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Johanna Piispala

ATYPICAL ELECTRICAL BRAIN ACTIVITY RELATED TO ATTENTION AND INHIBITORY CONTROL IN CHILDREN WHO STUTTER

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
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OULU UNIVERSITY HOSPITAL

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ATYPICAL ELECTRICAL BRAIN ACTIVITY RELATED TO ATTENTION AND INHIBITORY CONTROL IN CHILDREN WHO STUTTER

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 8 of Oulu University Hospital (Kajaanintie 50), on 1 February 2019, at 12 noon

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Supervised by
Docent Mika Kallio
Professor Eira Jansson-Verkasalo

Reviewed by
Assistant Professor Riikka Möttönen
Associate Professor Paul Sowman

Opponent
Professor Esa Mervaala

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University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

The aim of this study was to discover attention- and inhibitory control-related differences in the electrical activity of the brain in 6- to 9-year-old children who stutter (CWS) compared to typically developed children (TDC). For studies I and II, the study group consisted of 11 CWS (mean age 8.1 years, age range 6.3–9.5 years; all boys) and 19 fluently speaking children (mean age 8.1 years, age range 5.8–9.6 years; 7 girls). In study III, the participants were twelve boys who stutter (mean age 7.97 years, range 6.3–9.5 years) and 12 typically developed, fluently speaking boys (mean age 8.01 years, range 5.8–9.6 years). The CWS were recruited through local speech therapists and special teachers and newspaper advertisements, while controls were recruited from schools and preschools and among families of department staff and friends.

Electroencephalography (EEG) was recorded during a visual Go/Nogo task, which forms a conflict between the pre-potent Go-response and inhibition of response in the Nogo condition, demanding inhibitory control. This EEG data was investigated with conventional event-related potentials (ERP) analysis, potential map and global field power (GFP) analysis and a time-frequency analysis including the periods between tasks.

In the ERP analysis, the CWS had a delayed N2 component in the Go condition and a poorly defined P3 component. The potential maps and GFP waveforms confirmed the findings in the Go condition, but also revealed differences in the Nogo condition, described as a prolonged and excessive N2component and an absent P3 component in the CWS. These results indicate problems in the evaluation and classification of the stimulus and the response preparation and inhibition of the response. In the time-frequency analysis, the CWS showed reduced occipital alpha power in the "resting" or preparatory period between visual stimuli, particularly in the Nogo condition. Therefore, the CWS demonstrate reduced inhibition of the visual cortex in the absence of visual stimuli, which is likely related to problems in attentional gating. This newly discovered lack of occipital alpha modulation indicates elementary differences in the regulation of visual information processing in CWS. These findings support the view of stuttering as part of an extensive brain dysfunction involving also attentional and inhibitory networks.

Keywords: attention, children, electroencephalography, event-related potential, Go/Nogo, Inhibitory control

Piispala, Johanna, Tarkkaavuuteen ja inhibitiokontrolliin liittyvä poikkeava aivojen sähköinen toiminta lapsilla, jotka änkyttävät.

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala

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Tiivistelmä

Tutkimuksen tavoitteena oli tunnistaa tarkkaavuuteen ja inhibitiokontrolliin liittyviä eroja aivojen sähköisessä toiminnassa 6–9-vuotiailla lapsilla, jotka änkyttävät verrattuna tavanomaisesti kehittyviin lapsiin. Osatöissä I ja II koeryhmässä oli 11 änkyttävää lasta (iän keskiarvo 8.1 vuotta, ikäjakauma 6.3–9.5 vuotta) ja verrokkiryhmässä 19 sujuvasti puhuvaa lasta (keskiarvo 8.1 vuotta, jakauma 5.8–9.6 vuotta; 7 tyttöä). Osatyössä III koeryhmässä oli 12 änkyttävää poikaa (keskiarvo 7.97, jakauma 6.3–9.5 vuotta) ja verrokkiryhmässä 12 sujuvasti puhuvaa poikaa (keskiarvo 8.01 vuotta, jakauma 5.8–9.6 vuotta). Koehenkilöitä haettiin puheterapeuttien ja erityisopettajien välityksellä sekä lehti-ilmoituksilla. Verrokkiryhmän osallistujat rekrytoitiin kouluista, esikouluista sekä henkilökunnan ja ystävien perheiden joukosta.

Elektroenkefalografia (EEG) rekisteröitiin visuaalisen Go/Nogo-tehtävän aikana. Tehtävässä ennakoidun Go-vasteen ja Nogo-tilanteessa vaadittavan reaktiosta pidättäytymisen välille syntyvä ristiriita kuormittaa inhibitiokontrollia. EEG-dataa arvioitiin herätevasteiden avulla, tutkimalla jännitekarttojen ja koko pään jännitevaihteluiden eroja sekä käyttämällä aika-taajuusanalyysia, mihin sisältyi myös tehtävien välinen aika.

Herätevasteanalyysissä änkyttävillä lapsilla oli viivästynyt N2-vaste Go-tilanteessa ja huonosti erottuva P3-vaste. Jännitekarttojen ja koko pään jännitevaihteluiden perusteella tämä löydös vahvistui, mutta ryhmät erosivat toisistaan myös Nogo-tilanteessa. Änkyttävillä lapsilla N2-vaste oli pidentynyt ja voimakkaampi ja P3-vaste puuttui. Löydökset viittaavat ongelmiin ärsykkeen arvioinnissa ja luokittelussa sekä reaktion valmistelussa ja inhibitiossa. Aika-taajuusanalyysissa änkyttävillä lapsilla oli okkipitaalialueilla merkittävästi vähemmän alfataajuista toimintaa tehtävien välisen ”lepotilan” tai valmistautumisvaiheen aikana erityisesti Nogo-tilanteessa. Änkyttävillä lapsilla näköaivokuoren inhibitio ärsykkeen puuttuessa on näin ollen heikentynyt, mikä viittaa häiriöön tarkkaavuuden suuntaamisessa. Tämä todettu alfatoiminnan säätelyn puuttuminen ilmentää perustavanlaatuisia eroja näköärsykkeen käsittelyssä änkyttävillä lapsilla. Löydökset tukevat näkemystä änkytyksestä osana laaja-alaista aivojen toiminnan häiriötä, joka käsittää todennäköisesti myös tarkkaavuuteen ja inhibitiokontrolliin liittyviä verkostoja.

Asiasanat: elektroenkefalografia, Go/Nogo, herätevaste, inhibitiokontrolli, lapset, tarkkaavuus, änkytys

To Enni and Senja

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Oulu, November 2018 Johanna Piispala

Abbreviations

ACC	anterior cingulate cortex
AWS	adults who stutter
AD/HD	attention deficit / hyperactivity disorder
BOLD	blood oxygenation level dependent
CNV	contingent negative variation
CPT	continuous performance task
CWS	children who stutter
DAN	dorsal attentional network
DMN	default mode network
EEG	electroencephalography
ERD	event-related desynchronization
ERP	event-related potential
ERS	event-related synchronization
FFT	fast Fourier transformation
fMRI	functional magnetic resonance imaging
FPN	frontoparietal network
G(M)FP	global (main) field power
GMV	grey matter volume
IAF	individual alpha frequency
MEG	magnetoencephalography
MMN	mismatch negativity
MRI	magnetic resonance imaging
PET	positron emission tomography
RT	reaction time
TDC	typically developed children
TMS	transcranial magnetic stimulation
SMA	supplementary motor area
VAN	ventral attentional network
WMV	white matter volume

List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Piispala, J., Kallio, M., Bloigu, R. and Jansson-Verkasalo, E. (2016). Delayed N2 response in Go condition in a visual Go/Nogo ERP study in children who stutter. *J Fluency Disord*, 48, 16-26.

II Piispala, J., Määttä, S., Pääkkönen, A., Bloigu, R., Kallio, M. and Jansson-Verkasalo, E. (2016). Atypical brain activation in children who stutter in a visual Go/Nogo task: An ERP study. *Clin Neurophysiol*, 128(1), 194-203.

III Piispala J., Starck T., Jansson-Verkasalo E., Kallio M. (2018). Decreased occipital alpha oscillation in children who stutter during a visual Go/Nogo task. *Clin Neurophysiol,* 129(9), 1971-1980.

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1 Introduction

Speech is an elemental part of our communication with other people and any predicament in this area affects many aspects of our everyday lives. The main topic of this thesis is developmental stuttering, which is a particular childhood-onset, clinically distinct speech disorder. In stuttering, speech is dysfluent because of repetitions, prolongations and blocks, which affects communication negatively.

It has been estimated that around 5–8% of children stutter at some point in their lives (Månsson et al., 2005; Reilly et al., 2009; see review by Yairi & Ambrose, 2013). Usually, stuttering begins during the time period of the most rapid speech development at around 2–3 years of age, but in most cases the speech dysfluency resolves with age (Howell et al., 2008; Reilly et al., 2009; Yairi & Ambrose, 1999, 2005). However, developmental stuttering persists in some children, more so in boys than girls, and approximately 1% of adults stutter. Stuttering is thus a common speech disorder. Even though the quality of life seems unaffected in the early years of the disorder (de Sonneville-Koedoot et al., 2014; Reilly et al., 2013), it may cause anxiety and afflict school performance, career choices and the quality of life later on (Bloodstein & Bernstein Ratner, 2008; Craig et al., 2009; see review by Guttormsen et al., 2015).

Despite years of research, the exact background of stuttering is still unknown. Current theories suggest that stuttering arises from neurobiological and neurophysiological differences in brain areas mostly related to speech and auditory processing (Giraud et al., 2008; Jansson-Verkasalo et al., 2014; Watkins et al., 2008; for an overview, see review by Alm, 2004). An often proposed mechanism of stuttering is impaired internal timing of the highly coordinated motor sequences involved in speech due to malfunctioning basal ganglia and cortico-striato-thalamo-cortical networks (Alm, 2004; Chang et al., 2016; Etchell et al., 2014). Multiple studies have shown white and grey matter structural as well as functional brain abnormalities both in adults (Beal et al., 2007; Salmelin et al., 2000; Sommer et al., 2002; Watkins et al., 2008) and in children who stutter (CWS) (Beal et al., 2013; Chang et al., 2008; Chang & Zhu, 2013; Chang et al., 2017). Recent studies have also associated stuttering with temperamental factors such as high emotional reactivity (Bloodstein & Bernstein Ratner, 2008; Conture et al., 2006; Eggers et al., 2010; Smith & Weber, 2017) and attention deficits, impulsivity or hyperactivity (Eggers et al., 2012; Eggers & Jansson-Verkasalo, 2017; please see also review by Alm, 2014). In regard to speech, impaired self-regulation could cause dysfluency via increased anxiety and reactivity in speech

situations or the release of premature motor sequences during speech. On the other hand, attentional deficits could lead to poorer motor sequence learning as shown in adults (Smits-Bandstra et al., 2006; see review by Smits-Bandstra & De Nil, 2007), involving also speech.

Attention and inhibitory control of children who stutter (CWS) has previously been studied using questionnaires and behavioral measurements such as reaction time (RT) and errors as indicators in various cognitive tasks. In a questionnaire study, CWS showed poorer inhibitory control (Eggers et al., 2010), and a flanker study revealed atypical attentional orienting (Eggers et al., 2012). CWS also performed more poorly than controls in an auditory set-shifting task (Eggers & Jansson-Verkasalo, 2017). The Go/Nogo paradigm is a commonly used inhibitory control task where the Go-signal calls for a response while the Nogo-signal requires inhibition of the response. In a study employing a visual Go/Nogo task with equiprobable Go/Nogo stimuli, CWS showed atypical inhibitory control indexed by more false alarms, premature responses and difficulties in adjusting their response style after errors (Eggers et al., 2013). Contradictory, some studies have not shown any differences in the inhibitory control of CWS (Anderson & Wagovich, 2010; Eggers et al., 2018).

However, the major problem with the questionnaires and behavioral measurements used in these previous studies is that they only assess the endpoint of a cognitive procedure and in the case of questionnaires, usually rely on caregivers' evaluation. These methods give vague or no information of the actual underlying neural activities leading to the response. For this reason, electroencephalogram (EEG) and event-related potential (ERP) recordings during a Go/Nogo task are often implemented in the study of inhibitory control (Johnstone et al., 2009; Johnstone et al., 2005; Jonkman, 2006; Jonkman et al., 2003; Spronk et al., 2008). EEG and ERP measures have excellent temporal resolution and are therefore good tools for investigating the fast cognitive processes involved in inhibitory control and attentional tasks. In children who stutter, previous EEG and ERP studies are scarce in general, and none exist regarding the brain activity related to inhibitory control and attention.

This thesis intends to evaluate brain activity and behavioral measures of CWS during a visual Go/Nogo task in order to verify differences in attentional and cognitive control abilities. The use of ERP analysis as well as EEG voltage and spectral analysis gives more specific knowledge of the different phases of the cognitive processes from signal classification to response selection and even preparatory processes. In addition, EEG phenomena may show atypical spatial

distribution due to the structural and/or functional brain anomalies discovered earlier in imaging studies (Beal et al., 2013; Chang et al., 2008; Chang & Zhu, 2013; Chang et al., 2017; review by Chang, 2014). Children are of particular interest in the study of the etiology of stuttering because they represent the early years of the disturbance and are thus likely to show less compensatory changes. As the paradigm does not involve speech, abnormalities in this task would demonstrate wider, non-speech related disturbances. This information could affect the therapeutic approach and provide a new aspect on the origin of stuttering.

The thesis consists of a conventional ERP analysis of the main components affected by the Go/Nogo task, an expanded analysis of the task-induced EEG activity over the scalp, and an EEG spectral analysis of the main oscillatory frequencies related to attention and cognitive processing, also including the preparatory phase of the task.

2 Literature review

2.1 Developmental stuttering

Developmental stuttering is a speech disorder where unintentional repetitions, blocks or prolongations render speech dysfluent. Due to the speech dysfluency, communication may be impaired and the dysfluency may cause anxiety and excess stress in speech situations (see review by Guttormsen et al., 2015). Stuttering may have a detrimental effect on the quality of life later in adulthood (Craig et al., 2009; Bloodstein & Bernstein Ratner, 2008) even if not so much in the early years (de Sonneville-Koedoot et al., 2014; Reilly et al., 2013), perhaps due to increasing demands in the social as well as school and work environment with age. This thesis focuses on developmental stuttering, where the onset is in childhood and there is usually no history of brain injury or lesion, in contrast to neurogenic stuttering. Neurogenic stuttering may develop from injury to various parts of the brain and is more common in adults (Theys et al., 2008).

2.1.1 Developmental stuttering prevalence and incidence

Most often developmental stuttering starts during the most rapid phase of speech, language and articulatory development between 2 and 3 years of age, usually before the age of 6 (Buck et al., 2002; Månsson, 2000, 2005; Reilly et al., 2009; Yairi & Ambrose, 2005; see review by Yairi & Ambrose, 2013), although studies using older subjects have also shown higher starting ages (Howell et al., 2008). The lifespan incidence of stuttering is commonly estimated as 5%, depending on the definition of stuttering and the age of the study group. However, if short periods of stuttering are included, the incidence may be higher, over 8% (Månsson et al., 2005; Reilly et al., 2009; see Yairi & Ambrose, 2013).

Early childhood stuttering has high recovery rate within the 3–4 years after its onset or during the first school years (Howell et al., 2008; Reilly et al., 2009; Yairi & Ambrose, 1999, 2005). The prevalence among children varies from around 2.2–2.6% in younger 2- to 5-year-old children (Proctor et al., 2008; Okalidou & Kampanaros, 2001) to prevalence ranges between 0.27–1.14% in adolescents (Boyle et al., 2011; Craig et al., 2002; Van Borsel et al., 2006). According to Yairi & Ambrose, in school-aged children the mean prevalence from nine studies is around 0.8% (Yairi & Ambrose, 2013). Boys are affected more

than girls, but in the youngest age groups male-to-female ratios of prevalence are smaller, approximately 2:1, increasing with age to even 6:1. Persistent developmental stuttering is thus more common in boys (Yairi & Ambrose, 1999; see review by Yairi & Ambrose, 2013).

