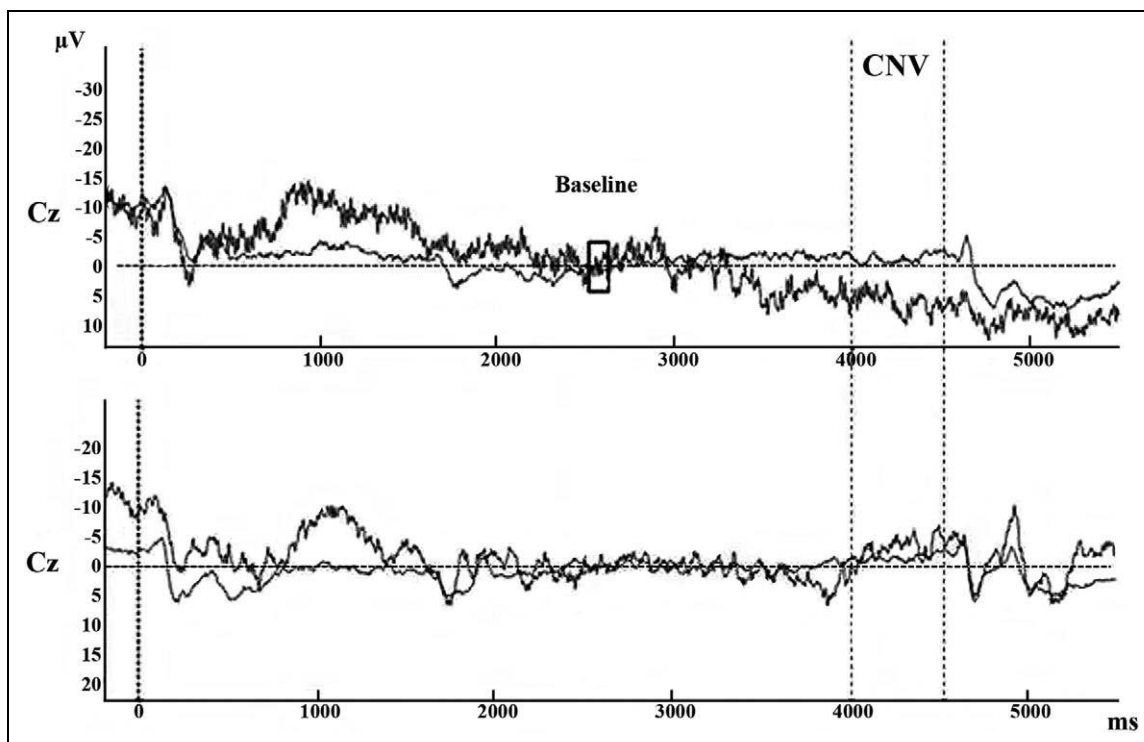


Figure 2. Central contingent negative variation for correct responses (gray line) and for error responses (black line) of the patient group (upper row) and of the control group (lower row). In the patient group, decreased negativity related to error responses can be perceived compared with the control group.

According to neuroscience, the better the motor preparation, the more pronounced is the amplitude of the contingent negative variation before actual responding takes place. Figure 2 shows that the amplitude of the contingent negative variation for the correct responses was the same in the 2 groups

( $-2.50 \mu\text{V}$ ). However, for the error responses, the amplitude of this component was less pronounced in the patient group ( $5 \mu\text{V}$ ) compared with the control group ( $-5 \mu\text{V}$ ): the group by response type interaction was  $F_{1,21} = 4.4$ ,  $P < .05$ . Consequently, this finding indicates that motor preparation of error responses was weak in the group of patients.

To test whether the patient group was detecting their errors, the amplitude of the response-locked negativity was calculated for error responses and correct responses. Findings are depicted in the left panel of Figure 3. The mean reaction times of error responses followed by the subsequent correct trial are depicted in the right panel of Figure 3.

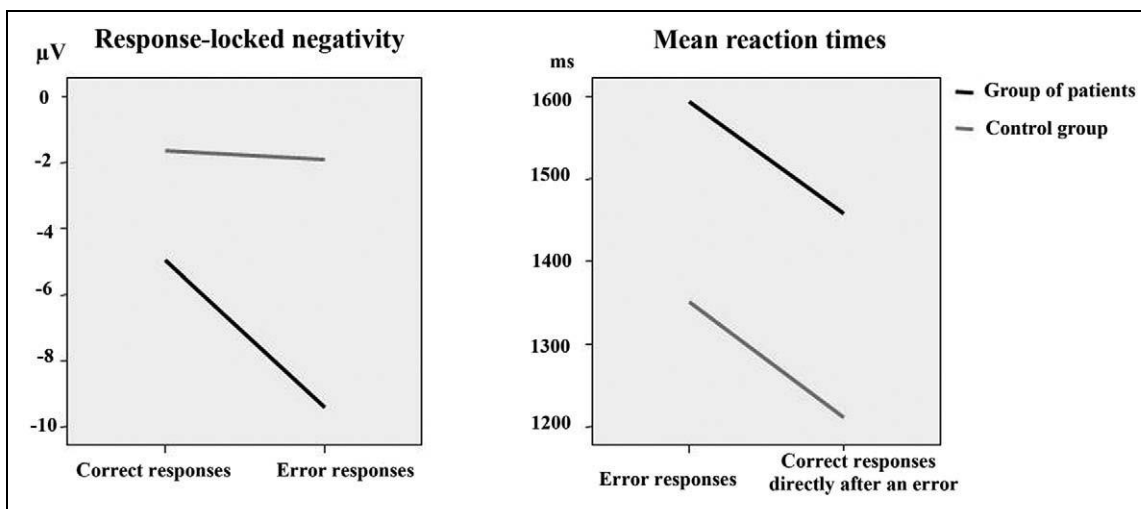


Figure 3. The mean amplitudes of the response-locked negativities together with response adjustment directly after error making of the 2 groups.

According to neuroscience, the more aware of error making, the more pronounced is the peak of the error-related negativity observed directly after the mistake. The left panel shows that the response-locked negativity was more pronounced in the patient group, especially after an error response: the group main effect was  $F_{1,21} = 7.1$ ,  $P < .01$ , and the interaction response type by group was near significance ( $F_{1,21} = 5.2$ ,  $P < .06$ ). Consequently, findings indicate that the patient group was detecting their own errors.

The right panel shows that both patients and controls improved their reaction times directly after error making; that is, responses became faster after an error: the response type effect was  $F_{1,21} = 10.83$ ,  $P < .003$ . This phenomenon was similar in both groups: the group effect was  $F_{2,21} = 2.52$ ,  $P = .13$ , and the group by response type interaction was  $F_{2,21} = 0$ ,  $P = .96$ . In addition, in the patient group, 87% of

the errors were followed by a correct response. In the control group, the percentage was 86. Consequently, the performance improvement after error making was similar in both groups with respect to reaction time speed and reaction time accuracy.

Figure 4 presents the grand-averaged response-locked negativities in both groups. The figure shows 2 negative peaks in the time window of 100 milliseconds after the error response of the group of children with mild spastic cerebral palsy. No such negativity was found in the control group.