2.1.2 Etiology and mechanisms of developmental stuttering

Despite advances in research over the last decades, the etiology of developmental stuttering is still unknown. Conture et al. proposed the Communication-Emotional model of stuttering (Conture et al., 2006) in which stuttering is caused by both distal and proximal factors. Genetics and environment are distal factors that affect proximal factors, such as the planning and production of speech and language. In harmony with this model, the multifactorial, dynamic pathways theory suggests that developmental stuttering is caused by neurodevelopmental impairment of the sensorimotor processes of speech production, but the onset, persistence and severity of the speech disturbance is strongly modified by linguistic and emotional factors (Smith and Weber, 2017). These approaches acknowledge the heterogeneous nature of the disorder, with children showing highly variable development on some motor, language or psychosocial skills

Most likely there are subgroups with different distal factors or etiologies of the neurodevelopmental defects, perhaps so that persistent and recovering stuttering diverge, which could also explain the gender ratio (see review by Alm, 2004). In some families there is evidence of inborn genetic factors (Viswanath et al., 2004; Kraft &Yairi, 2012; Drayna & Kang, 2011; Kang & Drayna, 2012). On the other hand, in some children who stutter perinatal and birth-associated complications and subtle hypoxic-ischemic events have been proposed as possible causes of basal ganglia and dopaminergic system injury and stuttering (Alm & Risberg, 2007; review by Mawson et al., 2016). The effects of these injuries would be most visible during the physiological plateau of brain metabolism at around 3 years of age, which could explain the peak age of stuttering onset (Alm, 2004; Mawson et al., 2016).

There are various proposed mechanisms of how and why stuttering occurs. In stuttering, external rhythmic conditions, such as the use of a metronome, chorus speech, singing or altered auditory feedback, can improve fluency drastically (Bloodstein & Bernstein Ratner, 2008). These findings have led to the internal timing-hypothesis of stuttering (see Alm, 2004). Normally, speech is composed of a series of motor sub-movements tied together in a rhythmic sequence and paced

by the basal ganglia via the supplementary motor area (SMA). In stuttering, this internal timing is deficient, causing disruption of the speech flow through rhythm perception and speech sequence difficulties. However, providing external timing, e.g. chorus speech, can bypass this defect and result in fluency. Supporting this hypothesis, many recent studies on children have connected developmental stuttering to malfunctioning basal ganglia and internal timing networks of the brain (Chang et al., 2016; Etchell et al., 2014; Wieland et al., 2017). The effects extend beyond speech as the learning of motor sequences seems compromised not only in speech (Smits-Bandstra & De Nil, 2009) but in other motor tasks, too (Smits-Bandstra et al., 2006; see also review by Smits-Bandstra & De Nil, 2007).

Additionally, many studies have associated constant or biological temperamental factors and traits with stuttering. Smith and Weber suggested that the course and development of the speech disorder is conditioned by emotional aspects (Smith &Weber, 2017). Emotional reactivity and self-regulation influence the way in which children react to and manage speech disruptions (Conture et al., 2006; Bloodstein & Bernstein Ratner, 2008; Ntourou et al., 2013). Innate temperamental factors, such as higher impulsivity and reduced inhibitory control, may cause heightened reactivity to moments of speech dysfluency, which may then increase the level of disruption and in turn trigger more reactivity. Children who stutter may also show inattention, impulsivity, excessive motor activity and learning problems or delayed motor development similarly to Attention-Deficit/Hyperactivity Disorder (ADHD) (Conture et al., 2006; Eggers et al., 2010; see review by Alm, 2014). As increased attention and deautomatization of speech (and speech motor movements) may increase fluency in harmony with the internal timing -hypothesis (see Alm, 2004), defective attentional abilities may corrupt the use of such coping mechanisms. On the other hand, reduced executive control may allow the premature release of speech segments, leading to poorer pacing of speech.

However, these temperamental features are not consistent and may be characteristic of certain subgroups, perhaps so that stuttering due to subtle brain lesions would involve more concomitant neuropsychiatric symptoms than hereditary cases (Alm & Risberg, 2007; see review by Alm, 2014). This thesis focuses on the self-regulation and particularly on the attentional and inhibitory control aspects in developmental stuttering.

2.1.3 Structural and functional brain abnormalities in stuttering

Multiple imaging studies using magnetic resonance imaging (MRI), positron emission tomography (PET) or transcranial magnetic stimulation (TMS) have shown structural and functional brain abnormalities both in adults who stutter (AWS) (Beal et al., 2007; Belyk et al., 2015; Brown et al., 2005; Budde et al., 2014; Chang et al., 2009; Giraud et al., 2008; Neef et al., 2018; Preibisch et al., 2003; Salmelin et al., 2000; Sommer et al. 2002; Sowman et al., 2017; Watkins et al., 2008; see review by Etchell et al., 2017) and in children who stutter (CWS) (Beal et al., 2013; Chang et al., 2008; Chang & Zhu, 2013; Chang et al., 2017; review by Chang, 2014).

The location of the functional or structural anomalies has diverged between studies. However, there is usually abnormal lateralization. In vocal tasks with fMRI or PET imaging, hypo-activation and/or structural anomalies are frequently seen in speech-related areas in the left hemisphere along with simultaneous over-activation of right-sided areas such as right frontal operculum and pre-SMA (Belyk et al., 2015; Budde et al., 2014; Brown et al., 2005; Chang et al., 2011; Preibisch et al., 2003). Similar atypical distribution of brain activity has also been shown in non-speech motor studies using TMS (Alm et al., 2013; Neef et al., 2011; see also reviews by Neef et al., 2015 and Busan et al., 2017); AWS show higher motor thresholds or reduced excitability in left motor areas. Many recent studies have implicated atypical connective white matter tracts between auditory and motor areas rather than specific cortical areas in adults who stutter (Cai et al., 2014; Civier et al., 2015; Connally et al., 2014; Kronfeld-Duenias et al., 2016; Kronfeld-Duenias et al., 2018; Neef et al., 2015).

In studies on children there is also evidence of atypical white matter tracts between auditory and motor cortices or between hemispheres (Chang et al., 2015; Chow & Chang, 2017; Misaghi et al., 2018) along with grey and white matter volume abnormalities (Chang et al., 2008; Beal et al., 2013). Interestingly, CWS have also shown reduced volume of the caudate nucleus of the basal ganglia on the right (Foundas et al., 2013). In conclusion, studies have reported reduced GMV and WMV mostly in the left hemisphere and decreased connectivity within the left hemisphere or between hemispheres, although the right-left asymmetry is not significant as in adults. The right-sided over-activity or increased grey and white matter volume in AWS could therefore at least partially be a consequence of compensation of left-sided defects, as also proposed by Neef et al. (2018) and Sowman et al. (2014).

Besides structural differences or due to them, the functional brain networks may be affected. Functional networks consist of spatially separate brain regions that show temporally correlated task- or rest-related activity. In AWS, one study implemented a simultaneous motor Go/Nogo task and fMRI and discovered atypical network activation involving the basal ganglia during the preparation of the task in adults who stutter (Metzger et al., 2018). FMRI-studies in CWS have shown attenuated left-sided structural and functional connections between auditory-motor and cortical-basal ganglia areas (Chang &Zhu, 2013) and reduced functional connectivity in the putamen-motor-auditory network related to rhythm discrimination (Chang et al., 2016).

Many of these structural and functional anomalies correlate well with the internal timing deficit hypothesis and could explain disturbances in speech production through delays in planning, execution and coordination of speech motor sequences. However, these weakened connections may also disrupt the balanced feedback system between sensory and motor areas, for example the bi-directional regulation of the articulatory motor and auditory systems needed in speech perception (Liebenthal &Möttönen, 2017). Additionally, a recent large fMRI study in CWS described abnormalities in the connectivity of multiple functional networks related to attention and executive control (Chang et al., 2017). In children, these abnormalities predicted persistent stuttering. Since similar widespread changes in functional network connectivity have been demonstrated in adults who stutter (Qiao et al., 2017; Xuan et al., 2012), it seems to be a constant abnormality. The balance between these various brain networks is crucial for executive control and attention (Corbetta et al., 2008; Fox et al., 2005; Raichle, 2015; Stevens et al., 2007). Furthermore, some of the discovered brain differences in CWS and AWS overlap structures related to inhibitory control (Steele et al., 2013; for an overview, see Chambers et al., 2009). These wide-spread abnormalities in brain networks and structure are therefore likely to affect not only speech but also cognitive functions, such as inhibitory control and attention.

2.2 Stuttering, attention and inhibitory control

2.2.1 Attention and inhibitory control

As proposed by Posner and Petersen, attentional systems can be divided into three subsystems that operate via individual networks (Posner & Petersen, 1990). The

vigilance network is responsible for maintaining alertness while the orienting network selects essential information from the stream produced by sensory systems. The executive control system provides top-down control, which is needed e.g. when deciding between conflicting responses. These attentional components operate through interacting functional brain networks (Visintin et al., 2015; Xuan et al., 2016; see review by Petersen & Posner, 2012). In this thesis, the main focus is on executive control although the orienting and vigilance networks are also engaged to some extent throughout any task.

Inhibitory control is part of executive control and it is defined as the ability to suppress, interrupt or delay an inappropriate response (Rothbart, 1989), or the ability to ignore irrelevant information (Rothbart & Posner, 1985). Inhibitory control is essential in the regulation of impulsivity and enables focused attention on relevant stimuli and as a result, accurate responses (Eggers & Jansson-Verkasalo, 2017; Rothbart, 1989; Rothbart & Posner, 1985). Self-regulatory processes, such as inhibitory control and effortful control of attention, modulate reactivity (Rothbart, 1989). Reactivity may involve somatic, autonomic, cognitive and neuro-endocrine responses to internal and external stimuli. Some constant biological personality traits in an individual, or aspects of temperament, can be described via tendencies of reactivity or self-regulation, such as the level of attention and inhibitory control.

2.2.2 Self-regulation in children who stutter

The role of temperament dimensions in stuttering has been examined by psychological questionnaires for children and their parents as well as various cognitive tasks (for an overview, see reviews by Jones et al., 2014 and Alm, 2014). In general, questionnaires on temperament traits in CWS have not shown higher level of anxiety or shyness although anxiety is commonly reported in adults who stutter. Instead, some CWS have showed traits typical for ADHD, such as inattention and impulsivity or hyperactivity (see review by Alm, 2014).

Eggers et al. (2010) used a questionnaire and found that CWS differed significantly from the controls by scoring lower on scales of Inhibitory Control and Attentional Shifting and higher on Anger/Frustration, Approach and Motor Activation (Eggers et al., 2010). Another study by Eggers et al. (2012) found attention orientation deficiency in a cued flanker test in CWS (Eggers et al., 2012). Therefore they suggested a role for poorly functioning attentional processes in developmental stuttering, although overt performance as RT and accuracy did not

differ between groups. Quite recently, in an auditory set-shifting task the CWS committed more errors than controls both in the Attentional set-shifting and Inhibitory control settings (Eggers & Jansson-Verkasalo, 2017). Inhibitory control in CWS seemed atypical also in a visual Go/Nogo task since the CWS showed more false alarms, premature responses and difficulties in adapting their response style when compared to controls (Eggers et al., 2013). However, the findings regarding inhibitory abilities in CWS are not consistent as some studies have shown contrary findings in questionnaires (Anderson & Wagovich, 2010) or e.g. the Stop signal task with behavioral measures (Eggers et al., 2018).

2.2.3 The Go/Nogo paradigm

The Go/Nogo paradigm is an inhibitory control task where a stimulus requires either a response (Go) or withholding the response (Nogo). Go and Nogo stimuli may be equiprobable, or the Nogo stimuli may be fewer and infrequent, increasing the pressure towards a Go response and inhibitory control demands (for an overview, see Huster et al., 2013). The Go/Nogo task is believed to address mainly the attentional control of response inhibition, i.e. inhibitory control while for example another frequently used inhibitory paradigm, the Stop-signal task, measures the ability to inhibit an already initiated response (Krämer et al., 2013; for an overview, see Bari & Robbins, 2013). Compared to questionnaires, laboratory tasks such as the Go/Nogo task give a more objective view of the inhibitory control.

Performance in the task can be assessed by using behavioral measures such as reaction time (RT) or amount of errors. These measures are highly influenced by task parameters, such as stimulus probability or stimulus interval. Error rates usually increase by task difficulty and decrease by practice, but particularly so when the task demands are on an optimal level between too high or too low difficulty (Benikos et al., 2013a, 2013b). Reaction time, on the other hand, decreases with shorter inter-stimulus intervals and lengthens when there is less time pressure, often indicating a speed-accuracy trade-off (Benikos et al., 2013a, 2013b). In the study of inhibition, poorer inhibitory control could be seen as more Nogo errors. Increased impulsivity could induce premature Go responses or a shortened RT to Go stimuli. These measures are, however, quite imprecise and do not give much information of the actual cognitive processes during the task. Therefore the Go/Nogo task is frequently combined with the simultaneous recording of electrical brain activity with electroencephalography (EEG) and

event-related potentials (ERP). Regarding inhibitory control or impulsivity, questionnaires, behavioral measures and ERP components measure partially different aspects. Therefore their correlation is not always consistent (Bari & Robbins, 2013; Shen et al., 2014; see also review by Huster et al., 2013).

2.3 Electrical activity of the brain related to attention and inhibitory control

2.3.1 Electroencephalography (EEG)

EEG measures the summed extracellular field potentials produced by the postsynaptic activity of neurons and glia cells of the brain. Across brain layers and the cortex, the spatial arrangement and orientation of the synapses varies, causing phase reversals and opposite potentials, and the conductivity of different tissues of the head is not homogeneous (Speckmann et al., 2010). This causes significant reduction of the recorded field potential amplitude at the scalp level. Thus the EEG recorded on the scalp only shows the synchronous activity of multiple parallel neurons and is more sensitive to radial sources than tangential sources of the brain. The solution of the inverse problem, e.g. locating the intracerebral source of a scalp potential, is therefore just an estimation of the real location (Fisch et al., 2010). Varying source strength may also confound scalp distribution and the localizing of actual neural generators (McCarthy &Wood, 1985). For this reason, the spatial resolution of EEG is rather poor. However, the temporal resolution of EEG is good as the electrical activity changes related to brain activities can be measured by milliseconds. In the study of stuttering the temporal aspect is particularly important since according to current theories, the problems lie within fast-acting functional connections and the continuous interaction of sensorimotor brain areas and the basal ganglia (Alm, 2004; Chang et al., 2016; Etchell et al., 2014).

2.3.2 Event-related potentials (ERP) in the Go/Nogo task

Various cognitive and motor tasks induce task-related electrical activity in the brain. These event-related potentials (ERP) are usually very small and may not be easily distinguished from the background EEG in a single trial. Traditionally and in most clinical ERP applications, averaging of many trials eventually cancels

out the more random EEG oscillation, while the time-locked activity is enhanced and becomes visible. The averaging can be performed by triggering to the stimulus or the response in order to detect stimulus-related or response-related processes (Näätänen, 1992; for an overview, see Luck, 2005). However, also single-trial EEG phase and power dynamics analyses have been increasingly used in cognitive research in a pursuit to better understand the less phase- or time-locked task-specific activity (Alba et al., 2007; Yamanaka & Yamamoto, 2010).

The event-related (ERP) waveform contains multiple successive and sometimes overlapping positive (P) and negative (N) components. The deflections or peaks are usually named by their polarity and either latency, their serial order or cognitive meaning (Näätänen, 1992). In the research of attentional processes with the visual Go/Nogo paradigms, commonly found ERP components are called N1, P2, N2 and P3 (Jonkman et al., 2003; Luck, 2005). The N1 and P2 peaks are early exogenous evoked responses to a stimulus (Johnstone et al., 2007; Jonkman et al., 2003; Jonkman, 2006). They are usually seen between 90–200 ms (N1) and 180–270 ms (P2) post-stimulus in visual Go/Nogo tasks among 6- to 12-year-old children (Johnstone et al., 2007; Jonkman et al., 2003; Jonkman, 2006).

The main ERP components modulated by the Go/Nogo paradigm are N2 and P3. In studies on children between 6 and 12 years of age their latencies vary between 200–400 ms (N2) and 250–650 ms (P3) post-stimulus depending on the paradigm (Johnstone et al., 2007; Jonkman et al., 2003; Jonkman, 2006). These components are usually enhanced in Nogo compared to the Go condition (the Nogo effect) (Donkers & Van Boxtel, 2004; Falkenstein et al., 1999; Jonkman et al., 2003; Jonkman, 2006). Task parameters such as Go/Nogo stimulus ratio, stimulus interval and use of cues further modify the ERP components. Therefore these components do not reflect only the inhibitory control, but are also influenced by attentional abilities. In addition, they are affected by age, more precisely the maturation of the brain networks and consequently the decision-making processes (Brydges et al., 2013; Johnstone et al., 2005; see also review by Huster et al. 2013).

N2 component

The N2 component has a maximum fronto-parietally and according to developmental studies, the topography becomes more frontally distributed with age (Brydges et al., 2013). The N2 is largest in younger children and diminishes linearly with age from 6 to 10 years (Jonkman et al., 2006), until reaching a

plateau in adulthood (Johnstone et al., 2005). The N2 is enhanced in the Nogo condition compared to Go (Nogo effect) in children, but the effect is reduced by age, and the opposite is true in late adulthood (Johnstone et al., 2005). The latency of N2 is also shortened by age (Brydges et al., 2013; Johnstone et al., 2007; Jonkman, 2006).