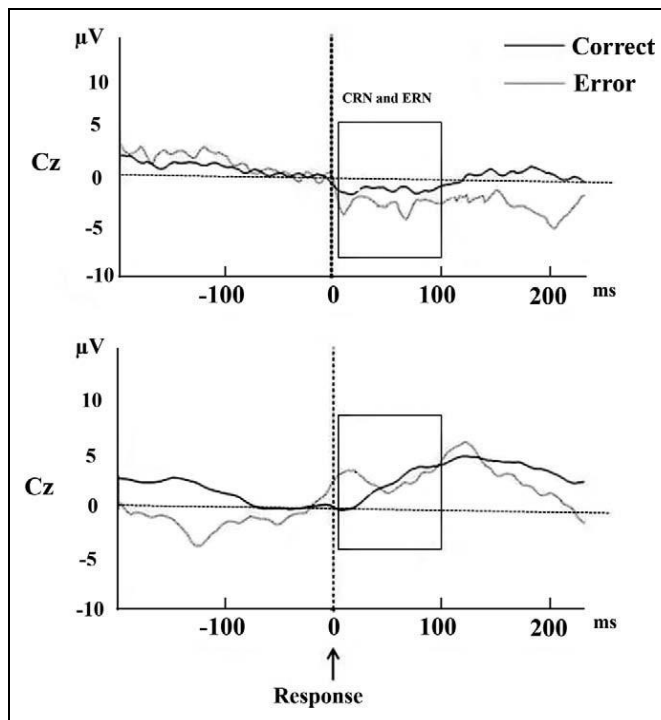


Figure 4. The response-locked grand-averaged waveforms for correct and error responses of the patient group (upper row) and of the control group (lower row).

Note that one methodological problem in exploring error processing is that, in general, the control group is producing fewer errors than the patient group. In addition, the contribution of the individual members per group to the mean average of dependent variables of interest may be skewed. In the present study, on average, 45.7 correct trials and 6.9 error trials per patient were included to calculate the event-related potentials. In the control group, the number of correct trials was 53.9, and the number of error trials was 4.5. Consequently, with respect to mean averages, the contribution of each participant in the study was about the same.

## Discussion

This study addressed the issue of error detection and performance adjustment in order to prevent errors in a subsequent trial in youth with mild spastic cerebral palsy and a peer control group. The



results indicate that, especially in the patient group, error responses were associated with poor motor preparation. However, patients identified their errors, as was reflected by an increase of their error-related negativity potential directly after error making. This error detection was an internal process because external feedback about their performance was not given to the participants. Also, detecting the error led to improvement of future performance in the patient group, as was also the case in the control group. Arriving at this point, it is important to note that a recent study<sup>12</sup> showed that, in normal adults, feedback activates the performance monitoring system and results in a similar reset of brain activity pattern as detecting errors without external feedback. All in all, findings of this modest study suggest that a critical key in learning, that is, error monitoring and subsequent performance adjustment, is intact in the group of patients.

Some researchers suggest that the amplitude of the error negativity is related to error significance rather than error detectability.<sup>13</sup> Since the amplitude of the error negativity was most pronounced in the patient group, findings suggest that they were more sensitive about their error making than the control group. Consequently, a second key in learning might also be intact in the patient group, that is, motivation.

The suggestion of an intact top-down executive function ability (error detection and performance adjustment after error making), together with a compromised motor action system in the patient group (decreased contingent negative variation before error making), fits well with the outcome of 2 earlier event-related potential studies on this population. The first study<sup>14</sup> evaluated the frontal central N2 and the centroparietal P300 complex. It was concluded that orientation toward visual stimuli and evaluation of stimulus novelty are intact in the group of patients. The second study<sup>15</sup> explored the amplitude and latency of the parietal P300 during stimulus recognition. It was concluded that the ability to evaluate and recall complex stimuli is intact in the patient group. The results of the 2 earlier event-related response studies, together with the present outcome, may suggest that slowness of correct responses in youth with mild spastic cerebral palsy is not associated with weak executive function abilities but is probably the result of their compromised motor system.

In summary, in the patient group, patterns of brain activity 500 milliseconds before the presentation of the display set, and hence, before preceding action execution, might be causally responsible for error making, not correcting mechanism after error making. Therefore, in-depth investigation of patterns of brain activity preceding errors is needed to understand the source of error making in youth with mild spastic cerebral palsy. The key question to answer in the near future is why the motor preparation state in the patient group fluctuates from optimal to less optimal, resulting in respectively correct and error responses.

The outcome of the present modest study might challenge the popular poor executive function hypothesis in mild spastic cerebral palsy. The hypothesis is primarily based on research using manual, oral, and eye movements. Cognitive testing of youth with mild spastic cerebral palsy without controlling for motor preparation may lead to wrong conclusions about their cognitive abilities. This point has to be taken into account in future research.

### **Limitation of the Study**

This article presents the data of a small sample of patients with mild spastic cerebral palsy. Using a larger sample, findings await replication. In addition, it has to be tested whether findings hold in other (more severe) subtypes with cerebral palsy.

### **Conclusion**

This modest study suggests that patients with mild spastic cerebral palsy identify errors and adjust their performance to prevent future errors. Error performance is foreshadowed with weak motor preparation.

### **Acknowledgments**

The study was performed at the Department of Pediatric Neurology, Tampere University Hospital, and at the Human Information Processing Laboratory, University of Tampere. The authors thank the parents and children for participating in this study.

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## **CHAPTER 6: Brain state before error making in young patients with mild spastic cerebral palsy**

E. Hakkarainen<sup>1</sup>, S. Pirilä<sup>1,2</sup>, J. Kaartinen<sup>3</sup>, J. J. van der Meere<sup>4</sup>

<sup>1</sup>School of Social Sciences and Humanities, University of Tampere, Tampere, Finland

<sup>2</sup>Department of Pediatrics, Tampere University Hospital, Tampere, Finland

<sup>3</sup>Department of Psychology, University of Jyväskylä, Jyväskylä, Finland

<sup>4</sup>Department of Clinical and Developmental Neuropsychology, University of Groningen, Groningen, The Netherlands

Journal of Child Neurology (2015), 30, 1489-1495

## **Abstract**

In the present experiment, children with mild spastic cerebral palsy and a control group carried out a memory recognition task. The key question was if errors of the patient group are foreshadowed by attention lapses, by weak motor preparation, or by both. Reaction times together with event-related potentials associated with motor preparation (frontal late contingent negative variation), attention (parietal P300), and response evaluation (parietal error-preceding positivity) were investigated in instances where 3 subsequent correct trials preceded an error. The findings indicated that error responses of the patient group are foreshadowed by weak motor preparation in correct trials directly preceding an error.

## **Introduction**

Cerebral palsy is the term used for a group of nonprogressive disorders of movement and posture caused by abnormal development of, or damage to, the motor control centers of the brain.<sup>1</sup> The disorder is caused by events before, during, or after childbirth. The abnormalities of muscle control that define cerebral palsy are often accompanied by other neurological and physical abnormalities such as mental retardation, learning disabilities, behavior disorders, seizure disorders, visual impairment, hearing loss, speech impairment, and abnormal sensation and perception. It is obvious that the severity of the motor disorder together with the amount and nature of comorbidities determines, to a large extent, the quality of life in children with cerebral palsy.<sup>2,3</sup> Whether cerebral palsy is associated with weak executive function abilities is a relevant issue. Broadly defined, executive function skills are the abilities to plan, organize, and manage the complex tasks the authors encounter every day. Strong executive function skills make it possible to live, work, and learn with an appropriate level of independence and competence.

Recent studies show altered performance in executive function tasks in children with cerebral palsy,<sup>4-6</sup> Patients with mild spastic cerebral palsy scored significantly lower than a control group on a planning, attention, and inhibition task,<sup>6</sup> with 30% to 50% of the cases in the clinical range. However, the executive function hypothesis in mild spastic cerebral palsy confined itself to outcomes in reaction time research, and it can therefore be challenged for 2 reasons. First, patients' slow and inaccurate performance on executive function tests might be caused by their compromised motor system, instead of reflecting poor cognitive skills per se. Second, errors and slow reaction times in cognitive tasks are attributed to poor cognitive skills, with poor cognitive skills being marked by the occurrence of errors and slow performance.

All in all, measuring nonmotor functions (here executive function abilities) in motor disordered patients might be complicated, because tests also load motor aspects of the information processing system. As a result, symptoms of executive function deficits can go undiagnosed or misdiagnosed in children with mild spastic cerebral palsy. Using the event-related brain potential methodology in cognitive research on youth with mild spastic cerebral palsy provides 1 route out of the conceptual circularity, because the methodology is apt to break down reaction time performance into a cognitive-related part and a motor-related part.

In their earlier study,<sup>7</sup> the authors investigated reaction time performance in youth with mild spastic cerebral palsy while carrying out a visual stimulus recognition task with increasing complexity. During task execution, 2 event-related brain potentials were registered. The first was the positive parietal P300 amplitude and latency, indexing cognitive processes before motor execution takes place.<sup>8</sup> The second was the amplitude of the frontal late contingent negative variation, also termed the readiness to respond potential or *Bereitschaftspotential*, indexing motor preparation/stimulus anticipation.<sup>9</sup> The findings indicated that the mean correct reaction times of the patient group were slower compared to the control group, which was related to post-P300 processes (ie, motor execution). Patients' cognitive processes related to stimulus intake, stimulus evaluation, and decision making and indexed by the amplitude and the latency of P300 were intact. Besides being slow, patients committed many commission errors, which was associated with poor motor preparation, as indexed by the contingent negative variation before stimulus presentation. Hence, slow and inaccurate performance of the patient group was related to compromised motor processes, not to deficits in cognitive operations.

In a subsequent study,<sup>10</sup> the authors tested whether patients were aware of their error making. To this end, characteristics of the response-locked error-related negativity were examined. This potential peaks about 50 ms after an error response has been executed, and reflects the activity of a neural system involved in action monitoring and error detection.<sup>11</sup> Compared to the control group, it appeared that the peak was more pronounced in the patient group, suggesting that patients spontaneously realized that they have committed an error. This conclusion was validated by a performance analysis indicating that after error making, patients normalized their motor preparation, as indexed by the late negative contingent variation, and improved their reaction time performance.

In sum, the authors' 2 event-related potential studies indicate that poor motor preparation 500 ms before the stimulus presentation is causally responsible for error making in the patient group, not action monitoring or error-detection mechanisms, subserved by the anterior cingulate cortex.<sup>12</sup>

The aim of the present study is to examine the patterns of brain activity preceding errors in the patient and control group. For this purpose, 3 event-related potential components will be examined in

3 successive correct trials before the actual error occurred. The late contingent negative variation indicates motor preparation before stimulus presentation and subsequent actual motor response. It is tested whether poor response preparation in the error trial is foreshadowed in earlier correct trials. Research on adults without cerebral palsy suggest that errors are associated with a significant relative reduction in the amplitude of the preceding P300, indicating a loss of sustained control over action seconds before the error occurs.<sup>12,13</sup> The third physiological manifestation that can foreshadow error making in the patient group is the positive polarity after correct responses preceding errors. The errorpreceding positivity component has been interpreted in terms of a neural index of transient deficiencies of the monitoring system prior to the actual execution of an error.<sup>14,15</sup> Thus it is tested if errors are foreshadowed by weakened responseevaluation processes.

### Methods Study Population

Eleven patients (4 girls) with cerebral palsy (mean = 15 years 0 months, SD = 3 years 6 months, range 9-18 years) participated in the study. All were diagnosed with mild spastic cerebral palsy when they were between the ages of 1 year and 3 years. Brain magnetic resonance imaging data during the first year of life or later were used to check the lesion side. Patients were recruited through the Department of Pediatric Neurology at Tampere University Hospital in Finland. All had experienced peri/neonatal complications. Four patients were born preterm (birth weight < 1500 g) but none had severe visual or hearing impairments, or epilepsy. One child had hydrocephalus. The clinical characteristics of the patient group are shown in Table 1.

Table 1. Group Characteristics.

Patient	FIQ	VIQ	PIQ	GMFCS	MACS	Diagnosis	Lesion site	Prematurity
1	61	71	52	1	1	Diplegia	Bilateral	–
2	94	103	85	3	2	Diplegia	Bilateral	–
3	117	133	100	1	1	Hemiplegia	Bilateral	þ
4	65	80	50	3	2	Hemiplegia	Unilateral	–
5	82	99	65	2	1	Hemiplegia	Bilateral	þ
6	83	89	78	1	1	Diplegia	Bilateral	–
7	77	79	77	1	1	Hemiplegia	Unilateral	–
8	108	100	118	1	3	Hemiplegia	Unilateral	–

9	62	68	56	3	1	Diplegia	Bilateral	þ
10	83	100	68	3	2	Diplegia	Bilateral	–
11	72	80	64	1	1	Diplegia	Bilateral	þ

Abbreviations: FIQ, Full-Scale Intelligence Quotient; GMFCS, Gross Motor Function Classification System (1 = ambulatory, 2 = some limitations in walking, 3 = some assistive devices); MACS, Manual Ability Classification System (1 = average fine motor functionality, 2 = some limitations, 3 = pronounced limitations); PIQ, Performance Intelligence Quotient; VIQ, Verbal Intelligence Quotient. Intelligence was estimated using the Wechsler Intelligence Scale for Children–Third Edition

Twelve control children (6 girls) and adolescents (mean = 14 years 3 months, SD = 2 years 8 months, range 10-18 years) participated. They were recruited from mainstream elementary schools and upper secondary schools in the same city. The 2 groups did not differ significantly with respect to age,  $t(21) = 0.52$ ,  $P = .61$ . The IQs of the control group were not measured, because IQs in the patient group were within a normal range.<sup>16</sup> Data from the same participants have been examined in the authors' earlier studies.<sup>7,10</sup> Informed consent was obtained from all participants. Ethical approval was obtained from the Regional Ethics Committee of Tampere University Hospital.

## Study Design

The participants were seated in front of a monitor, about 80 cm from the screen. A variant of the Sternberg short-term memory scanning paradigm<sup>17</sup> was employed. The task is probably the most used test in clinical, developmental, and psychophysiological research.<sup>18</sup> All stimuli were white letters (consonants only), measuring 1.5 cm on a black background. A memory set was presented of 2 target letters, which the participants had to memorize temporarily. These letters were simultaneously shown on a single row in the center of the screen. Subsequently, a new set of 4 letters was presented, making up a square of 8 X 8 cm. One of the letters of the memory set or neither was presented in this set. A varied mapping procedure was followed: targets and distracters were randomly intermixed over trials.

Participants placed their dominant hand between 2 response buttons. When the target was present in the display set (positive set), participants pressed the yes button (on the left) with their dominant hand. When the target was not present (negative set), participants pressed the no button (on the right) with their dominant hand. The probability that the target was present in the display set was 0.5.



The letters in each trial were randomly selected with the restriction that no letter occurred as a target in 2 consecutive trials and that no more than 3 consecutive positive or negative trials occurred in sequence. In addition, it was ascertained that the frequencies were approximately equal for the target appearing in 1 of the 4 positions of the display set (left up, right up, left down, right down). All participants were presented the same random sequence of memory and display sets.