The N2 component is usually considered either a marker for inhibition (Falkenstein et al., 1999; Gonzales-Rosa et al., 2013; Pliszka et al., 2000) or conflict monitoring (Donkers et al., 2004; Randall & Smith, 2011; Smith, 2011; review van Veen 2002 & Carter). The N2 component has been linked to inhibitory performance in both Go/Nogo (Falkenstein et al., 1999) and Stop Signal paradigm (Pliszka et al., 2000) with higher amplitude and faster latency in successful Nogo or Stop trials. However, the N2 has also been shown to increase in paradigms not demanding inhibition, but where conflict between response choices arises, for example when using valid and invalid cues in a Go Nogo task (Randall & Smith, 2011). In agreement with this view, recent data showed a rather clear novelty effect particularly in N2, as both infrequent Go and Nogo conditions evoked similar N2 components (Albert et al., 2013). Nevertheless, the N2 may also represent response selection (Gajewski et al., 2008) or stimulus categorization to Go (and the need to respond) or Nogo (the need to inhibit response) (Barry & De Blasio, 2013). Some studies have identified N2 subcomponents that are activated differently depending on the task manipulation regarding visual mismatch, conflict or response inhibition, thus explaining the diverse results (Kropotov et al., 2011; for an overview, see also Folstein & Van Petten, 2008).

By using source localization of ERPs the N2 component generators have frequently been situated at the anterior cingulate cortex (ACC) (Bekker et al., 2005; Jonkman et al., 2007; Nieuwenhuis et al., 2004). The activation of the ACC is associated with self-regulation processes such as conflict monitoring, response selection and outcome evaluation (Botvinick et al., 2004; for an overview see van Veen & Carter, 2002).

P3 component

The research on the P3 component has been intensive using various paradigms, but the neural correlates of the P3 components are still somewhat unclear. The P3 can be divided into separate, individually behaving subcomponents. Because these components have different topography in Go and Nogo they probably have separate neural generators and reflect unique cognitive processes (Bokura et al.,

2001; Gajewski et al., 2010; Gonzales-Rosa et al., 2013; Tekok-Kilic et al., 2001; for an overview, see review by Polich 2007).

The Go P3 in a Go/Nogo paradigm most likely indicates the same processes as the classic P3b seen in the frequently used oddball paradigm (Barry & Rushby, 2006; see also Polich, 2007). The P3b component has been associated with target orienting, stimulus evaluation and classification (see reviews by Linden, 2005; Picton, 1992), response selection (Gonzales-Rosa et al., 2013) or a monitoring process from stimulus discrimination to response selection and possibly memory updating (Verleger et al., 2005). The P3 amplitude is modulated by the task relevance, inter-stimulus interval and stimulus probability. It is increased when more resources can be allocated to the stimulus processing and reduced when the task is more demanding or the inter-stimulus interval is short (see reviews by Polich, 2007 and Picton, 1992). On the other hand, the latency of the P3 component in the Go condition might reflect stimulus evaluation and discrimination time (for an overview, see Polich, 2007) but also response selection and response program retrieval processes (Leuthold &Sommer, 1998). The Go P3 amplitude is maximal in centro-parietal regions in adults (Barry & De Blasio, 2013; Bokura et al., 2001; Tekok-Kilic et al., 2001) and children (Barry et al., 2014).

In contrast, the P3 component seen and enhanced in the Nogo condition is maximal fronto-centrally (Bokura et al., 2001; Johnstone et al. 2007; Jonkman, 2006; Smith, 2011; Tekok-Kilic et al., 2001). In developmental studies, the Nogo P3 component becomes prominent rather late, from 9 years of age, and it grows linearly with age along with more efficient inhibition in behavioral tests (Johnstone et al., 2007; Jonkman, 2006; Spronk et al., 2008). The Nogo P3 may represent the same activation as the P3a or novelty P3 in the frontal lobe area seen in oddball paradigms (see review by Polich, 2007). There is evidence of a context-monitoring role of the P3 in a Stop signal task; the P3 was more enhanced when conflict was increased even without stopping, compared to the simple motor stopping (Nogo) situation (Chatham et al., 2011). Interestingly, another Stop signal study in normal adults showed a correlation between higher self-reported impulsivity and inattention and a diminished P3 component in successful Stop trials (Shen et al., 2013). Regarding its role in inhibition, many studies have supported the theory of the Nogo P3 as a specific marker of the inhibition process (Albert et al., 2013; Donkers &Van Boxtel, 2004; Smith et al., 2006; Smith et al., 2013). In contrast to Chatham et al. (2011), the Nogo P3 in a Go/Nogo task has been proposed to arise from motor deactivation related positivity that is

associated with inhibition (Smith et al., 2013). In the study by Smith et al. (2013), ERPs and fMRI were combined to a complex Go/Nogo task with either motor or silent count responses. During successful Nogo condition the Nogo P3 was more enhanced in the motor versus the non-motor inhibition task, although no response was required in either condition. In Go condition the P3 did not differ between motor and count situations. The fMRI showed deactivation of a network of motor related regions during the motor inhibition task, more on the left side. Therefore, Smith et al. inferred that the Nogo P3 in a motor inhibition task results from active motor suppression.

The Nogo P3 component generators in inhibitory tasks have usually been located in the right frontal lobe (Enriquez-Geppert et al., 2010; Kropotov et al., 2011; Strik et al., 1998), particularly the inferior-frontal cortex and the supplementary motor cortex. However, inhibition-related activity in visual tasks spreads over a wide frontal and fronto-parietal network in both hemispheres and even temporo-parietal regions (Jamadar et al., 2010; Steele et al., 2013; please see also review by Huster et al., 2013).

2.3.3 Oscillatory activity of the brain

As first shown by Hans Berger, the ongoing electric activity of the human brain is oscillatory by nature (Berger, 1929). Brain oscillation is traditionally divided into many different frequencies, usually delta range (below 4 Hz), theta (4–7 or 4–7.5 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (over 30 Hz) (Amzica & Lopes Da Silva, 2010), although their definitions, particularly the upper limit of theta, vary across studies. The relation, magnitude and predominance of these frequencies vary depending on age, state of arousal and cognitive demands as well as anatomical brain area. These oscillations mediate information between separate brain areas and coordinate neural activity in cognitive processes. The amount and distribution of the oscillations as well as responses to a stimulus, task or other condition can be examined visually, as is usually done in the clinical context, but also by time-frequency analysis of the oscillations. Of these frequency bands, particularly the alpha but also theta oscillations play an essential role in attention and inhibitory control.

2.3.4 Alpha oscillation, attention and inhibitory control

Alpha-band oscillation is the most prevalent rhythm in the human brain (Berger, 1929; Klimesch, 1999; Klimesch, 2012), often with a main frequency of 10 Hz (Klimesch, 2012). Alpha range activity can be seen throughout the brain, but during relaxed wakefulness, occipitally prominent alpha activity is a classic feature in human EEG. Distinct occipital background activity can already be seen from around 4–6 months of age, but with slower, delta- and theta-range frequency. The dominant frequency gradually increases with age, reaching alpha limits usually from the age of 6–7 years (Riviello et al., 2010), although the peak alpha frequency continues to rise even to early adolescence (Cragg et al., 2011). On the other hand, the background alpha is replaced by slower theta oscillation physiologically during drowsiness and light sleep as well as in many neurological disorders.

Based on human and animal studies, these background alpha and theta oscillations are produced in the visual cortex, but can also be recorded in the thalamus (Amzica & Lopes Da Silva, 2010), a central structure containing relays of sensory and motor pathways, including those to and from the basal ganglia. The prevalent background alpha and theta oscillations are regulated by thalamo-cortical and cortico-cortical loops (Hughes et al., 2004; Lopes da Silva et al., 1973; Lopes da Silva et al., 1980; Suffczynski et al., 2001; see also reviews by Hughes & Crunelli, 2005, 2007).

Alpha modulation is a regular occurrence in response to tasks or when preparing for a task. Desynchronization of alpha oscillation (event-related desynchronization, ERD) is generally seen in brain areas that actively process task-relevant, attended information while task-irrelevant areas show synchronization (ERS) or increase of amplitude (Pfurtscheller, 1992; see reviews by Frey et al., 2015; Klimesch, 2012; Neuper & Pfurtscheller, 2001; Pfurtscheller & Lopes da Silva, 1999). Clinically, the most common manifestation is the suppression of occipital, visual cortex alpha when eyes are opened, but alpha modulation occurs also in auditory and sensorimotor tasks. For example, in motor tasks, alpha ERD and ERS are seen on the contralateral or ipsilateral motor area, respectively (Pfurtscheller et al., 1997; Jäncke et al., 2006), although motor tasks (or imagery of a motor task) involve also beta rhythm modulation at the motor cortex (Neuper et al., 2006; Pfurtscheller et al., 1997).

Alpha desynchronization/synchronization pattern is also evident in more complex cognitive processes such as attention. Current theories suggest that alpha

modulation operates as an attentional control mechanism via inhibition; high alpha activity (or synchronization) restrains the processing of irrelevant or distracting information (Foxe & Snyder, 2011; Jensen & Mazaheri, 2010; see also reviews by Freunberger et al., 2011; Frey et al., 2015). Additionally, alpha synchronization has been linked to the active inhibition of learned responses or the retrieval of motor memory traces (see review by Klimesch et al., 2007) and desynchronization has been positively correlated with e.g. long-term memory performance (Klimesch, 1999).

Pre-stimulus alpha modulation targets attentional resources towards the appropriate stimulus as in tasks using cues alpha is desynchronized over areas processing the attended stimuli and enhanced in other, task-irrelevant areas (Slagter et al., 2016, see reviews by Frey et al., 2015, Klimesch, 1999). In accordance with the attentional control via inhibition -theory, alpha modulation has been correlated with task performance accuracy. In visual tasks, high alpha power on task-relevant areas prior to the stimulus correlates negatively with perception and stimulus discrimination, but reduced alpha predicted good performance (van Dijk et al., 2008; Yamagishi et al., 2008; see also review by Hanslmayr et al., 2011). On the other hand, high alpha power in task-irrelevant, posterior areas correlated with better performance in a working memory task (Haegens et al., 2010, see also review by Freunberger et al., 2011).

Combined studies with EEG and other brain imaging methods have connected alpha oscillations to neural level function of the brain. By using EEG and transcranial magnetic stimulation, reduced posterior alpha power could be linked to increased cortical excitability and vice versa (Romei et al., 2007) in agreement with the proposed ERS/ERD model of Pfurtscheller (Pfurtscheller, 1992). In addition to cortical excitability, simultaneous EEG-fMRI-studies have correlated alpha activity to the blood-oxygenation-level-dependent (BOLD) response related to functional brain networks (Laufs et al., 2003) and response to visual stimuli (Mayhew et al., 2013, Mo et al., 2013).

2.3.5 Theta oscillation, attention and inhibitory control

Theta oscillation has been linked to executive control across different interference and inhibitory situations, including the Go/Nogo task (Kirmizi-Alsan et al., 2006; Nigbur et al., 2011). It is most likely critically involved in inhibitory control, particularly when seen in the frontal midline area (for an overview, see review by Cavanagh & Frank, 2014). In addition, theta has been associated with other

mental processes, such as encoding new information, learning and working memory function (Chaieb et al., 2015; see reviews by Benchenane et al., 2011; Freunberger et al., 2011 and Klimesch, 1999).

A developmental study using the Go/Nogo task showed increasing relative theta power with age, along with improving performance in the task (Liu et al., 2014). Liu et al. localized this increasing medio-frontal theta activity in the region to the anterior cingulate cortex (ACC). This corroborates the findings of an EEG/MEG-study localizing frontal midline theta rhythm in dorsal ACC and the neighboring medial prefrontal cortex during a calculation task (Ishii et al., 2014). The ACC has been often linked to conflict monitoring, response selection and inhibitory control (Bekker et al., 2005; Jonkman et al., 2007; Nieuwenhuis et al., 2004; Steele et al., 2013; Van Veen & Carter, 2002).

2.3.6 ERP components and EEG oscillations

The ERP components present the phase-locked neural activity induced by the task, but pre-stimulus oscillations, and particularly their phase dynamics distinctly affect the shape and amplitude of the subsequent event-related waveforms (Barry & De Blasio, 2012; Barry et al., 2010; see review by Klimesch et al., 2007). Few studies have investigated the relation between ERP components and pre-stimulus brain oscillation power by implementing the Go/Nogo paradigm. In studies using an auditory equiprobable Go/Nogo task, alpha and theta were the major pre-stimulus oscillations that affected the main ERP components related to inhibitory control (De Blasio &Barry, 2013a, 2013b). In contrast, pre-stimulus beta only had an impact on the early exogenous components (De Blasio & Barry, 2013b) while delta influenced all components globally (De Blasio & Barry, 2013a).

High pre-stimulus alpha activity increased the P3 amplitudes independent of condition in an auditory Go/Nogo task (De Blasio & Barry, 2013b). On the other hand, low pre-stimulus theta power produced higher Nogo-N2 and Go-P3, but reduced Nogo-P3, linking low pre-stimulus theta to improved cognitive processing (De Blasio & Barry, 2013a). However, one study did not show pre-task alpha and theta correlation to Go-related behavioral measures or ERP amplitudes (Karamacoska et al., 2017), which the authors speculated to be due to methodological issues.

Theta oscillation has been shown to specifically participate in the generation of the N2 component in Go/Nogo tasks (Harper et al., 2014). Mid-frontal theta also contributed to the N2 component in other tasks involving response conflict,

novelty and error (Cavanagh et al., 2012), all factors shown to modulate the N2 component (see reviews by Folstein & Van Petten, 2008; Van Veen & Carter, 2002). During development from adolescence to adulthood, pre-stimulus slow delta and theta seem to decrease in a visual oddball task while an increase was seen in the post-stimulus phase. This affected the P3 topography by increasing frontal P3 amplitudes (Mathes et al., 2016). The results were interpreted as the development of more precise neural mechanisms, particularly in frontal brain areas, even during late adolescence. In addition, the study highlights the utility of time-frequency analysis in in-depth evaluation of cognitive processes.

2.3.7 Stuttering and electrophysiological studies

An increasing number of studies have used electrophysiological measurements such as event-related potentials or time-frequency analysis of brain oscillations in the study of stuttering. The main body of event-related potential studies in stuttering has focused on speech and language processing and used semantic and linguistic tasks, which are outside the range of this study. Time-frequency analyses of brain oscillations have been performed both with EEG and MEG data, mostly in adults with stuttering and using speech paradigms, but also during resting state and attentional and inhibitory tasks. In children who stutter, electrophysiological studies are scarce in general and have mostly used auditory and speech tasks. Considering the scope of this study, the most interesting electrophysiological studies involve event-related potential analysis in motor, attentional and inhibitory control tasks or EEG or MEG analysis during or preceding such tasks. In CWS, however, some studies regarding auditory processing are discussed as well. They display probable anomalies in the early stimulus processing which may be affected by attention and later, more complex processes, which may represent poor connectivity of auditory areas. Tables 1 and 2 report the main findings of such studies in AWS and CWS, respectively (Tables 1 and 2).

Attention and inhibitory control

Studies of attention and inhibitory control in stuttering utilizing event-related potentials are very limited. Ning et al. (2017) used a cued, visual Go/Nogo task with a speech response and discovered a reduced P3 component to both the cue and the Nogo stimulus in AWS, indicating problems in the inhibition of the

response in addition to speech preparation. Maxfield et al. (2016) performed an auditory oddball task combined with a picture-naming task with distractor words to induce interference and increase the attentional demands of the tasks. In the study, the simple oddball task did not show differences in the P3 amplitude between AWS and controls. However, during a picture-naming condition with word-picture incongruence the AWS showed reduced P3 amplitude, indicating a more resource-demanding task and atypical regulation of attention in AWS compared to controls (Maxfield et al., 2016). Another study with an auditory oddball paradigm did not show significant P3 amplitude changes in AWS, either, although the P3 tended to be smaller in AWS (Hampton & Weber-Fox, 2008). However, Kaganovich et al. (2010) implemented an auditory oddball task in children and found a lacking P3 component to rare tones in CWS, indicating working memory and attention allocation differences (Kaganovich et al., 2010).