Starting from the appearance of the display set, participants had 4500 ms to respond. For each response, the interval between the onset of the display set and button-press was measured as the reaction time. The accuracy of the target identification was also recorded, including incorrect responses (button-press errors) and failure to press a button within 4500 ms (error of omission). Precipitate responses (reaction time < 200 ms) were excluded from the analysis. Participants were given a short practice period, which generally lasted about 2 minutes, until they completely understood the task. The experiment, including instruction and practice, lasted about 15 minutes. During the test, the researcher sat out of sight of the participant, and no interaction was allowed.

### **Selection of Trials for Data Analysis**

In the present study, the authors were interested in the 3 successive correct trials before an error (E-3, E-2, and E-1). The sequence of 3 successive correct trials was isolated from an original sequence of 4 correct trials. This was done to ensure that the E-3 trial was not preceded by an erroneous trial.

### **Electrophysiological Measures**

Electroencephalograms (EEG) were recorded by Neuroscan using Ag/AgCl electrodes at 9 electrode sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4). The reference electrodes were placed on the mastoids. Four additional tin electrodes were attached for a bipolar recording of the vertical electrooculogram from above and below the left eye and for the horizontal electrooculogram from the outer canthi of both eyes. Impedances were kept below 5 k $\Omega$  at all electrodes. Digital data together with triggers marking specific events were stored on hard disk for later analysis.

Data were first digitally filtered with a high-pass filter of 0.1 Hz and a low-pass filter of 30 Hz at 12 dB/octave for the errorpreceding positivity and P300 components. For the contingent negative variation, a high-pass filter of 0.01 Hz and a low-pass filter of 30 Hz at 12 dB/octave were employed. For each event-related potential component, the EEG from individual trials was visually inspected and corrected for horizontal and vertical eye movements using the Gratton, Coles, and Donchin algorithm<sup>19</sup> before averaging the epochs.

Contingent negative variation. Data from Fz were epoched into 5700ms segments starting 200 ms before the onset of the memory set. To investigate a change of the wave across the time, a baseline was set at 2500-2600 ms, and an average time window was created at 4400-4500 ms, 100 ms before the onset of the display set.

P300. Only the EEG associated with 3 successive correct trials before an error was analyzed. Signals were epoched offline with a window from 150 ms before to 900 ms after the onset of the display set. All event-related potentials were aligned to a prestimulus baseline of -50 to 0 ms before the onset of the display set. After averaging, components were scored in the event-related potentials based on inspection of the grand-average waveforms. P300 components were identified at Pz for each subject. The mean amplitude of the P300 component was determined over a time interval of 300 to 600 ms poststimulus.

Error-Preceding Positivity. The positive polarity at parietal scalp distribution was measured as a mean voltage from 0 to 150 ms after correct responses in each trial separately. A baseline of -50 to 0 ms before the response was employed.

Figure 1 shows an overview of the time windows of the event-related potentials under study and essential task parameters. It also illustrates that the brain potentials studied do not overlap in time.

Section	M	Warning	D	Mask	M	Warning	D	Mask	M	Warning	D	Mask
Time (ms)	1500	3000	1500	3000								
Component		CNV	P3	EPP								
Trial	E-3				E-2				E-1			

Figure 1. Time windows used to calculate the event-related potentials. Letters M and D denote memory set and display set, respectively.

## Statistical Analyses

Mean reaction times, the contingent negative variation, P300 amplitudes, and the error-preceding positivity were analyzed using a repeated measures ANOVA, with Group (cerebral palsy and control) as the between-subject factor and response type (E-3, E-2, E-1) as the within-subject factor. An alpha level of .05 (2-tailed) was used for all statistical tests. An independent-samples t-test was performed for group comparisons.

## Results

In total, 41 sequences of 3 correct trials before an error were found in the patient group, and 47 in the control group.

### Behavioral Data

The mean accuracy was .81 in the patient group and .88 in the control group. However, the difference between the 2 groups remained nonsignificant ( $t = -1.86$ ,  $P = .08$ ). Mean reaction times for 3 correct trials before an error are presented in Table 2.

Table 2. Mean Reaction Times (RTs) on 3 Correct Trials Before an Error.

Trial	Patient (Mean RT in ms, SD)	Control (Mean RT in ms, SD)
E – 3	1472 (402)	1191 (343)
E – 2	1570 (470)	1349 (449)
E – 1	1545 (524)	1312 (359)

Although the patient group was overall slower, the group effect was not significant,  $F(1, 21) = 2.34$ ,  $P = .14$ . The trial number before error-making effect was  $F(2, 42) = 1.95$ ,  $P = .16$ , indicating no tendency of response speed alterations before error making. The finding was the same in both groups: the interaction of trial number before error making by group was nonsignificant,  $F(2, 42) = .11$ ,  $P = .90$ .

### Contingent Negative Variation

Figure 2 presents the frontal late contingent negative variation 3 trials (E-3), 2 trials (E-2), and 1 trial (E-1) before error making. (Note: Data from 2 control subjects at the E-3 condition were noisy and they were therefore eliminated from the grand average figure.)

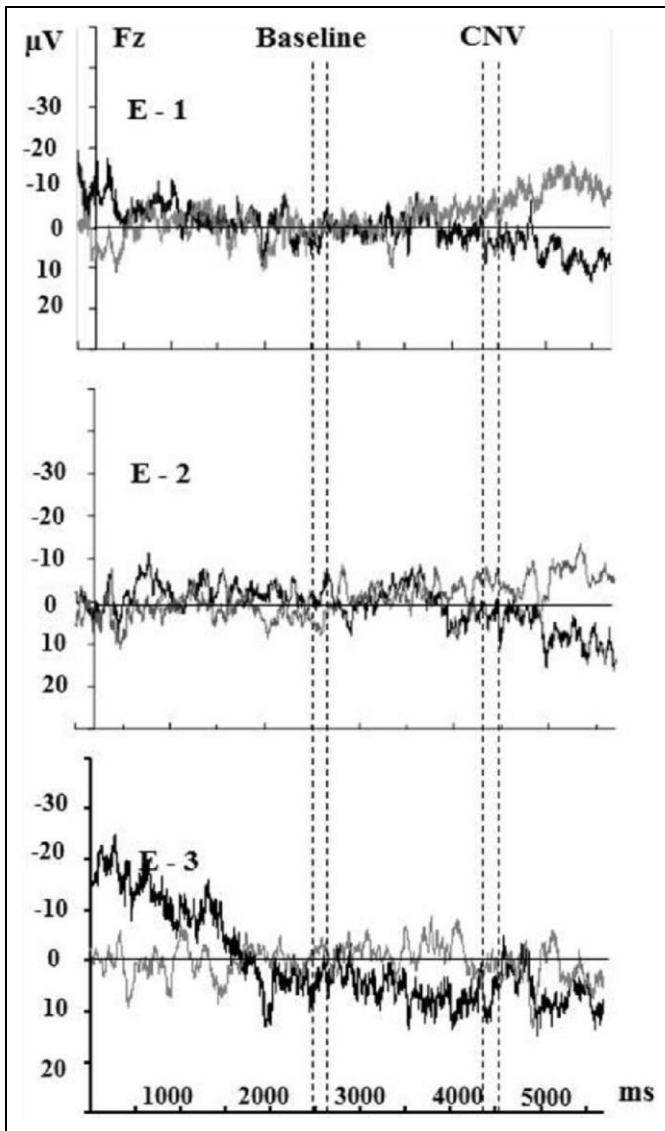


Figure 2. Contingent negative variation at Fz for E-1 (a), E-2 (b), and E-3 (c) conditions in the patient group (black line) and in controls (gray line).