Preparatory activity in motor tasks

A few studies have analyzed preparatory processes in motor speech tasks showing significant differences in persons who stutter. Preceding motor tasks, the contingent negative variation (CNV) represents early preparation for the upcoming task. During a picture-naming task, the CNV was increased in AWS compared to controls (Vanhoutte et al., 2015). The CNV was also enhanced preceding fluent words compared to stuttered words (Vanhoutte et al., 2016), indicating atypical preparation of speech motor processes and increased activity of the basal ganglia–thalamo-cortical network. In support of these findings, Ning et al. (2017) found earlier modulation of the CNV in AWS (Ning et al., 2017).
Additionally, two studies using magnetoencephalography (MEG) showed spectral modulation differences mainly in higher, beta frequency range during speech preparation (Salmelin et al., 2000; Mersov et al., 2016) and an abnormal sequence of activation: the speech motor area was activated before the articulatory planning area (Salmelin et al., 2000). During speech preparation, the AWS first showed stronger beta suppression and then increased beta synchronization and early right-sided mouth motor cortex activation compared to controls, which points towards impaired coordination of the speech-motor network (Mersov et al., 2016). In accordance with these findings, a case study using MEG during a vowel production task showed a pattern of increased activity on the right frontal areas and bilateral sensorimotor and auditory areas along with reduced activation of the left frontal areas preceding blocks (Sowman et al., 2012). However, in children

the brain activation lateralization during picture naming in a MEG study did not differ between children with and without stuttering (Sowman et al., 2014). This suggests that the aberrant lateralization seen in AWS may be due to plastic, compensatory changes.

Time-frequency analysis, brain networks and functional connectivity

Regarding brain networks and functional connectivity, there are few studies implementing electrophysiological measures (Ghaderi et al., 2018; Joos et al., 2014; Sengupta et al., 2016; Sengupta et al., 2017). EEG during resting state in AWS has revealed decreased functional inter-hemispheric connectivity at beta and gamma frequency between motor speech and premotor areas, while increased connectivity at theta and alpha oscillations was correlated to stuttering severity (Joos et al., 2014). Another resting state EEG study found differences in the connectivity in fast beta frequencies correlating with overactivity of the right speech-motor areas and decreased neural connectivity in the right primary motor cortex in addition to disruption in theta networks (Ghaderi et al., 2018). In two studies using EEG, spectral power and phase coherence have shown differences on multiple frequency bands in AWS, suggesting impaired sensorimotor integration (Sengupta et al. 2016), also preceding dysfluency (Sengupta et al., 2017).

Two studies analyzed the alpha and beta Mu (μ) rhythms produced by the premotor and motor areas during auditory tasks to investigate sensorimotor integration and feedback in AWS (Jenson et al., 2018; Saltuklaroglu et al., 2017). AWS showed reduced beta μ amplitudes in a tone and syllable discrimination task during noise, indicating increased motor activity, as μ suppression is associated with sensorimotor function (Saltuklaroglu et al., 2017). In addition, AWS showed diminished alpha μ amplitudes, suggesting less sensory gating of information (Saltuklaroglu et al., 2017). Jenson et al. also found reduced alpha and beta μ rhythms in the left hemisphere during fluent or covert speech, interpreted as weaker sensorimotor feedback and forward modeling (Jenson et al., 2018).

Table 1. Electrophysiological studies in adults who stutter.

Reference	Subjects	Paradigm	Electrophysiological measures	Main results
Ghaderi et al., 2018	19 AWS, 52 controls	Resting state	EEG connectivity in theta (4-8 Hz), alpha (8-12 Hz), beta1 (12-20 Hz), and beta 2 (20-30 Hz) bands	Theta and beta band connectivity differences in AWS correlating to anomalous DMN, functional segregation/integration of theta networks and right speech-motor area over-activity.
Hampton & Weber-Fox, 2008)	11 AWS, 11 controls	Auditory oddball paradigm (1 kHz frequent tones, 2 kHz rare tones)	Event-related potentials (N100, P200, P300 components)	No difference in amplitude or latency. In AWS the N100 and P200 amplitudes correlated with better performance. The P300 was slightly reduced in AWS.
Jenson et al., 2018	24 AWS, 27 controls	Speech production (spontaneously fluent overt and covert speech production)	EEG mu (μ) rhythm	Reduced μ-alpha and μ-beta desynchronization during speech in AWS in the left hemisphere, no differences on the right side.
Joos et al., 2014	11 AWS, 11 controls	Resting state	EEG activity and functional connectivity	Reduced functional beta and gamma connectivity between motor speech areas and contralateral premotor and motor areas.
Maxfield et al., 2016	15 AWS, 15 controls	Auditory oddball task with frequent 1 kHz and infrequent 1,5 kHz stimuli combined with a picture naming task with distractor words.	Event-related potentials (P3 component)	In the simple oddball task, performance and P3 amplitude did not differ. P3 to rare tones was reduced in AWS in more demanding picture-naming condition (picture-word interference).
Mersov et al., 2016	12 AWS, 12 controls	Speech production (reading words)	MEG activity prior to and during speech	During speech preparation, AWS showed stronger beta suppression followed by stronger beta synchronization in bilateral mouth motor cortex. The AWS also showed earlier right-sided mouth motor cortex activation.
Ning et al., 2017	15 AWS, 15 controls	Cued visual Go/Nogo task, speech response	Event-related potentials (CNV, P3)	AWS showed a reduced P3 to the cue and the Nogo stimulus. CNV was early in AWS.
Salmelin et al., 2000	9 AWS, 10	Speech production (Reading nouns in	MEG cortical activation, evoked	In the speech preparation period, activation proceeded from the left

Reference	Subjects	Paradigm	Electrophysiological measures	Main results
	controls	a delayed reading paradigm)	activity and task-related suppression of 20 Hz oscillation	motor cortex to the left inferior frontal cortex in AWS, contrary to controls. During speech, the right motor cortex showed no evoked activation in AWS. The suppression of motor cortical 20 Hz oscillation was dominant on the right in AWS and on the left in controls.
Saltuklaroglu et al., 2017	27 AWS, 27 controls	Passive listening and auditory discrimination in quiet and noisy background	EEG mu (μ) rhythm	Reduced μ-beta amplitudes across conditions in AWS, significantly increased μ-beta desynchronization during noise and reduced μ-alpha synchronization in discrimination.
Sengupta et al., 2017	8 AWS, 8 controls	Speech production (reading of visually displayed target words)	EEG spectral power of theta, alpha, beta and gamma bands and gamma phase-coherence	Prior to dysfluent speech, rise in alpha and gamma power at frontal electrodes and beta power at central electrode. Alpha-gamma and theta-gamma showed mostly increased coherence.
Sengupta et al., 2016	8 AWS, 8 controls	Speech production during a motor adaptation protocol (reading of target word with and without auditory feedback)	EEG spectral power of theta alpha, beta and gamma bands and theta-alpha and beta-gamma phase-coherence	Reduced adaptation to the feedback error in AWS with evolving anomalies in EEG spectral power and phase coherence throughout the training.
Sowman et al., 2012	1 AWS (case report)	Speech production (Vowel production task)	MEG activity preceding blocks and fluent vowel production	Reduced activation of the left and extra activation of the right orbito- and inferio-frontal cortices as well as bilateral sensorimotor and auditory areas preceding blocks.
Vanhoutte et al., 2016	7 AWS	Speech production (Picture-naming task)	Event-related potentials (CNV) preceding stuttered and fluent words	CNV preceding stuttered words was reduced compared to fluent words in AWS.
Vanhoutte et al., 2015	25 AWS, 35 controls	Speech production (Picture-naming task)	Event-related potentials (CNV)	CNV was increased in AWS compared to controls and correlated with stuttering severity.

AWS= adults who stutter, CNV= contingent negative variation, EEG= electroencephalography, MEG= magnetoencephalography

Table 2. Electrophysiological studies in children who stutter.

Reference	Subjects	Paradigm	Electrophysiological measures	Main results
Beal et al., 2011	11 CWS, 11 controls (age 6-12 years)	Speech vocalizations and non-speech tones, passive listening vs. active generation	MEG activity, evoked fields, M50 component	Speech-induced suppression of auditory fields was similar in both groups. In CWS the M50 latency was delayed in vowel listening, but not in tone listening.
Etchell et al., 2016	10 CWS, 10 controls (age 3-9 years)	Auditory stimuli with either rhythmic or randomly varying pace	MEG time-frequency analysis, low beta band (12-15 Hz)	CWS showed delayed beta modulation peak after the onset of the stimulus sequence.
Ismail et al., 2017.	30 CWS, 30 controls (age 8-18)	Auditory speech stimuli (Smart Evoked Potentials of Intelligent Hearing system).	Event-related potentials (P1-N2 complex)	Children with more severe stuttering showed prolonged latencies and smaller amplitudes of P1, N1, P2 and N2.
Jansson-Verkasalo et al., 2014.	10 CWS, 12 controls (age 6-9 years)	Auditory stimuli with syllables and syllable changes	Event-related potentials (P1, N2, MMN)	Similar P1 and N2 responses, but reduced MMN in CWS. Only the duration change induced a MMN in CWS.
Kaganovich et al., 2010	18 CWS, 18 controls (age 4-6 years)	Auditory oddball paradigm; 1 kHz frequent tones and infrequent 2 kHz tones	Event-related potentials (P1, N1, P3, MMN)	Similar P1 and N1 components and MMN in both groups. Only controls showed a P3 component for rare tones.
Sowman et al., 2014	12 CWS, 12 controls (age 2-6 years)	Speech production (Picture naming)	MEG activity prior to speech production, lateralization of activity	Activation was lateralized to the left hemisphere in both groups, no differences between groups.
Özge et al., 2004	26 CWS, 21 controls (age 3-12 years)	Resting state and hyperventilation	Visual and quantitative EEG analysis	Increased delta activity in right frontal and parietal areas, decreased alpha in frontal areas bilaterally.

CWS= children who stutter, EEG= electroencephalography, MEG= magnetoencephalography, MMN= mismatch negativity

Other ERP and time-frequency analyses in children who stutter

Most electrophysiological studies in CWS have investigated speech with linguistic tasks, but some have studied auditory processing (Beal et al., 2011; Ismail et al., 2017; Jansson-Verkasalo et al., 2014; Kaganovich et al., 2010). Jansson-Verkasalo et al. (2014) used mismatch negativity (MMN) and found poorer responses to syllable changes in CWS, although the exogenous P1 and N2 responses to standard sounds were similar (Jansson-Verkasalo et al., 2014). Based on these results, central auditory processing is abnormal in CWS, which is supported by findings of atypical auditory evoked potentials related to more severe stuttering (Ismail et al., 2017). On the other hand, Beal et al. (2011) examined auditory-motor integration by MEG during a passive listening and active generation task with vowels and tones. In CWS the evoked component was delayed in vowel listening, but not in tone listening, suggesting specific problems in the timing of speech sounds processing (Beal et al., 2011). Supporting this finding, Kaganovich et al. (2010) did not discover differences in early event-related auditory N1 and P1 components or MMN when using pure tone stimuli (Kaganovich et al., 2010); instead an absent P3 component was found. In conclusion, it is likely that there are abnormalities in the processing of auditory information, particularly when more complex cognitive procedures are involved.

There are few studies using time-frequency analysis in CWS (Etchell et al., 2016; Özge et al., 2004). A MEG study during a rhythm tracking auditory task showed an atypical beta response at the low 12–15 Hz range: CWS showed a peak in low beta activity significantly later than the controls, indicating poorer prediction of the next upcoming sound, which may affect rhythm detection (Etchell et al., 2016). Özge et al. (2004) examined quantitatively the resting state EEG of CWS and fluently speaking children and found more slow, delta range activity in the right frontal areas and less faster, alpha and beta range activity in CWS compared to controls (Özge et al., 2004).

To date, there have not been any studies in CWS using electrophysiological measurements during a non-speech, motor, visual Go/Nogo task.

3 Aims of the study

The purpose of this study was to investigate by electrophysiological means the brain activity related to attention and inhibitory control in CWS.
In particular, the study had the following aims:

a) To investigate the attentional and inhibitory control related processes during a visual, motor Go/Nogo task in CWS by event-related potentials (ERP) in order to assess possible differences in these non-speech functions compared to TDC (studies I and II).
b) To examine possible differences in the behavioral measures related to attention and inhibitory control, such as errors or reaction times (study I).
c) To explore potentially atypical inhibitory control or attentional mechanisms in CWS by comprehensive electrophysiological measurements such as evaluation of brain activation patterns and time-frequency analysis of the electroencephalogram (EEG) (studies II and III).

4 Materials and methods

4.1 Subjects

The study group participants were recruited by advertising in local newspapers and by contacting personally speech therapists working in local health centers and special teachers in the Oulu region. The control group consisted of children recruited from local schools and pre-schools as well as some children of staff members, their friends and neighbors. Prior to the study, all participants and their parent(s) received written information about the study. A verbal approval was obtained from participants and the parent(s) gave an informed written consent. The ethical committee of Oulu University Hospital approved the study in accordance with the Declaration of Helsinki.

Parents filled in a questionnaire to confirm that all children were healthy with no neurological, cognitive, speech, language or learning deficits other than speech dysfluency in the stuttering group. All participants passed a hearing screening for normal hearing (tone-audiometry, SA 50, Entomed, Sweden). At the time of the measurements, no standardized tests existed to assess the morphology and syntax of school-aged children in the Finnish language. The participants' language production was therefore assessed based on spontaneous speech samples by a qualified speech and language therapist (Eira Jansson-Verkasalo) and was found to be normal.

Cognitive development of all the children was assessed by the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1991) as described by Jansson-Verkasalo et al., 2014. These subtests were chosen for their good correlation with the WISC-III overall score (Groth-Marnat, 2009). In the Vocabulary subtest the child is asked to define provided words. The Block Design measures perceptual reasoning: the child is asked to put together red-and-white blocks in a pattern according to a displayed model.

Study I and II

The participants were 11 CWS (all boys and right-handed, mean age 8.1 years, SD = 1.22, age range 6.3–9.5 years) and 19 typically developed children (TDC) with fluent speech (12 boys, 1 left-handed, mean age 8.1 years, SD = 1.17, age

range 5.8–9.6 years), matched for age. There was no significant age difference between the groups (p = .966, Mann-Whitney U-test). No significant between-group differences were found for either Vocabulary (p = .241, t-test) or Block Design (p = .573, t-test] subtests of the WISC-III.

Study III

For article III, one additional subject was recruited, and in the analysis 12 CWS (mean age 7.97 years, range 6.3–9.5 years; right-handed boys) and 12 typically developed, fluently speaking boys (mean age 8.01 years, range 5.8–9.6 years; one left-handed) from the earlier control group were used. The groups did not differ significantly by age (p=.938, t-test) or performance in the Vocabulary (p = .163, t-test) and Block Design (p =.636, t-test) subtests of WISC-III.

4.2 Data acquisition

4.2.1 Stimuli and procedure

The visual Go/Nogo paradigm used was similar to the Go/Nogo task of the Amsterdam Neuropsychological Tasks (De Sonneville, 2009) with equiprobable Go and Nogo stimuli. The Go stimulus was a green walking figure and the Nogo stimulus a red standing figure, both of which were displayed on an equal-sized (111x124 mm) grey background (Fig. 1). Each task started with a non-informative cue (a 13-mm white cross) for 500 ms, then either a Go or Nogo stimulus for 800 ms, followed by an empty, black screen for the remaining 1500 ms of the trial, resulting in a 2800-ms fixed inter-stimulus interval. One block contained 24 Go and 24 Nogo stimuli in a pseudo-random order and each child performed 4–6 blocks, depending on the quality of the EEG. The children were instructed to press a special mouse button for the Go stimulus and to refrain from pressing for the Nogo stimulus. A Go response was considered correct if the button was pressed within a 300–2300 (250–2300 ms in article III) ms time window after the onset of the Go stimulus, and a correct Nogo response was no press after a Nogo stimulus.

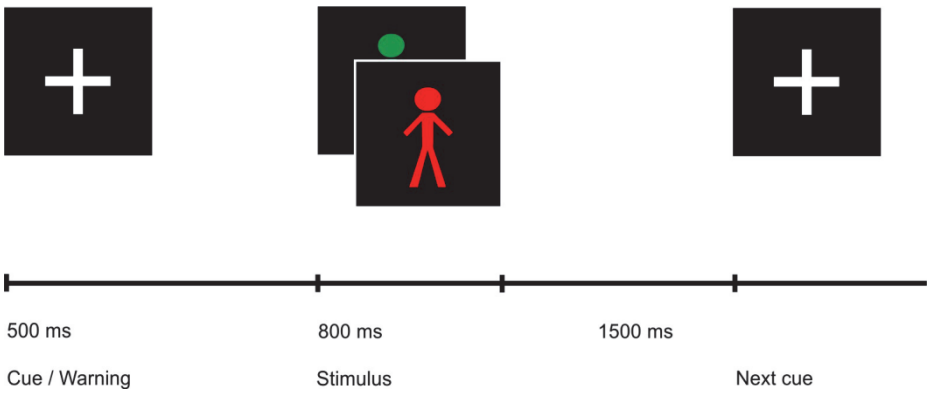

Fig. 1. A schematic representation of the Go-Nogo task. The Nogo signal was a red, standing figure and the Go signal a green, running figure. The child was instructed to press a special mouse key as soon as possible when the Go signal appears. (Study I, published by permission of Elsevier.)

During the EEG recording the child was comfortably seated in a dimly lit, electrically shielded, quiet room in front of a computer screen and all children practiced the task before starting the actual experiment. If the child was anxious, a parent sat behind the child so that the child could not see her/him, and the parent was instructed to stay quiet and still during the experiment. The experiment was monitored by video camera and when necessary, short breaks between blocks were taken to maintain vigilance or for technical reasons.

4.2.2 EEG recording and processing

Continuous EEG was recorded during the task using Brain Products software and the BrainAmp DC amplifier with an electrocap (Acticap) consisting of 64 Ag/AgCl electrodes. The sampling rate was 5000 Hz with 0.1 μV resolution and 0.016–1000 Hz on-line band pass. For recording of eye movement, two electrodes were attached below or above the outer canthi of the left and right eyes, respectively. The common reference during the recording was FCz. All EEG data were subsequently analyzed with the Brain Vision Analyzer software (Brain Products GmbH, Brain Vision Analyzer 2.1).

Study I and II

For the analysis used in studies I and II, the data were digitally filtered off-line with a 0.01–40 Hz band pass filter before ocular correction with the Gratton and Coles algorithm of the Brain Vision Analyzer software and then using a 0.01–20 Hz band pass filter before segmentation (-100–0 ms pre-stimulus for baseline correction and 800 ms after the stimulus onset). The epochs containing voltages ±125 μV at any electrode were omitted from the averaging procedure. Averaging was done by combining trials separately for correct Go and correct Nogo tasks as well as incorrect Go and Nogo tasks. After averaging of the trials, the data were re-referenced off-line to the linked mastoids.

Study III

For the time-frequency analysis in study III, the most lateral channels (FT9, FT10, PO9, PO10) were rejected because of increased probability of EMG-artifacts and the analysis was continued with 60 channels. The data were digitally filtered with a 0.1-25 Hz band pass filter to minimize EMG artifacts. After ocular correction as in studies I and II all epochs containing higher than 250 μV voltages were excluded. The data were re-referenced to the linked mastoids and segmented (700 pre-stimulus to 2100 ms post-stimulus) separately for correct Go and Nogo responses. Then the segments were manually checked for artifacts and any segment with excessive EMG or other artifacts was discarded from further analysis. The segments were averaged separately for each condition and at this point, the data were downsampled to 64 Hz.

4.2.3 Behavioral measures

During the task, correct and incorrect responses were measured in relation to the stimulus triggers, as well as reaction times (RT) for correct Go responses. Reaction times (RT) were measured as the latency from the onset of a Go stimulus to the button press response. Errors were either premature responses (a button press earlier than 300 ms from stimulus onset) or false alarms (a press at the Nogo stimulus). An erroneous Go response was no press at the Go stimulus before the next stimulus.

4.3 Data analysis

4.3.1 ERP analysis (N2, P3)

As errors were very few and some children did not commit any errors at all, only the ERPs for correct responses were analyzed.

Before peak detection, time windows for each ERP peak were estimated by visual evaluation of grand average figures using the midline channel with maximum amplitude for each waveform (Fig 2). The estimated time frame for the N2 component was 300–420 ms and for the P3 component 380–500 ms for both groups and components, in harmony with the broad range of latencies in previous studies using various visual Go/Nogo tasks (Baving et al., 2004; Jonkman et al., 2003; Jonkman, 2006; Wiersema and Roeyers, 2009). Brain Vision Analyzer software was then used for automatic peak detection. However, if the marker was placed on a slope the marker was manually moved to the closest peak within the chosen time window.

However, in the individual ERP waveforms the P3 component was rather small and imprecise, especially in the CWS. Therefore, in study I the P3 peak was individually defined as the maximal positive deflection in the Fz channel between 380–500 ms and the latency of this location was used in the automated analysis at all channels both in Go and Nogo conditions. Furthermore, an additional analysis was performed for the Go condition using the peak latency of P3 in the Pz channel in a similar manner, because the Go P3 component is maximal in the parietal region (Barry & De Blasio, 2013; Barry et al., 2014; Bokura et al., 2001; Tekok-Kilic et al., 2001).

4.3.2 Global field power, mean amplitude and EEG voltage maps

For study II, the grand average ERP waves of each condition and group were again inspected to estimate the N2 and P3 time windows as described in study I. Global main field power (GFP) waves were then computed using 60 channels, leaving out only the most lateral (FT9, FT10, PO9, PO10) electrodes due to EMG contamination. The GFP was calculated in order to better examine differences in brain activity in these time windows, since the individual ERP waves showed rather large variation and indistinct P3 components, particularly in the CWS.

Global field power (GFP) is a computed measure of EEG activity across all electrodes over the scalp (Lehmann& Skrandies, 1980) and it represents the

standard deviation of the momentary electrical field potential. GFP is effective in the identification of widely distributed peaks when average latencies may not be useful (Lehmann & Skrandies, 1980). By using GFP waveforms it is possible to detect changes and differences in global EEG activity. Global main field power is calculated as follows:

$$GMFP(t) = \sqrt{\frac{[\sum_i^k (V_i(t) - V_{mean}(t))^2]}{K}} \quad (1)$$

where t is time, K the number of channels, V_i the voltage in channel i averaged across subjects and V_{mean} is the mean of the voltages in all channels.

The GFP difference waves between groups were calculated separately for Go and Nogo condition to point out the most differing time frame within the N2 and P3 component time window. Furthermore, the time point of the maximal GFP difference was used as a middle point to determine a 40-ms time window for mean amplitude measurements from the ERP waves. To avoid the problem with indefinite peaks, these mean amplitudes were used instead of peak amplitudes in the statistical analysis, following the guidelines of the Society of Psychophysiological Research (Picton et al., 2000).

The most interesting brain activity in the Nogo condition was visualized with potential maps ranging from 80 ms before to 80 ms after the maximal difference seen in the GFP waves, thus overlapping the N2 and P3 time windows seen in the grand average waves. The potential maps between 350 ms–510 ms were formed from the data using Brain Vision Analyzer software and its mapping view. The potential maps were visually evaluated separately for each group and condition using the optimal scaling for voltage differences in the Go and Nogo conditions.

4.3.3 Behavioral measures

The mean reaction times per Go trial for each child were used in the group RT, since the children completed various numbers of blocks of trials (4-6). For the same reason, the number of errors was calculated from the mean error counts per block of trials.

To exclude possible learning effects due to the use of multiple blocks of trials, the RTs of the first and the last block as well as the change of RT were compared between groups. In order to get a more precise estimation of this non-Gaussian data the median RT was used instead of mean in these comparisons.

4.3.4 EEG time-frequency analysis

In study III, the EEG was analyzed using wavelets and fast Fourier transformation (FFT). For the determination of an appropriate baseline period, a combined TDC and CWS group mean wavelet graph was formed with the Brain Vision Analyzer software and visually analyzed. Based on this evaluation, the period between -600–(-500) ms was chosen as baseline because it contained the least activity. A baseline corrected continuous wavelet transformation was then performed for the averaged data of the trials of each child. The transformation was carried out with complex Morlet wavelet (Morlet parameter = 5) using Gabor normalization. The frequency range of interest was limited to 3–20 Hz with 1 Hz steps resulting in 18 frequency bins. The individual wavelet graphs on each channel were then analyzed visually in both conditions.

In order to evaluate further the clearest differences seen in the wavelets as well as the cluster analysis a fast Fourier transformation (FFT) was carried out in the Nogo condition. For this analysis, the time frame was narrowed to the 900–1800 ms post-stimulus, when the combined wavelet graph of both groups showed the most activity in the alpha frequency range. Both the grand average and individual FFT graphs were then assessed visually. For an extra statistical estimation of the shift towards slower frequencies seen in the CWS in the wavelet and FFT graphs, an Alpha/Theta-ratio was calculated. This was done by comparing the mean power within the 7.5–12.5 Hz frequency range for alpha and 4–7.49 Hz for the theta band in the 900–1800 ms time window.

4.3.5 Statistical analysis

Event-related potentials amplitudes and latencies

In study I, 9 central and lateral electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) were kept for further visual and statistical analysis based on previous ERP literature (Bekker et al., 2005; Bokura et al., 2001; Johnstone et al. 2007; Jonkman et al., 2003; Jonkman, 2006; Jonkman et al., 2007). A logarithmic transformation was used to reduce the variability in the ERP data before the statistical analysis. A four-way repeated-measures ANOVA of the SPSS statistical program (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) was used for the analysis of all other measures except the P3 latencies. In the model, Group (TDC, CWS) was a between-subject

factor and Condition (Go, Nogo), Anterior-Posterior [Frontal (F3, Fz, F4) x Central (C3, Cz, C4) x Parietal (P3, Pz, P4)] and Hemisphere [Right (F4, C4, P4) x Midline (Fz, Cz, Pz) x Left (F3, C3, P3)] were within-subject factors. If a Condition x Group interaction was significant, the analysis was continued with a three-way repeated-measures ANOVA separately for the Go and Nogo conditions using Group (TDC, CWS) as a between-subject factor and Anterior-Posterior [Frontal (F3, Fz, F4) x Central (C3, Cz, C4) x Parietal (P3, Pz, P4)] and Hemisphere [Right (F4, C4, P4) x Midline (Fz, Cz, Pz) x Left (F3, C3, P3)] as within-subject factors. The Huynh-Feldt correction was applied when suitable and observed power was used for effect size estimation. Because the P3 component was locked in either the Fz or Pz channel in the analyses, the latencies did not differ between channels. The P3 latencies between the groups were therefore compared by independent samples t-test. In the Nogo condition the P3 latencies in the Fz channel were used. In the Go condition the P3 latency was determined both in the Fz and Pz channels and therefore the comparisons between the groups were also performed separately for the P3 peaks locked in both Fz and Pz.

Mean amplitudes in Nogo condition

For the statistical analysis of the mean amplitudes in the Nogo condition in study II, the most lateral and occipital electrodes were discarded and the remaining 36 channels were used. The data were restructured and the electrodes were divided into 9 regions: Right Frontal (AF4, F2, F4, F6), Midline Frontal (Fz), Left Frontal (AF3, F1, F3, F5), Right Central (FC2, FC4, FC6, C2, C4, C6), Midline Central (Cz), Left Central (FC1, FC3, FC5, C1, C3, C5), Right Parietal (CP2, CP4, CP6, P2, P4, P6), Midline Parietal (CPz, Pz) and Left Parietal (CP1, CP3, CP5, P1, P3, P5). A linear mixed model analysis was chosen because the data of the subjects at different electrodes are correlated. The analysis was performed using the SPSS statistical analysis program (IBM Corp. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). In the model, Mean amplitude in the selected time range was a dependent variable, Region (Right Frontal, Right Central, Right Parietal, Midline Frontal, Midline Central, Midline Parietal and Left Frontal, Left Central and Left Parietal) and Group (CWS, TDC) were fixed effects, and subject ID a random effect. In case of a significant Group x Region interaction a *post hoc* analysis was run to determine the areas with significant differences between or within groups. For the *post hoc* analysis two variables,

Group (CWS/TDC) and Region (Right Frontal, Right Central, Right Parietal, Midline Frontal, Midline Central, Midline Parietal and Left Frontal, Left Central and Left Parietal) were combined into one variable. The new Group-Region variable was then used as a factor in the mixed linear model. The analysis was performed separately for Go and Nogo conditions. Because of the low number of comparisons corrections for multiple testing were considered unnecessary (Rothman, 1990).

Behavioral measures

Non-parametric Mann-Whitney U-test was used for all the statistical comparisons of the reaction times and the number of errors between groups due to the non-normal distribution of the data. When comparing the number of subjects committing multiple errors, the Chi-Square test was used.

Wavelets

For the statistical analysis of the three-dimensional time-frequency data of 60 electrodes a cluster-based nonparametric method (Maris & Oostenveld, 2007) was chosen in order to control for multiple comparisons, since there are over 192,240 elements (60 channels x 18 frequency bins x 178 time points). With this method, a cluster-level correction for multiple comparisons is carried out by the permutation procedure. The analysis was conducted with the FieldTrip MATLAB toolbox (Oostenveld et al., 2011) over channels defined by the Acticap electrode layout. For every channel-frequency-time triplet the T-statistics was computed by non-parametric test for independent samples. The statistical approach applied was permutation resampling with 1,000 permutations. In this analysis, space clusters were adjacent samples with a threshold of $p=0.025$ for the two-sided test. In the cluster permutation procedure, cluster-level statistics were calculated by taking the sum of t-values over each cluster. The cluster-level significance level between the CWS and TDC groups was then calculated by a permutation method where the p-value was based on comparing the observed cluster statistics to the Monte-Carlo reference statistics. For this p-value the threshold was set to $p=0.025$ for the two-sided test.

FFT and Alpha/Theta ratio

For between-group comparison of the FFT Alpha/Theta-ratio 12 frontal, central, parietal and occipital electrodes (F3, Fz, F4, C3, CZ, C4, P3, PZ, P4, O1, Oz, O2) and a linear mixed model analysis with the SPSS statistical analysis program ((IBM Corp. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) were used. This model was chosen because the data from various electrode locations are correlated and since it is well suitable for a small sample, even though the use of a non-parametric test could have been more sensitive in this skewed data. In the model, Alpha/Theta ratio was the dependent variable, Laterality [Left (F3, C3, P3, O1), Midline (Fz, Cz, Pz, Oz), Right (F4, C4, P4, O2)], Anterior-Posterior [Frontal (F3, Fz, F4), Central (C3, Cz, C4), Parietal (P3, Pz, P4) and Occipital (O1, Oz, O2)] were the fixed effects, and subject ID was a random effect. Because a significant Group x AP main effect was seen, analysis of the significantly differing areas between and within groups was continued by combining two variables, Group (CWS, TDC) and Anterior-Posterior into one variable. This Group-Anterior-Posterior variable was then used as a factor in the mixed linear model.

5 Results

5.1 ERPs (study I)

The grand average waveforms showed clear N1, P2 and N2 components and in TDC, also a P3 component especially in the Nogo condition. The N2 amplitude was slightly enhanced in Nogo condition in both groups. In TDC, the P3 was also increased (more positive) in Nogo compared to Go (Table 3 and Fig. 2). The individual ERP waveforms showed variability especially in the CWS group (Fig. 3). However, the main waveforms were consistent.

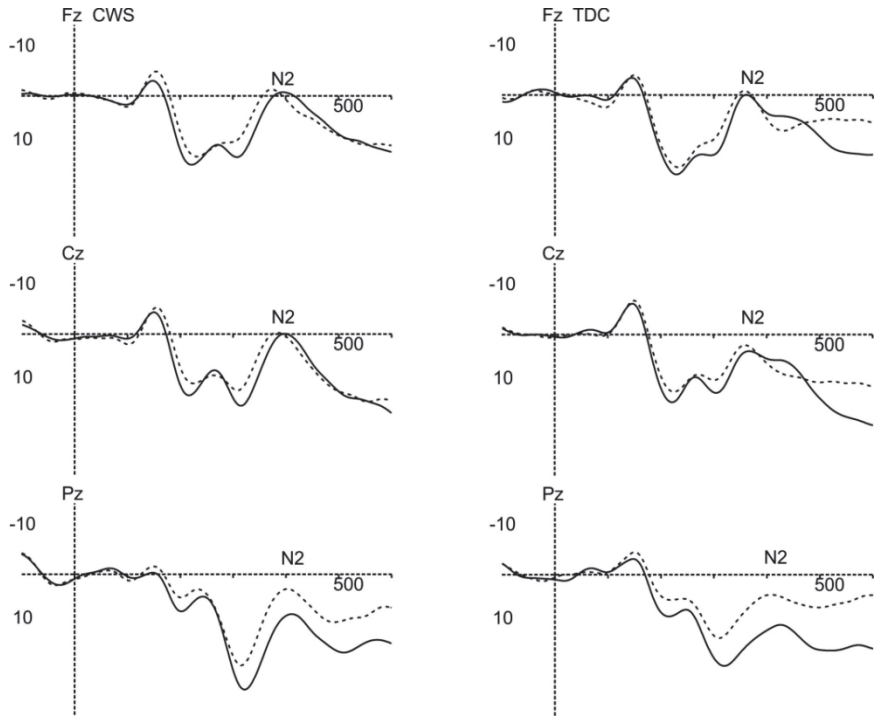

Fig. 2. The grand average waves at the Fz, Cz and Pz channels of children who stutter (CWS, on the left) and typically developing children (TDC, on the right) in Go (solid) and Nogo (dashed) conditions. The N2 amplitude was slightly enhanced in Nogo condition in both groups. In TDC P3 was also increased (more positive) in Nogo compared to Go. However, no significant differences were found between the groups in the amplitudes of the N2 or P3 responses in either condition. (Study I, published by permission of Elsevier.)