The omnibus test indicated no group differences,  $F(1, 21) = 1.07$ ,  $P = .31$ , no trial number effect before error making,  $F(2, 42) = 0.15$ ,  $P = .86$ , nor a trial number by group effect,  $F(2, 42) = 1.26$ ,  $P = .29$ . However, the figure suggested altered motor preparation in the patient group 1 trial before an error, and a planned comparison with a  $t$  test confirmed that the contingent negative variation component of the patient group was less pronounced in the E-1 condition,  $t(21) = 2.14$ ,  $P = .045$ , indicating weakened motor preparation directly before an error occurred. In addition, the Pearson correlation between contingent negative variation amplitude and accuracy was significant only in the E-1 condition ( $r = -.68$ ,  $P = .001$ ), indicating a connection between motor preparation 1 trial before an error and accuracy.

## P300

Figure 3 shows grand-averaged waveforms for the parietal P300 in the patient group and in the controls.

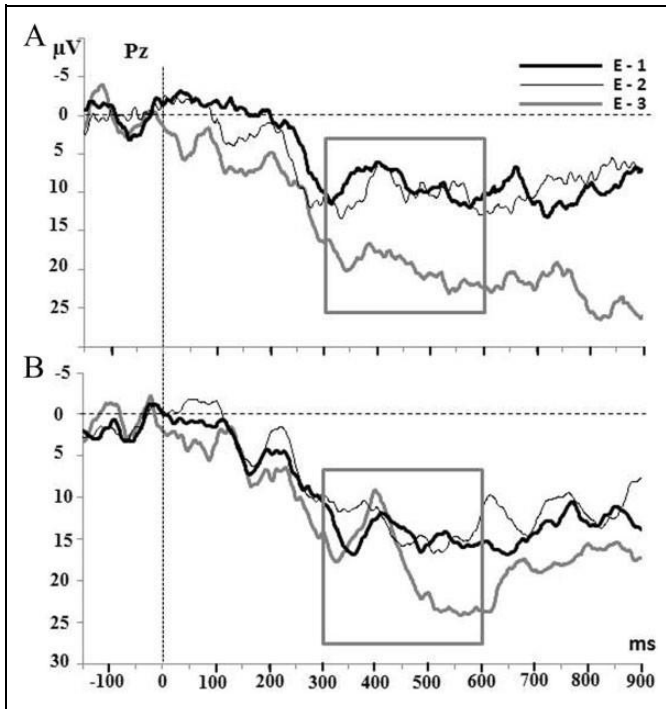


Figure 3. Grand-averaged wave forms for patient group (A) and for controls (B) on 3 correct trials before an error. The gray rectangle shows the time window used for the P300 mean amplitude.

Figure 4 shows the stimulus-locked P300 amplitudes for 3 correct trials before error making (E-3, E-2, and E-1).

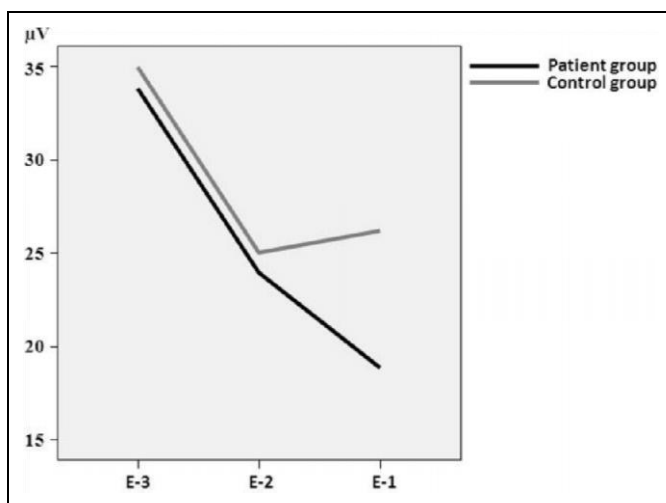


Figure 4. P300 amplitudes on 3 correct trials before an error.

The figure indicates that the P300 amplitude for correct responses diminished significantly before an error occurred: the trial number effect was  $F(2, 42) = 3.68, P = .034$ . This phenomenon was, however, equal for both groups: the group main effect was  $F(1, 21) = 0.15, P = .70$ , and the interaction of trial number before error making by group was  $F(2, 42) = 0.79, P = .46$ . Although the figure suggests a difference between the groups in trial E-1, a planned comparison with a t test indicated no differences,  $t(21) = -1.02, P = .32$ , in P300 amplitude between the groups. Hence, attention lapses before error making as indexed by the P300 amplitude in trials before error making were the same in both groups.

### Error Preceding Positivity

Figure 5 presents the averaged parietal mean values of positivity in 3 correct trials before the error.

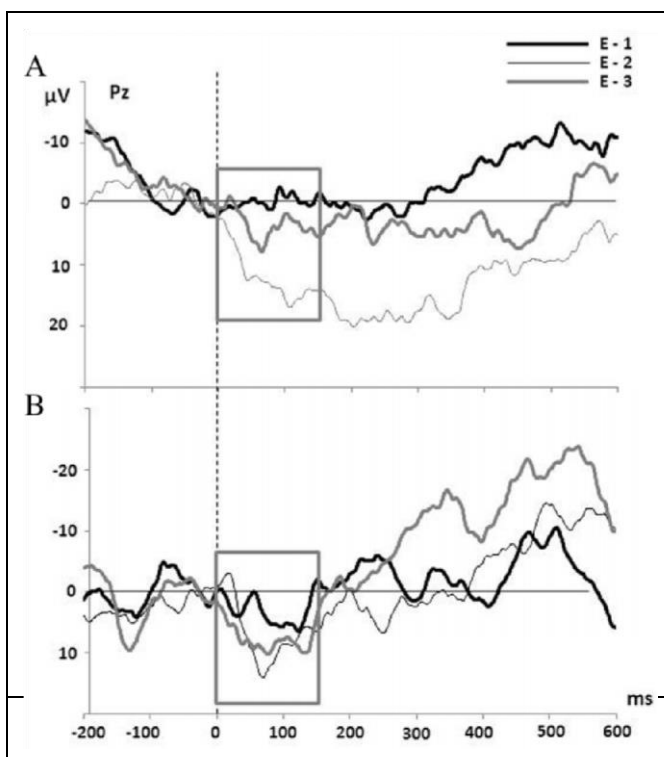


Figure 5. Response-locked components in the patient group (A) and in the control group (B). The vertical dashed lines show the response time, and the gray rectangle shows the time window used for the error-preceding positivity.

There was no number of trial main effect,  $F(2, 42) = 2.05, P = .14$ , or trial number by group effect,  $F(2, 42) = 1.28, P = .29$ , indicating that the response-locked positivity was equal in all 3 error-preceding conditions. Although the figure suggests more positive deflections in the patient group, the group main effect remained nonsignificant,  $F(1, 21) = 0.22, P = .64$ . Neither did a series of planned

comparisons per trial apart indicate any differences between the 2 groups. These results show that the groups did not differ in the quality of performance monitoring before an error occurred.

## Discussion

The results of the present study indicate that exceeded erroneous responses in youth with mild spastic cerebral palsy are, in comparison to the controls, preceded by poor motor preparation already 1 trial before the actual error took place, as indexed by the frontal late contingent negative variation. That is, the motor preparation starts to weaken already before the last correct trial preceding the error. Whether their poor motor preparation mirrors a starting cognitive disengagement, which would indicate an executive failure to monitor,<sup>20</sup> is dependent on the interpretation of the frontal late contingent negative variation, because agreement on the interpretation and source of the frontal late contingent negative variation is far from universal.<sup>21,22</sup> To date, the so-called lateralized readiness potential has been seen to be a more suitable psychophysiological measure for motor preparation free of cognition than late contingent negative variation.<sup>23</sup> However, the lateralized readiness potential is derived from an experimental procedure involving a choice between the 2 hands. In the target group, this choice was not feasible due to the motor limitations of the participants. Furthermore, the results indicate that error making was foreshadowed by a decrease in stimulus evaluation, as indexed by a decrease in the amplitude of the parietal P300, occurring 3 trials before the error trial appeared. However, the patient group did not differ from the control group in this phenomenon. In addition, the groups did not differ in cognitive monitoring control, as indexed by the positivity of the response-locked components for correct responses in the 3 trials before the error trial appeared. Based on these findings the authors can conclude that cognitive operations involved in response monitoring before error making were similar in both groups.

The authors' earlier results<sup>10</sup> indicated that the response-locked negativity after error making was more pronounced in the patient group than it was in the controls. In the present study, a positive response-locked component related to occasional failures of the action monitoring system<sup>14</sup> was similar in both groups. Error-preceding positivity has previously been associated only with trials immediately preceding errors (E-1).<sup>13</sup> The authors' results, however, showed no such specificity. Altogether, the findings indicate high levels of cognitive control before and after error making in the patient group. In spite of these high levels, however, they made more errors of commission.

The authors' research question was inspired by many studies carried out in other domains of clinical field, like Parkinson's disease.<sup>24</sup> Event-related potential components provide useful parameters for cognitive and motor processes when motor execution is impaired. At the electrophysiological level,

the results of the present study provide evidence that the executive function hypothesis in spastic cerebral palsy could be based on a myth. That is, the poor performance on cognitive reaction time test is due to their motor impairments, not cognitive deficits. The outcome of the study by Stadskleiv<sup>25</sup> points into the same direction: when children with cerebral palsy instruct other persons with intact hands to carry out executive function tests they perform like controls.

Taken together, the results suggest that the weakened motor preparation can also be a sign of rivalry between cognitive and motor effort. Because motor control requires more effort in the patient group than it does in the controls, it can induce motor execution decline, as indicated by altered contingent negative variation, but leave the cognitive measures intact. It is certain, however, that perception, decision, and action are closely linked and that more research is needed to disentangle these interacting processes.

### **Limitation of the Study**

The conclusions and interpretations are based on a small sample size and are therefore seen as preliminary. In addition, the results cannot be generalized to patients with more severe forms of cerebral palsy. In the present study, the authors measured event-related potentials and reaction times to study executive functions. In the future, other measures of executive functions could be studied together with psychophysiological measures in children with cerebral palsy.

### **General Conclusion**

The purpose of this study was to investigate whether error making in the target group was associated with poor cognitive abilities. The answer is no. The source of their error making is connected with their compromised motor system, which results in spurts of weak ability to anticipate future events.

### **Acknowledgments**

The study was conducted at Tampere University Hospital, Department of Pediatric Neurology, Tampere, Finland, and at the Human Information Processing Laboratory, University of Tampere, Finland. The authors thank the parents of the children who participated in this study.

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## **CHAPTER 7:**

### **SUMMARY AND GENERAL DISCUSSION**

It has been acknowledged that the interplay between cognitive and motor functions is that intimate, that scores on the traditional neuropsychological tests, including EF tests, are not easy to interpret. Therefore, the ERP methodology was used to explore cognitive performance in youth with mild spastic cerebral palsy. The main aim of the study was to test whether poor reaction time performance is actually partly caused by cognitive deficits in this group of children. The cognitive findings are discussed in the next section.

#### **7.1 Cognitive processing**

In our first study, we were interested in attention orientation and stimulus evaluation in the oddball paradigm where the children were instructed to direct their attention into infrequently presented deviant stimuli in a stream of frequently presented standard stimuli. During the task, no motor effort was required from the participants. We expected to see altered attention allocation in the patient group, since compromised attention allocation is a common finding in clinical studies (Campbell et al., 1986; Gaetz & Bernstein, 2001; Lew et al., 2004). Thus, it was expected that the N2–P300 complex in youth with cerebral palsy would be less pronounced when the phenotype of cerebral palsy is associated with poor attention. The results, however, showed uncompromised attention allocation and stimulus evaluation processes in the patient group. Our negative findings suggest that when no motor effort was required, children with mild spastic cerebral palsy were able to allocate and maintain their attention adequately.

In Study II, stimulus evaluation and decision making in a memory search task was examined. Unlike the first study, the memory search task required overt response to indicate one's decision making. We studied cognitive and motor processing in two memory load conditions, and only ERPs for correct responses were analyzed. Again, the covert indices of these cognitive processes (latency and amplitude of the P300) were intact in children with mild spastic cerebral palsy, whereas reaction times were delayed in comparison to the controls. The study offered an interesting insight to a typical phenomenon often encountered in everyday situations. When cognitive performance is assessed with devices which require motor effort, the results are a combination of these two processes, cognition and motor execution. Consequently, slow reactions are often interpreted as slow information processing. When these processes were examined separately, only

motor execution time differed between the groups. Consequently, we may suggest here that attention allocation directly after stimulus onset was uncompromised in adolescent with mild spastic cerebral palsy.

Since the findings of the Study II were based on the analyses of correct responses, we wanted to explore whether the two groups would differ in cognitive processing when committing an error. In Study III, uncompromised performance monitoring was found in youth with cerebral palsy. This was shown by their pronounced error related negativity.

Although the patient group had intact attention allocation processes on correct trials and their performance monitoring indices were not compromised either, they committed more errors than the controls. Thus, we wanted to find out whether attention allocation in the patient group was compromised *before* error making. In study IV, we investigated attention allocation indexed by P300 amplitude before error making. As expected, we found attention lapses indexed by the decreased P300 amplitude already three correct trials before the actual error took place. This phenomenon, however, was equal in both groups.

In sum, we found no differences in cognitive processing between the patient group and the controls. Next, motor processing in children with cerebral palsy will be discussed.

## 7.2 Motor processing and error making

In all our studies that required overt response (II-IV), reaction times were slower in the patient group. In addition, error responses tended to be slower than correct responses in both groups. Slow overt performance in children with cerebral palsy, however, was not entirely explained by their weak covert motor processing. In Studies II and III, ERPs related to motor processing, namely P2 and contingent negative variation, were equal to those of controls, when correct trials were examined. Nevertheless, fluctuations in motor preparation were characteristic for the patient group, and these fluctuations seemed to be associated to the error making of the patient group. Findings of Study III indicated that erroneous responses of the group with cerebral palsy were associated with weak motor preparation, as indexed by the amplitude of the late contingent negative variation. Further, Study IV showed compromised motor preparation indexed by diminished contingent negative variation already on a trial directly preceding the error trial. Although the discriminating power of CNV has been rather poor in earlier studies (Becker et al., 2004; van Deursen et al., 2009), we managed to find differences between the groups in motor presetting by measuring CNVs in error-free and error-related conditions.

As indicated in Study III, patients were detecting their errors (as indexed by the amplitude of the response-locked negativity) and thus improved their performance in the next trial indexed by shortened reaction times. After error making, individuals typically refocus to the task to prevent future errors by slowing down their performance. On reaction time level, this phenomenon is called post-error slowing. In our study, the participants improved their performance after error making by speeding up their responses directly after an error. Their weakened motor preparation, indexed by late contingent negative variation amplitude, was also normalized in trials immediately following the erroneous responses. Thus, findings of Study III showed that after error making, the adolescents with mild spastic cerebral palsy refocused to the task in an efficient way.