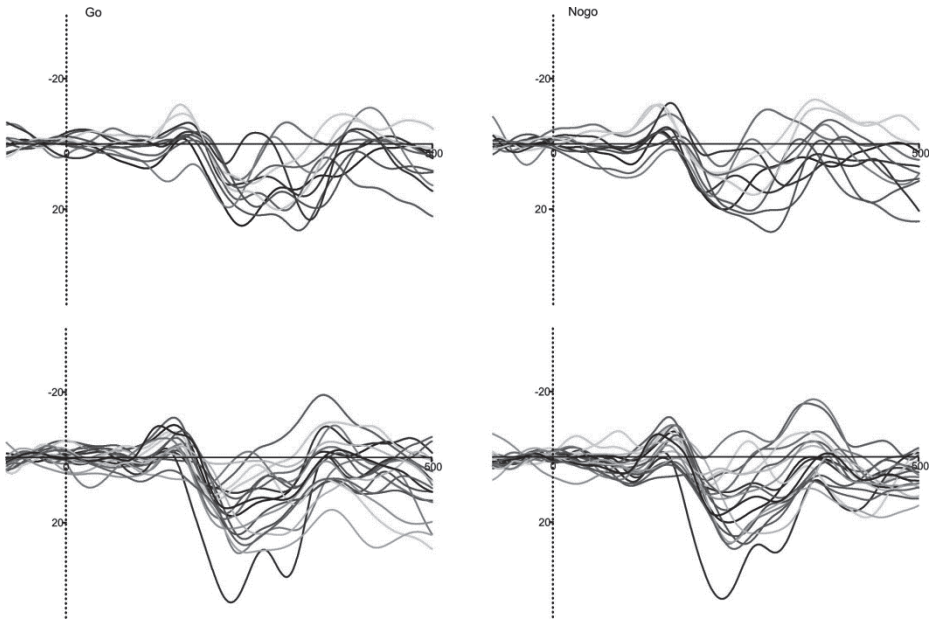

Fig. 3. Individual ERP waveforms of the CWS (upper row) and the TDC (bottom row) at Fz in Go (left) and Nogo (right) conditions (Modified from study II supplementary material, published by permission of Elsevier).

Table 3. The mean N2 and P3 peak amplitudes and latencies at channel Fz. CWS= children who stutter, TDC= typically developing children. (Study I, published by permission of Elsevier.)

Variable	Go				Nogo			
	CWS	SD	TDC	SD	CWS	SD	TDC	SD
Amplitude (μV)								
N2	-2,587	4,911	-,559	8,057	-3,540	6,655	-1,877	7,803
P3	5,667	5,690	6,980	9,045	6,930	8,419	9,240	5,219
Latency (ms)								
N2	391	22,490	367	17,471	366	27,103	356	13,177
P3	459	36,535	430	34,865	439	37,070	433	25,493

5.1.1 N2

The four-way ANOVA with Group as a between-subject factor and Condition, Anterior-Posterior and Hemisphere as within-subject factors showed a significant main effect for the N2 latency (p=.020) (Table 4). The analysis was continued using the three-way ANOVA with Group as a between-subject factor and Anterior-Posterior and Hemisphere as within-subject factors. This showed a Group main effect in the Go condition due to the significantly longer N2 latency in the CWS than in the TDC (p=.001) (Fig. 4). In Nogo condition the three-way ANOVA showed no significant main effect (p=.518).

For the N2 amplitude, there was no significant main effect or within-subject group effects (p=.286).

Table 4. The four-way ANOVA results for the N2 latency and N2 and P3 amplitudes with Group as a between-subject factor and Condition, Anterior-Posterior and Hemisphere as within-subject factors. For the N2 latency it showed a significant main effect and a Condition x Group effect. The CWS had significantly longer N2 latencies than TDC in the Go, but not in the Nogo condition. No significant main effect was seen for the amplitudes. (Study I, published by permission of Elsevier.)

Variable	Component	Four-way ANOVA main effects			Within-subject group effects, Condition x Group
		p	Observed power	F	p
Latency	N2	.020*	.661	6.049	.022
Amplitude	N2	.286	.183	1.181	
	P3	.556	.089	.355	

Degrees of freedom in variance analysis was 1. *p<.05 For within-subjects group effects, only effects with p<.05 are presented.

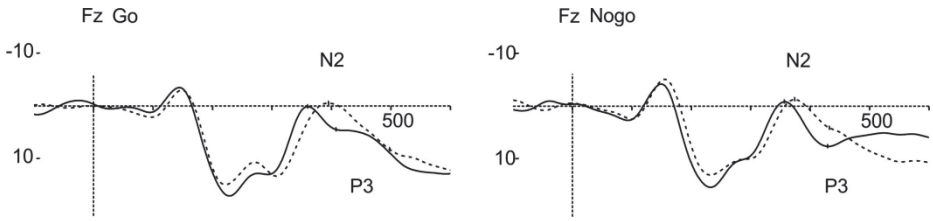

Fig. 4. The grand average waves of children who stutter (CWS, dashed line) and typically developing children (TDC, solid line) in Go (left) and Nogo (right) conditions at the Fz electrode, showing longer N2 latency in CWS in Go condition. (Study I, published by permission of Elsevier.)

5.1.2 P3

The CWS had significantly longer P3 latencies than the TDC in the Go condition, both when using latencies locked in the Fz channel (p=.038, independent samples t-test) or Pz channel (p=.009, independent samples t-test). However, in Nogo condition, the latencies did not differ significantly between the groups (p=.707, independent samples t-test).

For the P3 amplitude, no significant main effect was seen in the four-way ANOVA with Group as a between-subject factor and Condition Anterior-Posterior and Hemisphere as within-subject factors.

5.2 GFP, potential maps and mean amplitudes (study II)

5.2.1 GFP and potential maps

In the N2 and P3 time windows the GFP waveform showed a clear peak at around 350 ms in both conditions representing well the N2 component. In the Nogo condition another, smaller peak at 430 ms could be seen in the TDC, corresponding to the P3 component (Fig. 5).

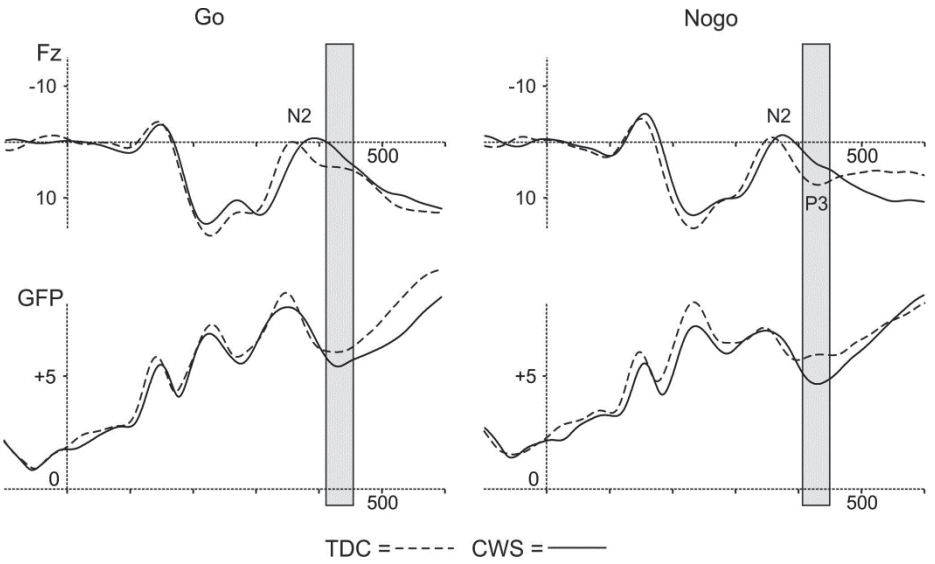

Fig. 5. The grand average (GA) and global field power (GFP, note the polarity) waveforms in the Go and Nogo conditions of the typically developed children (TDC, dashed line) and children who stutter (CWS, solid line). The electrical field potential shows greater deviation at the time of the focal ERP peak maxima and the GFP and ERP peaks are therefore temporally related. In this figure the 40 ms time windows around the maximal GFP difference (415–455 ms and 410–450 ms in the Go and Nogo condition, respectively) are highlighted. (Study II, published by permission of Elsevier.)

When comparing groups, the GFP difference wave showed a small peak at 435 ms in the Go and a distinct peak at 430 ms in the Nogo condition, both fitting in the P3 time frame (Fig. 6 and 7). The difference wave peaks were used to define 40-ms segments (415–455 ms in Go and 410–450 ms in Nogo) where mean amplitudes were extracted for statistical analysis of the brain activity in the P3 time window. Potential maps were created to visualize possible topographic differences between the groups in the N2 and P3 time windows.

The visual inspection of the potential maps showed clear differences between the groups in the activity in the time window between 350 and 510 ms post-stimulus (Fig. 6 and 7). The CWS showed a widely distributed and long-lasting, less positive activity at around 350–440 ms in both conditions, resulting in lower amplitudes. In contrast, in TDC this negatively oriented activation was limited to frontal areas and was much shorter in duration, disappearing already at 390 ms, fitting the N2 time window. In the P3 time window and in Go condition, neither

group showed any clear positively oriented activity in the fronto-central region; instead, it was seen in the parietal area. In Nogo condition at around 400–450 ms post-stimulus the TDC showed a distinct, nearly symmetrical positivity at the fronto-central leads while in the CWS this was hardly visible (Fig 7).

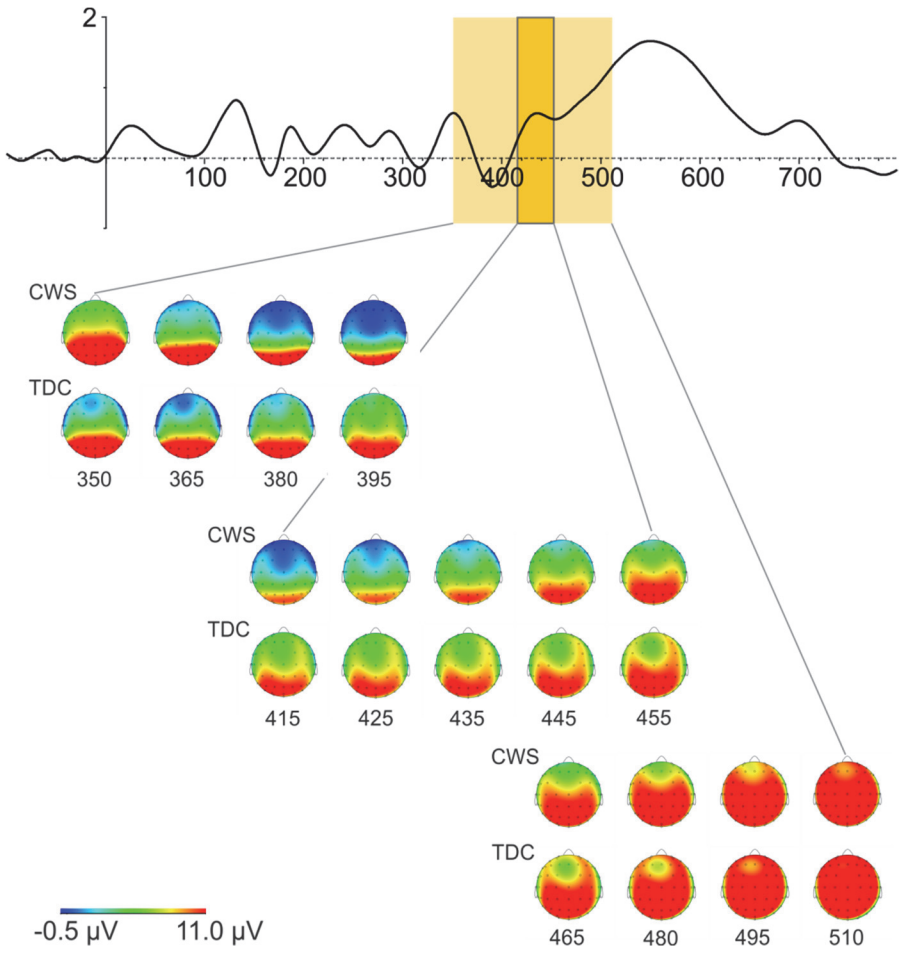

Fig. 6. The global field power (GFP) difference wave between children who stutter (CWS) and typically developed children (TDC) and their potential maps in the Go condition. For clarity, the figures present the potential maps every 10 ms for the most interesting 40-ms segment around the maximal GFP difference and four additional potential maps every 15 ms before and after this segment. The CWS show increased and prolonged negatively oriented activity in the frontal areas when compared to the TDC. (Study II, published by permission of Elsevier.)

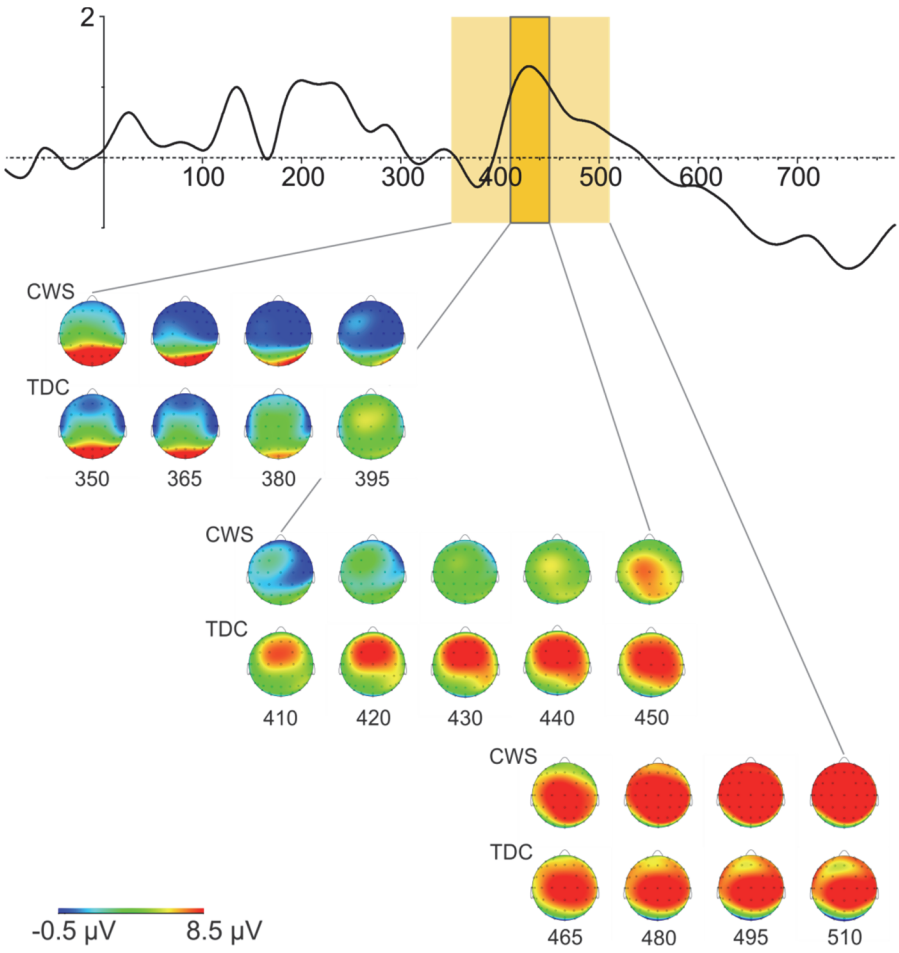

Fig. 7. The GFP difference wave between CWS and TDC and the potential maps in the Nogo condition. Similarly to the Go condition, the CWS show widened and prolonged negatively oriented activity in the frontal areas. In the time frame around the maximal GFP difference the TDC show clear fronto-central positively oriented activity, but in the CWS this is markedly reduced. (Study II, published by permission of Elsevier.)

5.2.2 Mean amplitudes

The mean amplitudes between 415 and 455 ms in the Go condition were compared using the linear mixed model analysis, which showed a significant

Group x Region main effect (p=.049). The mean amplitudes of the CWS were smaller throughout the regions (Table 5), but according to the *post-hoc* analysis the main effect was due to the difference in the Right Frontal area (p=.050).

In the Nogo condition there was a highly significant Group x Region main effect (p=.000). The mean amplitudes between 410 and 450 ms were higher in the TDC compared to the CWS, comparably to the Go condition. The *post-hoc* analysis showed that the result was due to a significant difference between groups in the Right Frontal region (p=.041).

Table 5. Mean amplitudes of the regions between 415–455 ms in the Go condition and 410–450 ms in the Nogo condition. Regions were defined as follows: Right Frontal (AF4, F2, F4, F6), Midline Frontal (Fz), Left Frontal (AF3, F1, F3, F5), Right Central (FC2, FC4, FC6, C2, C4, C6), Midline Central (Cz), Left Central (FC1, FC3, FC5, C1, C3, C5), Right Parietal (CP2, CP4, CP6, P2, P4, P6), Midline Parietal (CPz, Pz) and Left Parietal (CP1, CP3, CP5, P1, P3, P5). (Study II, published by permission of Elsevier.)

		Go		Nogo	
Region	Group	Mean amplitude (μV)	SD	Mean amplitude (μV)	SD
Left frontal	CWS	2.369	1.928	3.007	1.822
	TDC	6.070	1.467	6.718	1.386
Midline frontal	CWS	1.932	2.257	3.773	2.067
	TDC	4.714	1.717	7.383	1.573
Right frontal	CWS	2.187	1.928	1.922	1.822
	TDC	7.102	1.467	6.777	1.386
Left central	CWS	4.558	1.888	4.201	1.792
	TDC	6.810	1.437	6.691	1.364
Midline central	CWS	3.536	2.257	4.277	2.067
	TDC	5.988	1.717	8.297	1.573
Right central	CWS	4.355	1.888	2.968	1.792
	TDC	7.183	1.437	7.205	1.364
Left parietal	CWS	8.030	1.888	3.517	1.792
	TDC	10.241	1.437	4.747	1.364
Midline parietal	CWS	8.732	2.044	4.385	1.907
	TDC	10.028	1.555	5.352	1.451
Right parietal	CWS	8.411	1.888	4.179	1.792
	TDC	9.513	1.437	6.240	1.364

5.3 Behavioral measures

5.3.1 Reaction times

The mean reaction time (RT) per correct Go trial was 536 ms (SD = 50) for CWS and 498 ms (SD = 64) for the TDC. Although the CWS were slightly slower, the difference was not significant (p = 0.089, Mann-Whitney U-test).

When comparing the median RT between groups in the first (p = .553, Mann-Whitney U-test) or the last block (p = .085, Mann-Whitney U-test) there were no significant differences either, nor did the change from the first to the last trial differ between the groups (p=.413, Mann-Whitney U-test).

5.3.2 Errors

Errors were scarce in both groups in general. The number of all errors was not significantly different between the groups (p = .590; Mann-Whitney U-test) and the groups did not differ in terms of the change in the number of errors from the first to the last block (p = .419, Mann-Whitney U-test).

In both groups some individuals made many errors while others made none at all. There were more subjects committing multiple errors (mean number of errors 2 or more per block) in the CWS (5/11, 45.5%) than in the TDC (6/19, 31.5%), but the difference was not statistically significant (p = .447, Chi-Square test).

5.4 Time-frequency analysis (study III)

5.4.1 Wavelets

The grand average wavelets in both conditions showed more alpha range activity in the TDC after 600 ms post-stimulus, although it was slightly less prominent in the Go condition. In addition, during the cue and stimulus processing (-500–500 ms) the CWS had excess and widely spread slower, theta-range activity compared to the TDC (Fig. 8 and 9).

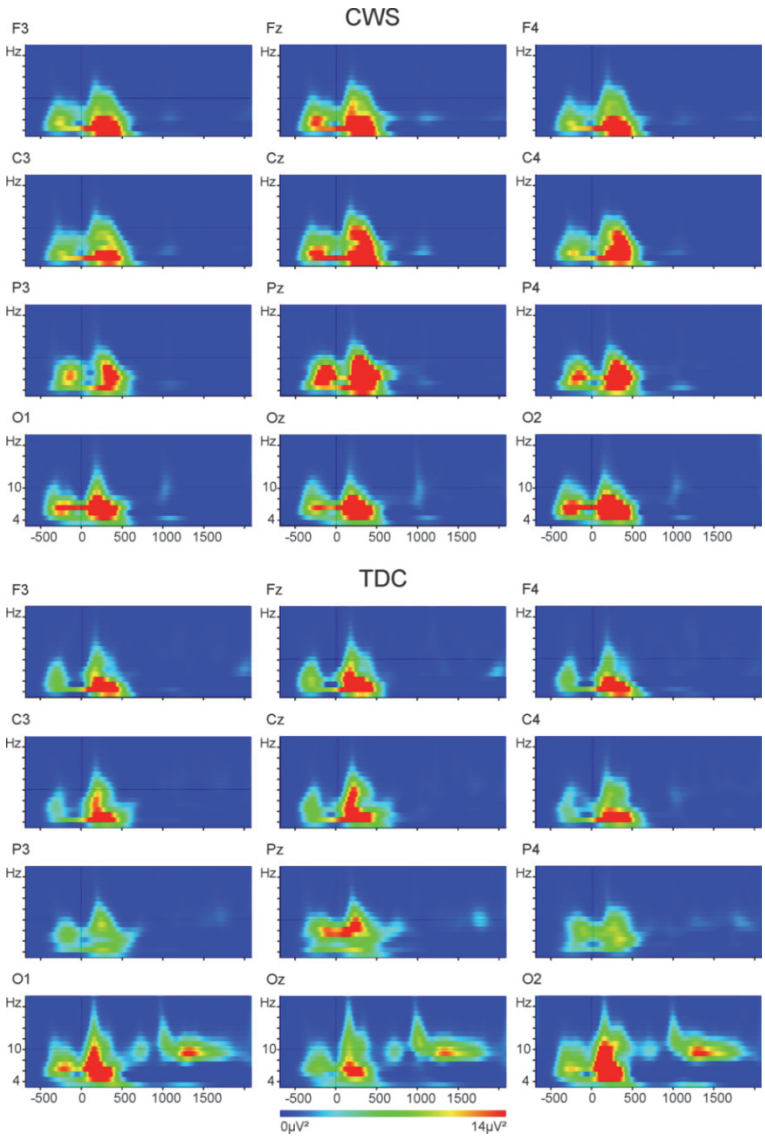

Fig. 8. The group mean wavelet graphs in the Nogo condition from -700 ms pre-stimulus to 2100 ms post-stimulus at frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4) and occipital (O1, Oz, O2) electrodes, children who stutter (CWS) on top and typically developed children (TDC) at the bottom. The TDC show pronounced alpha range activity in the posterior areas, particularly after 800 ms when the visual stimulus has ended. In CWS, there is clearly less alpha activity compared to the TDC. (Study III, published by permission of Elsevier.)

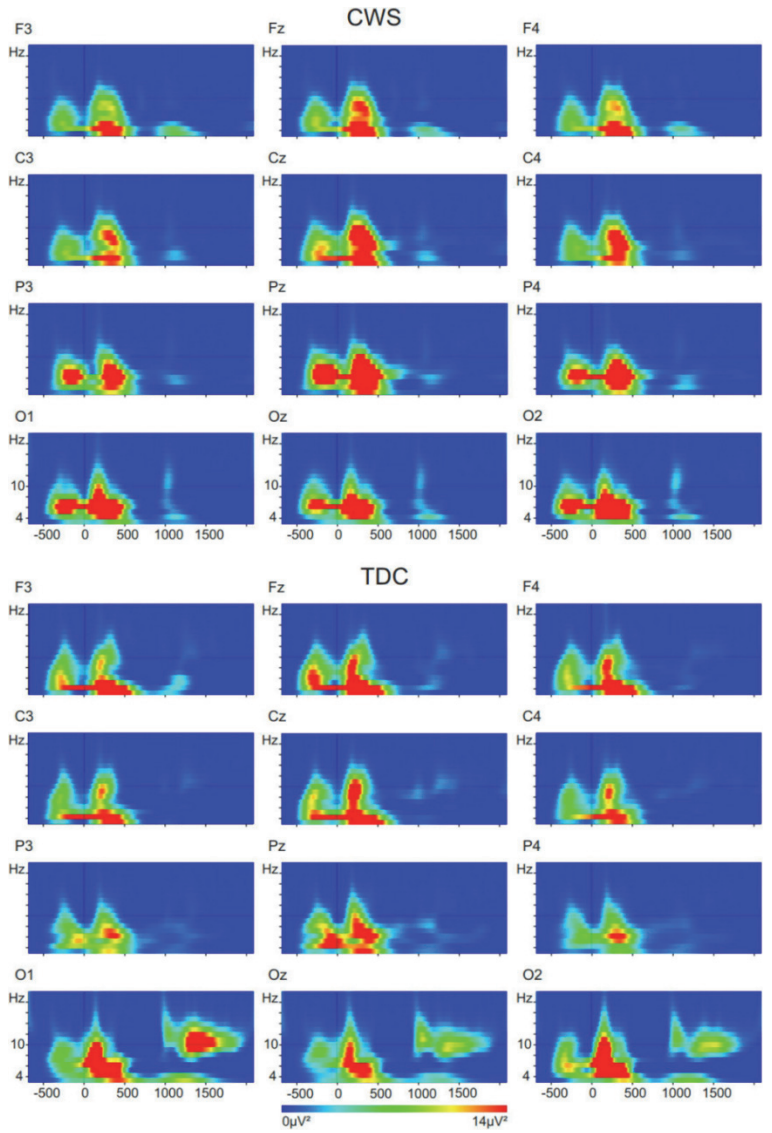

Fig. 9. The group mean wavelet graphs in the Go condition from -700 ms pre-stimulus to 2100 ms post-stimulus at frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4) and occipital (O1, Oz, O2) channels, children who stutter (CWS) on top and typically developed children (TDC) at the bottom. Similarly to the Nogo condition, the TDC show noticeable alpha activity in the occipital channels while it is remarkably reduced in the CWS. (Modified from study III supplementary material, published by permission of Elsevier.)

The statistical testing between groups using the cluster permutation procedure showed significantly less (p=0.014) alpha activity in the CWS during a time window from around 600 ms after the Nogo stimuli (Fig. 10). The cluster with decreased alpha activity cluster consisted mainly of parieto-occipital and frontal electrodes.

In the Go condition, however, the groups did not differ significantly (p=.15).

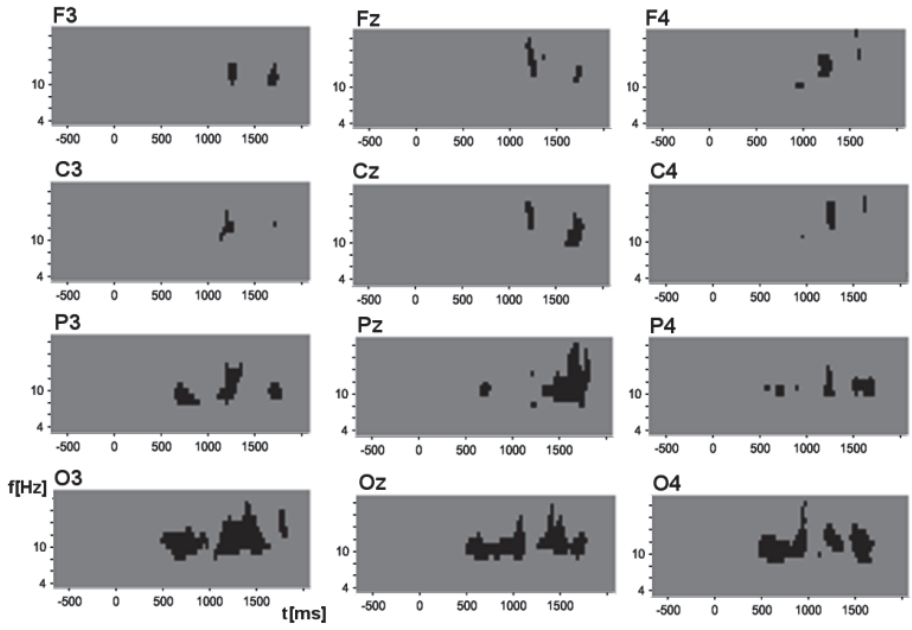

Fig. 10. The significantly differing cluster (black) between children who stutter (CWS) and typically developed children (TDC) in Nogo – condition in the statistical analysis of wavelet time-frequency space (cluster-level significance determination, p<0.025). For clarity, these central 12 electrodes were selected from the full electrode set. The CWS present significantly less parieto-occipital and frontal alpha activity in the late post-stimulus phase compared to the TDC. (Study III, published by permission of Elsevier.)

5.4.2 Fast Fourier transformation (FFT)

The grand average FFT graphs over the 900–1800 ms period in Nogo condition corroborated the wavelet analysis by showing high alpha band activity in the

posterior areas of the TDC group whereas theta activity was more prominent in CWS (Fig. 11). The median FFT alpha power (μV^2) at Oz channel was 0.035 (SD=.270) in the TDC and 0.019 (SD=.013) in the CWS. The median theta power was 0.024 (SD=.026) and 0.045 (SD=0.025) in the TDC and the CWS, respectively. When inspecting the individual FFT graphs (Fig. 12) high variability among the TDC was evident, with some individuals showing particularly enhanced occipital alpha compared to others, although in general, alpha was easily seen. However, in the CWS group the subjects showed consistently very little alpha activity.

5.4.3 Alpha/Theta ratio

The mean Alpha/Theta ratio at the Oz channel was 2.531 (SD 3.305) in the TDC and 0.418 (SD 0.235) in the CWS and the median Alpha/Theta ratio was 1.575 in TDC and 0.371 in CWS (Fig. 13). As individual FFT graphs as well as the boxplot of the Alpha/Theta ratio at Oz showed two distinct outliers with remarkable alpha peaks in the TDC, an additional analysis was performed. The Alpha/Theta ratios at the Oz channel were compared between groups by Mann-Whitney U-test either including (p=.001) or excluding (p=.005) these two subjects; in both cases the difference was statistically significant, indicating that the difference between groups was not due to these outliers alone. There was also no valid methodological reason to exclude these subjects from the control group, either, since the recruitment criteria and registering processes were identical to those of any other subjects. Their data is therefore included in the linear mixed model analysis.

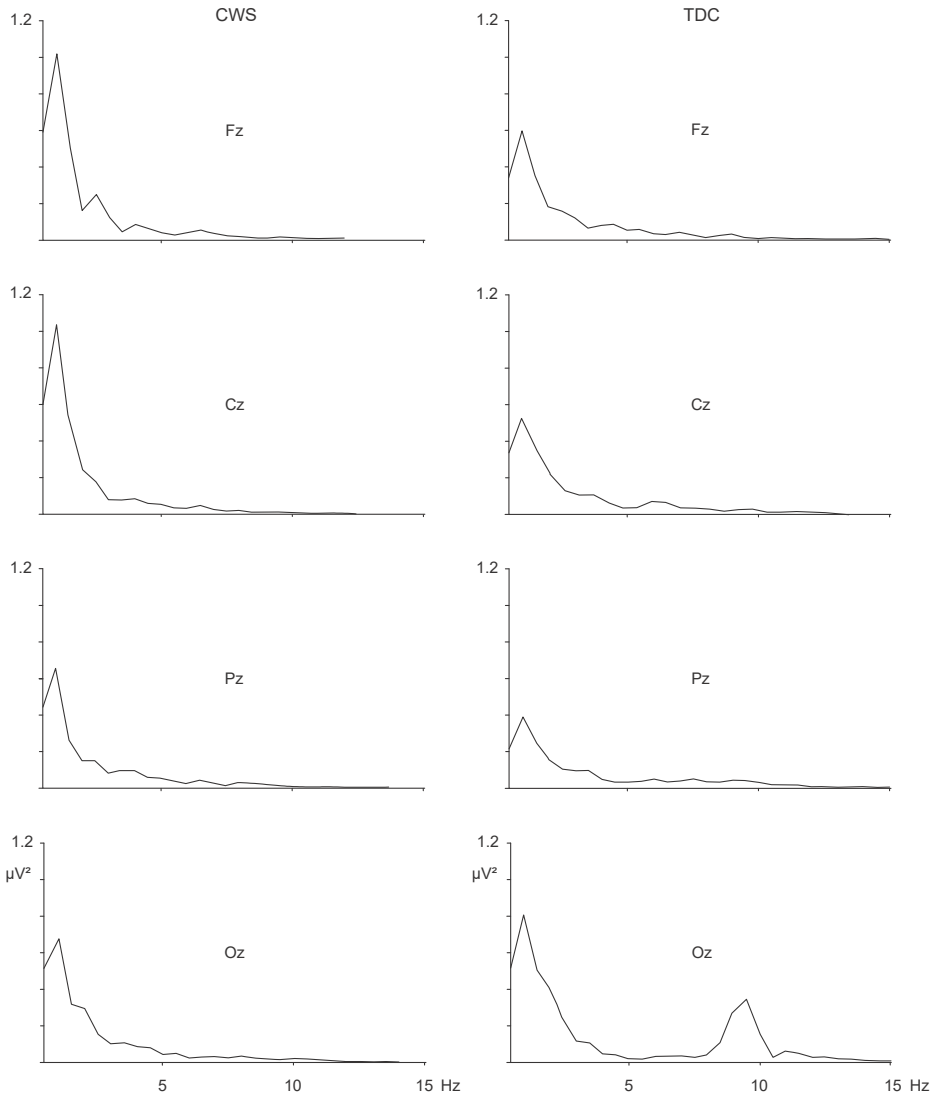

Fig. 11. The fast Fourier transformation (FFT) grand average graphs at frontal (Fz), central (Cz), parietal (Pz) and occipital (Oz) channels in the 900–1800 ms post-stimulus time window in Nogo condition; children who stutter (CWS) on the left and typically developed children (TDC) on the right. In the TDC group there is an apparent peak in the alpha frequency range between 7.5 and 12.5 Hz, especially in the occipital area. In the CWS group no such alpha peak is seen; instead, there is slightly more prominent theta range activity between 3.5 and 7.5 Hz. (Study III, published by permission of Elsevier.)