**All in all, results indicate that elementary cognitive processes, as measured in the present set of studies, are intact in children with mild spastic CP. The source of their errors lies in their compromised motor system which becomes already visible on the latest correct response before error making.**

Using ERPs, a small set of studies is available showing that motor planning (Craje et al., 2010), action selection (van Elk et al., 2010), and motor sequence learning (Gofer-Levi et al., 2013) are impaired in people with spastic cerebral palsy. Based on the outcome of the present thesis, the list can be enlarged by compromised motor preparation.

Our general finding that cognitive processes are intact together with a handicapped motor system is perfectly fitting with a recent study carried out by Stadskeiv et al. (2014). Here, children with severe motor impairments guided the so-called partner to perform EF tasks. Using unaffected hands of the other they were able to carry out executive function tasks like planning, monitoring, and impulse control. But of course, the use of language when directing others was delayed.

Now our findings suggest that basic cognitive abilities are intact in children and youth with mild spastic cerebral palsy a major question remains whether it implicates that scores on standardized cognitive tests are inflated in these children. First, we have to admit that there is a huge gap between laboratory tests apt to measure elementary aspects of cognition and tests used in clinical practice. That is to say, one might argue that standardized cognitive tests are more loading on a web of cognitive and motor functions than is the case in the present studies. Put into other words, the cognitive load in our tests might have been too simple to identify cognitive problems in our target group. This said, it must be underlined that the manipulations carried out in our design were difficult enough to identify cognitive problems in other clinical studies using other clinical

populations. For instance, with respect to the oddball paradigm, differences in the N2–P300 complex have been found in patients with sustained traumatic brain injury (Campbell et al., 1986; Lew et al., 2004) and in Parkinson’s patients (Sarıkaya et al., 2014). And, on a variety of stimulus response tasks, differences in P3 amplitude and/or latency have been noted between the controls and groups with attention deficit hyperactivity disorder (ADHD), in adults (Szuromi et al., 2011) and in children (Gow et al., 2012), both in visual and auditory domain (Barry et al., 2003). [*An exception is the study of Samyn et al. (2014) who failed to show group differences in P3 amplitude between typically developing children and children with ADHD, but the authors reported a reduced amplitude of the earlier negative N2 component in children (Samyn et al., 2014) (see also Gow et al., 2012; Missonnier et al., 2013)*]. Also impaired performance monitoring, reflected by reduced response-locked negativities directly after error making, have previously been reported in patients with Parkinson’s disease (Willemsen et al., 2008), in children with ADHD (Samyn et al., 2014), in patients with obsessive-compulsive disorder (Gehring et al., 2000), in heavy drinkers (Smith & Mattick, 2013) and individuals with schizophrenia (Bates et al., 2002; Mathalon et al., 2009; Morris et al., 2006, 2008).

Consequently, when the laboratory manipulations we used are powerful enough to detect cognitive impairments in other clinical groups except ours, we may conclude that at least in mild spastic cerebral palsy, elementary cognitive skills are intact. Thus, it is justified to suggest that the neuromotor disabilities and communication problems in people with cerebral palsy may overshadow their true cognitive potential (Fennell & Dikel, 2001; Pirila et al., 2007; Sabbadini et al., 2001).

All in all, during the past decades, promising efforts have been put forward into combining neuropsychological tests with ERP methodology. Harker and Connolly (2007) list the benefits of assessing cognitive functioning with neuropsychological tests together with ERP methodology. Firstly, they mention the advantage of being able to measure cognitive processes without overt responses. Secondly, they state that the clinicians are already familiar with the neuropsychological outcomes, which facilitates interpretations of the data. The third advantage is the information about neurophysiological mechanisms that mediate performance and cognition during the execution of neuropsychological tests. Using the ERP methodology the outcome of the present thesis may guide future research on CP to learn about characteristics of patients’s cognitive potential.

### 7.3 Clinical implications

About 40 % of children and adolescent with cerebral palsy require support for their learning, and the needs for special education together with psychological follow-up remains a necessity across the school age and adolescent (Majnemer et al. 2013). The knowledge that children with mild spastic cerebral palsy have intact elementary cognitive abilities including the awareness of error making and the willingness to adjust their response speed after error making might be a tool to sharpen the present learning and intervention goals.

For clinicians, our studies offer a preliminary framework to investigate motor and cognitive processes separately in children with cerebral palsy. We measured "on line" processes in the brain when the children completed various cognitive tasks. It seems that children with mild spastic cerebral palsy are struggling with the rivalry between cognitive and motor control. By minimizing motor effort in cognitive assessment, we come closer to estimate the true performance level of these children. This can be achieved by means of computerized tasks assisted with child's own implements. In addition, sufficient time resources are essential to reduce time pressure and thus load on motor control. Any modifications to traditional psychological tests are recommended.

### 7.4 Representativeness of the sample and study limitations

First, the sample size was very small (11 to 14 subjects per group), although typical in many clinical trials. The group of patients studied was a sample of convenience. However, the characteristics of the participants (severity of the motor disorder, impairments in IQ scores, prevalence of comorbidities, and prematurity) represent the overall profile of patients with mild spastic cerebral palsy. Because of the small sample size, the findings must be considered preliminary. This is a pilot study and asks for further research with larger samples.

Second, we used rather simple, although well-established, tasks. The task simplicity has to be considered when interpreting the ERP results (Duncan et al., 2009). In the future, it is necessary to test whether a more complicated task battery would produce differences between the groups in attention allocation, stimulus evaluation, and error processing. Possible alterations in attention in children and youth with cerebral palsy could therefore be detected by using different types of tasks and larger sample sizes.

Third, we limited ourselves in one subtype with two groups of patients, i. e. unilateral and bilateral mild spastic cerebral palsy. For the sake of homogeneity, non-spastic subtypes, such as dystonia or ataxia, were excluded. Our results are confined to the target group only.

## 7.5 General conclusions and study limitations

The results of the present studies suggest that cognitive processes related to attention, stimulus evaluation, and performance monitoring are intact in children with mild spastic cerebral palsy. Motor preparation was equal to the peer controls in correct trials, but deteriorated motor preparation was found in the patient group for erroneous responses. Weak motor preparation in the patient group was visible already one trial before the actual error, indicating slackening of motor control. We concluded that the rivalry between motor and cognitive processing capacities for its part caused the higher error rates in the patient group compared to the controls.

The outcome of our studies might challenge the popular poor executive function hypothesis in mild spastic cerebral palsy. The hypothesis is primarily based on research using manual, oral, and eye movements. Cognitive testing of youth with mild spastic cerebral palsy without controlling for motor preparation may lead to wrong conclusions about their cognitive abilities. This point has to be taken into account in future research.

The main finding of the thesis is not in congruence with the model of Surkar et al. (2015). Surkar and colleagues have proposed a model in which there is a rivalry between cognitive and motor control: when too much resources are allocated to the motor part, as a consequence, too little resources are left for the cognitive part of functioning. Our findings indicate intact elementary cognitive abilities together with compromised motor system. Since the rivalry hypothesis is developed on a set of studies focused on infants with CP, it could be the case that such of tradeoff between cognition and motor capacity becomes less pronounced as time proceeds. This suggestion calls for future research on the developmental trajectory in youth with cerebral palsy.

It can be suggested here that the weakened motor preparation before and during error making in adolescents with cerebral palsy might be a sign of rivalry between cognitive and motor control. Fluctuations in motor control may contribute to motor execution decline but in combination with uncompromised cognitive processing indexed by altered contingent negative variation and constant P3, respectively.

In spite of all the limitations in this thesis, the use of the event related methodology made it possible to explore the momentum where the action is: presetting the system, evaluation of stimulus characteristics, self monitoring, error recognition, and response adjustment. All processes are relevant in learning and seem to be intact in this small patient group.



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## LIST OF ORIGINAL PUBLICATIONS

This thesis consists of the following four publications, which will be referred to by their Roman numerals:

I Hakkarainen, E., Pirilä, S., Kaartinen, J., Eriksson, K., & van der Meere, J. J. (2011). Visual Attention Study in Youth with Spastic Cerebral Palsy Using the Event-Related Potential Method. *Journal of Child Neurology* 26, 1525-1528.

II Hakkarainen, E., Pirilä, S., Kaartinen, J., K., & van der Meere, J. J. (2011). Stimulus Evaluation, Event Preparation, and Motor Action Planning in Young Patients with Mild Spastic Cerebral Palsy: An Event-Related Brain Potential Study. *Journal of Child Neurology* 27, 465-470.

III Hakkarainen, E., Pirilä, S., Kaartinen, J., K., & van der Meere, J. J. (2012). Error Detection and Response Adjustment in Youth with Mild Spastic Cerebral Palsy: An Event-Related Brain Potential Study. *Journal of Child Neurology* 28, 749-754.

IV Hakkarainen, E., Pirilä, S., Kaartinen, J., K., & van der Meere, J. J. (2015). Brain State Before Error Making in Youth with Mild Spastic Cerebral Palsy. *Journal of Child Neurology* 30, 1489-1495.

## Tiivistelmä

CP-oireyhtymän syntyyn johtaa kehittyvissä aivoissa tapahtunut vaurio sikiöaikana, vastasyntyneenä tai varhaislapsuudessa. Liikettä säätelevillä aivoalueilla tapahtunut vaurio aiheuttaa liikuntavamman, johon liittyy usein kognitiivisia häiriöitä. Etenkin tarkkaavuuden, työmuistin ja toiminnan ohjauksen häiriöt ovat tavallisia kliinisiä havaintoja spastisessa CP-vammassa, joka on yleisin alatyyppeistä kaikista tapauksista. Tässä neljän herätevastetutkimuksen sarjassa tarkasteltiin kognitiivista ja motorista prosessointia lievästi spastisilla CP-vammaisilla lapsilla ja nuorilla. Tarkkaavuutta, työmuistia ja toiminnan ohjausta arvioitiin kahden tietokoneella esitetyn tehtävätyypin aikana. Ensimmäinen, nk. oddball-tehtävä ei edellyttänyt motorista ponnistelua. Toinen, viisuaalisen muistin tehtävä edellytti yksinkertaista motorista reagoitua.

Ensimmäisessä (I) tutkimuksessa havaittiin, että tarkkaavuuden perusprosessit (orientaatio ja ärsykkeiden erottelu) eivät poikenneet verrokkihenkilöistä, kun tehtävä ei edellyttänyt motorista reagoitua.

Toisessa (II) tutkimuksessa havaittiin, että CP-vammaisilla lapsilla oli hitaammat reaktioajat ja he tekivät enemmän virheitä ikäverrokkeihin nähden. Herätevasteteiden analysointi kuitenkin osoitti, että ärsykkeiden kognitiivinen prosessointi P3-komponentin voimakkuuden ja ajoituksen perusteella ei poikennut ikäverrokeista. Myöskään motorinen valmistautuminen CNV-komponentin voimakkuudella mitattuna ja motorinen suunnittelu P2-komponentin voimakkuudella ja ajoituksella mitattuna eivät poikenneet verrokeista. Johtopäätöksenä todettiin, että CP-vammaisten lasten motorinen hitaus liittyy motorisen liikkeen toimeenpanon hitauteen.

Kolmannessa (III) tutkimuksessa havaittiin, että CP-vammaisilla lapsilla virheitä edelsi heikentynyt motorinen valmistautuminen CNV-komponentilla mitattuna. CP-vammaiset lapset havaitsivat kuitenkin tekemänsä virheet, mikä tuli ilmi negatiivisena virhekomponenttina heti virheellisen reaktion jälkeen. He myös pystyivät verrokkien tavoin tehokkaasti orientoitumaan tehtävään uudestaan ja parantamaan suoritustaan virheen jälkeen. Johtopäätöksenä todettiin, että virheen jälkeinen prosessointi CP-vammaisilla lapsilla ei poikennut verrokeista.

Neljännessä (IV) tutkimuksessa havaittiin, että heikentynyt ärsykkeen arviointi edelsi virheitä sekä CP-vammaisilla lapsilla että verrokeilla. Lisäksi havaittiin, että toisessa (II) tutkimuksessamme ilmennyt heikentynyt motorinen valmistautuminen ennen virheitä oli nähtävissä jo ennen virhettä edeltävää oikeaa vastausta. Johtopäätöksenä todettiin, että CP-vammaisten lasten heikompi motorinen suoriutuminen liittyy motorisen liikkeen toimeenpanon vaikeuksiin sekä motorisessa valmistautumisessa havaittuihin notkahteluihin.

## Acknowledgements

First I want to thank the Finland's Slot Machine Association for funding the two research projects that enabled these studies.

My sincere thanks are devoted to all the children and their families that participated to these studies. Without your effort, these studies could not be realised.

I want to thank Professor Jaap van der Meere and PhD, neuropsychologist Silja Pirilä, who have spent countless hours for reading, commenting, and writing these studies. I admire your devotion to everything you work with, and I hope that I have learned something about it during these years.

My sincere thanks go to my co-author, PhD Jukka Kaartinen, for sharing his expertise and human mindset to these studies from the very first steps.

I want to thank Professor Timo Ahonen and Professor Jari Hietanen for their expertise and guidance in every critical corner of this path.

I want to thank my foremen Helena Viholainen, Jarno Purtsi and Tomi Kaasinen for their understanding and encouraging attitude towards this thesis.

I thank my co-workers at The Finnish Cerebral Palsy Association and at Niilo Mäki Institute for their great company, good conversations, and many unforgettable funny and inspiring moments during the project years. In addition, my warmest thanks go to the steering groups of our research projects, headed by sosiaalineuvos (Finnish honorary title) Aimo Strömberg.

I want to thank Sini Pälikkö for being so interested in my studies and for all the encouraging words. The long phone calls with you have clarified many questions and I am really grateful for your believe in me when I have had my doubts.

I am grateful for all technical support that I have received from the laboratory technicians at the HIP laboratory in Tampere, and at the University of Jyväskylä. I will always remember your adept and patient approach towards my various questions.

I thank my friends and family for being there and reminding me every day, what is really essential in life. The warmest thanks are devoted to my husband Aki and my children Liine and Arte, who have shared this journey with me.

## **Curriculum Vitae**

Elina Hakkarainen was born in Jämsä (Finland) in 1976. She finished her secondary education in Jämsä high school in 1995. In 2007, she graduated in Adult Education, at the University of Tampere, Finland. In 2009, she graduated in Psychology, at the University of Tampere, Finland. In her Master thesis in Psychology, the effects of vitamin D for information processing in patients with multiple sclerosis were described by using ERP methodology. From 2009 to 2014, she worked in a research project conducted by the Finnish Cerebral Palsy Association. At the same time, she started her PhD studies at The University of Tampere, under supervision of prof. Jari Hietanen from the University of Tampere, and prof. Jaap van der Meere from the University of Groningen. In 2015, Hakkarainen was accepted to the Graduate School of Behavioural and Social Sciences, at the University of Groningen, The Netherlands.