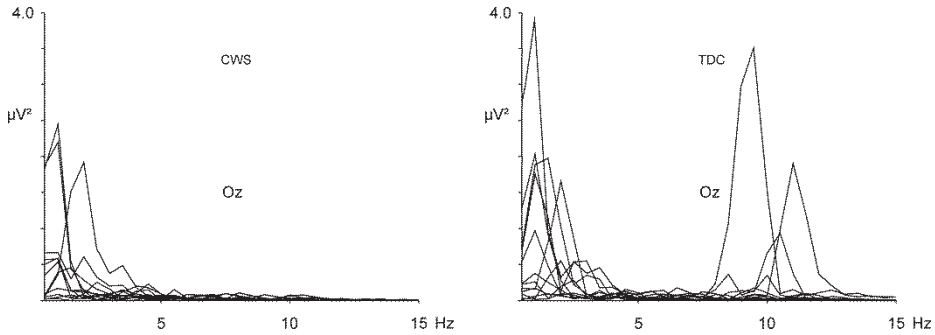

Fig. 12. The overlaid individual FFT graphs at the Oz channel demonstrate highly variable amounts of alpha activity in the TDC with two distinct outliers; however, a clear difference between groups as in CWS the lack of alpha activity is still consistent. (Study III, published by permission of Elsevier.)

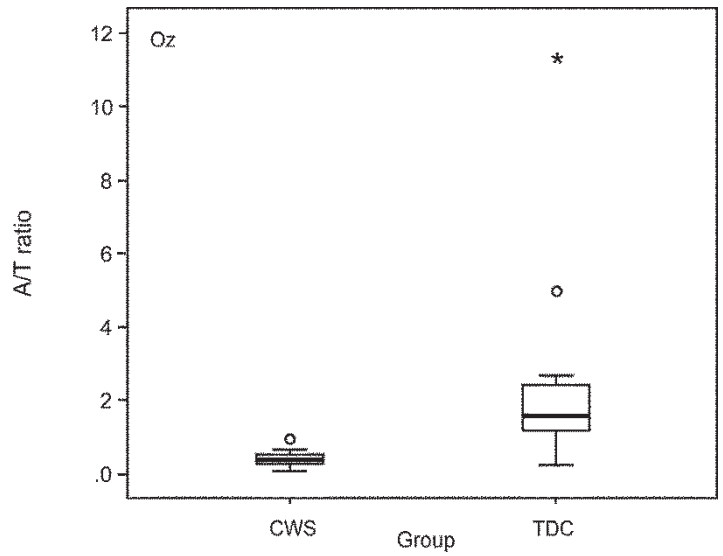

Fig. 13. The boxplot graph of the Alpha/Theta ratio in Nogo condition at Oz channel with children who stutter (CWS) on the left and typically developed children (TDC) on the right. (Study III, published by permission of Elsevier.)

The linear mixed model analysis of the Alpha/Theta ratio was performed to confirm the results of the visual analysis of the wavelet and FFT graphs in Nogo condition. The analysis showed a highly significant Group x Anterior-Posterior

main effect (p<.000) and the post hoc pairwise comparisons between regions indicated significantly higher Alpha/Theta ratio in the TDC than the CWS at the occipital channels (p<.000) (Fig. 14).

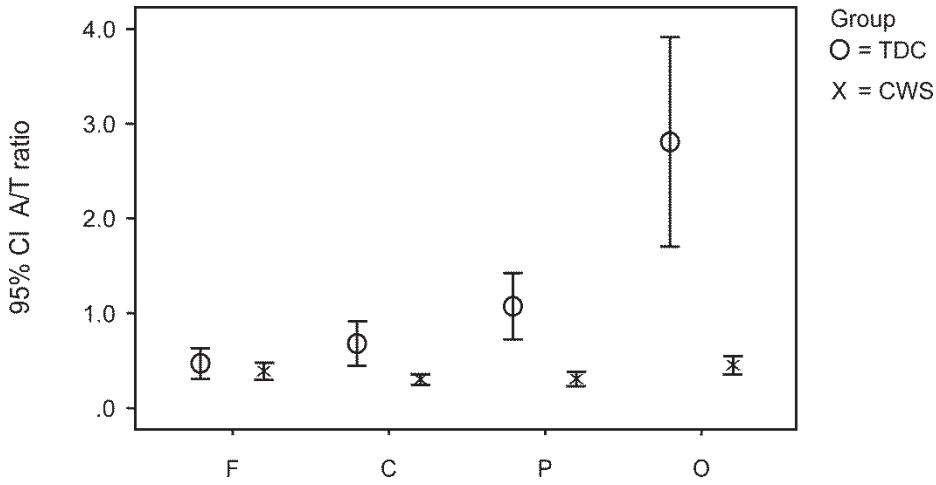

Fig. 14. The graph shows the 95 % confidence interval of mean for the Alpha-Theta-ratio of the frontal (F), central (C), parietal (P) and occipital (O) electrodes in the Nogo condition for typically developing children (TDC) and children who stutter (CWS). The TDC show higher Alpha-Theta-ratio than the CWS in the posterior areas and the difference was significant at the occipital channels. (Study III, published by permission of Elsevier).

6 Discussion

This work elaborated the cognitive processes involved in stimulus evaluation and classification, response selection and inhibitory control as well as the preparation for a task by means of fast electrophysiological measurements in addition to behavioral measures in children who stutter. Children who stutter differed from age-matched controls in this visual, motor inhibitory control task by the neurophysiological markers of many profound cognitive functions.

6.1 Event-related potentials as markers of atypical attentional and inhibitory control processes

The first study implemented classical ERP analysis on the EEG data using peak latencies and amplitudes of the nine central electrodes. Contrary to expectations, this approach revealed only a delayed N2 latency in the Go condition but no significant latency differences in the Nogo condition when the response needed to be inhibited. In addition, the P3 component was small and difficult to define in the CWS, but no amplitude differences could be verified.

This could be due to the large variation in the waveforms seen especially in the CWS, corroborating earlier findings of heterogeneity in this group (Jansson-Verkasalo et al., 2014). When using the peak latencies and amplitudes, the used tests may not be able to detect differences obscured by the variance in this study group. On the other hand, all the participants were at a critical age regarding the maturation of inhibitory control and attentional processes (Jonkman, 2006). The younger participants may not yet show a Nogo effect in P3 amplitude due to physiological reasons as it is usually visible only from 9–10 years of age (Johnstone et al., 2007; Jonkman, 2006; Spronk et al., 2008). The small Nogo P3 could thus indicate a wider developmental spectrum in the CWS despite the similar chronological age range. However, since an earlier study in AWS demonstrated a reduced Nogo P3, it is more likely a long-lasting deviation (Ning et al., 2017).

Because of the aforementioned problems the data were re-analyzed using the GFP waves and potential maps of a wide 60 electrode set in the second study. This approach showed major differences also in the Nogo condition. In both conditions, the potential maps showed frontal negatively oriented activity which fit the N2 component seen in the grand average figures by polarity, time window and topography (Donkers & Van Boxtel, 2004; Enriquez-Geppert et al., 2010;

Falkenstein et al., 1999; Pliszka et al., 2000; see review by Van Veen & Carter, 2002). In the CWS this N2-related activity was definitely widened, prolonged and asymmetrical compared to the TDC in both conditions.

Then again, in Nogo condition the TDC showed clear fronto-central positivity, consistent with the Nogo P3 in the literature by its topography and behavior in the task (Bokura et al., 2001; Johnstone et al., 2007; Jonkman, 2006; Tekok-Kilic et al., 2001). In CWS, however, this Nogo P3 activity was hardly evident. In Go condition both groups showed positively oriented activity in the parietal areas in the P3 time window, correlating well with the literature of the Go P3 component in adults (Barry & De Blasio, 2013; Bokura et al., 2001; Tekok-Kilic et al., 2001) and children (Barry et al., 2014). Although there were no significant differences in the latencies or amplitudes of the Go P3 by the classical ERP analysis, the potential maps show slightly reduced P3 activity in CWS compared to TDC.

In conclusion, in the CWS the N2-related activity was prolonged and consequently overrode the P3 component, affecting particularly the Nogo P3 component and its amplitude. However, also the spatial distribution of the event-related brain activity in the N2-P3 time window differed in the CWS compared to the TDC. The CWS showed significantly more negative amplitudes in the right frontal area, while in the TDC the activity was symmetrical and more positive. Altogether, the differences between the groups in the Nogo condition are likely to be related to changes in both the P3 and the N2 component related activity; a delayed, asymmetrical and excessive N2 and reduced P3 related processes in the CWS. Thus the stimulus-induced cognitive processes showed significant abnormalities in the CWS compared to the TDC both in the Go and the Nogo condition as measured by the ERP components.

6.1.1 The N2 component

In literature, the N2 component has been shown to represent response selection (Barry et al., 2014; and Barry & De Blasio, 2013; Gajewski et al., 2008; Gajewski et al., 2010) in addition to the previously suggested evaluation of conflict or interference (Donkers & Van Boxtel, 2004; Randall & Smith, 2011; Smith, 2011) or inhibition (Falkenstein et al., 1999; Gonzales-Rosa et al., 2013; Pliszka et al., 2000). In Go condition the N2 component may also be related to stimulus categorization and, together with the Go P3, response preparation and execution (Barry et al., 2013). On the other hand, the N2 response contains multiple individually behaving subcomponents, some of which are conflict-related and

others novelty-related (for an overview, see Folstein & Van Petten, 2008). These subcomponents have different topographies and may be activated in various degrees between subjects and test groups.

Based on this, the detected abnormally prolonged and widespread N2 component could indicate problems in multiple phases of the cognitive process. Considering the recent discoveries of problems in attention orientation and shifting in CWS (Eggers et al., 2012) as well as attentional network abnormalities (Chang et al., 2017) it is likely related to problems in attentional orientation leading to slower stimulus classification and thus prolonged response selection process. One possible explanation is that the CWS need to recruit more resources to perform the task, which would manifest as excessive or widened brain activation. Thus a delayed and prolonged N2 would represent the need to allocate more resources to this part of the process, resulting in disproportionate N2-related activity. The N2 amplitude correlates positively with successful inhibition in both stop-signal and Go/Nogo tasks (Falkenstein et al., 1999; Johnstone et al., 2007; Pliszka et al., 2000). On the other hand, in children with AD/HD the Nogo effect on N2 was higher than in controls despite equal behavioral results (Smith et al., 2004). The widened and excessive N2 activity in the CWS could therefore reflect compensatory mechanisms that enable adequate performance even with defects in stimulus processing and classification mechanisms. However, as the delay was very robust in the Go condition when a motor response was required, there may be additional difficulties in the response execution processes, such as the forming of automatic motor sequences.

6.1.2 The P3 component

Many studies support an association between the N2 and P3 components (Barry & De Blasio, 2013; Barry et al., 2014; Gajewski et al., 2008; Gajewski & Falkenstein, 2011). In the model by Barry and De Blasio, the Go N2 modulation stands for an early phase and the Go P3 the sequel of the response selection process (Barry & De Blasio, 2013; Barry et al., 2014). The P3 component abnormalities may therefore at least partially be due to the same factors that cause the delay in the N2 component. However, as the Nogo P3 component was so considerably reduced in the CWS it could reflect independent problems of later, explicitly inhibition-related phases of the process. Several studies have supported the role of the Nogo P3 as a specific indicator of inhibition (Albert et al., 2013; Donkers & Van Boxtel, 2004; Smith et al., 2006; Smith et al., 2013). Recently, the

Nogo P3 was proposed to arise from positivity related to motor deactivation due to inhibition of a motor response (Smith et al., 2013). Thus the diminished or even absent Nogo P3 in the CWS could result from malfunctioning inhibitory control mechanisms and inefficient motor deactivation when compared to the TDC.

6.2 Behavioral measures of inhibitory control and motor performance in relation to electrophysiological measures

Despite the marked differences in the electrophysiological measures during this inhibitory control task, the behavioral measures did not differ significantly between the groups. In the Go condition, the CWS had a slightly longer reaction time than the TDC, although the difference was not statistically significant. Neither were there significant differences in the number of false alarms or premature responses.

The relationship between motor inhibition, behavioral measures and ERP components or the actual cognitive processes has been widely discussed and is not unambiguous (Chatham et al., 2011; Huster et al., 2011; see review by Huster et al., 2013). Nonetheless, according to earlier studies, the N2 latency is concurrently modulated with the RT in, for example, task switch situations (Gajewski et al., 2010; Smith, 2011). Although the N2 component may not be involved in actual motor inhibition *per se*, it is crucial in the monitoring of conflict (Huster et al., 2011) and possibly response selection (Barry et al., 2013). The robustly delayed N2 in the Go condition along with the slightly slower RT could point towards difficulties in motor response preparation in CWS. The N2 component peak was generally seen around 130-150 ms before the reaction. It is possible, that the preparation of the manual response has already begun at the time of the N2 peak. Some of the difference reflected in the N2 may thus be related to motor preparation and not purely cognitive processing. Nevertheless, these processes are slower in CWS. This would comply with the findings of poorer motor sequence learning (Smits-Bandstra et al., 2006; see also review by Smits-Bandstra & De Nil, 2007), possibly so that the manual response is not as automatic as it is in TDC.

The results presented in this study oppose the findings of Eggers et al. (2013), who reported an increased number of errors and shorter RT in CWS in a similar Go/Nogo task of the Amsterdam Neuropsychological test. However, there are plausible explanations for the differences between this study and Eggers' study.

First, in the study by Eggers et al. (2013), the mean age of the participants was lower, which may have affected the performance in the task. It is also possible that although the participants were instructed to respond quickly, the children in this study preferred accuracy over speed. Then again, the recording of EEG during the task in this study may have raised the children's level of arousal, thus improving the results. In addition, in Eggers' study the participants only completed one block of 48 trials compared to our 4–6 blocks. The previous evidence of RT in stuttering persons has been converging, although usually showing less shortening of RT with practice when compared to fluently speaking people (see Smits-Bandstra, 2010). Nevertheless, the comparison of the first and last blocks in our study showed no significant differences in RT or the number of errors and any learning effect leading to improved accuracy in either group seems unlikely.

Recently, a study using behavioral measures in a Stop-signal task did not show differences in CWS (Eggers et al., 2018). The Go/Nogo and Stop signal tasks share common features, but show some major differences in the conflict monitoring and inhibition demands as well as the activated brain regions (Rubia et al., 2001), also affecting the ERP components (Enriquez-Geppert et al., 2010; Johnstone et al., 2007; Krämer et al., 2013). The main difference is that in the Go/Nogo task, inhibition concerns a prepotent, but not yet initiated response, while in Stop signal, an already-started response needs to be stopped. This may explain the inconsistency of the results in the Go/Nogo task (Eggers et al., 2013) and the Stop signal task (Eggers et al. 2018). If the CWS are actually slower in forming the motor response, they may be capable of stopping the response despite possible inhibitory problems, because the process is in an earlier phase compared to controls.

The P3 component latency showed close timing with the RT, which correlates well with the idea that the P3 marks the end of a stimulus evaluation and response selection process (Barry & De Blasio, 2013; Barry & De Blasio, 2014). However, the most P3 component difference between groups was seen in Nogo condition. The Nogo P3 component has been associated particularly with motor inhibition in Go/Nogo tasks (Enriquez-Geppert et al., 2010; Smith et al., 2013), but P3 correlated with vocal and manual inhibition also in a Stop signal task (Etchell et al., 2012). As the diminished Nogo P3 could be due to less efficient motor de-activation (Smith et al., 2013), the non-speech motor activation and suppression pattern in CWS seems altered. Therefore the electrophysiological findings here may indicate motor performance problems in CWS in addition to, or due to,

attentional and inhibitory control malfunction, although the behavioral measures show similar performance.

The controversial results of the behavioral and electrophysiological methods in this study further emphasize the need for more sensitive and accurate measurements in the study of inhibitory control. Reaction time and errors are the result of a highly complex series of cognitive and motor processes and do not reliably represent the actual cognitive process. In addition, the use and effect of e.g. compensatory mechanisms can usually not be predicted, assessed or controlled reliably. On the other hand, also in the light of this study, the classical ERP component analysis is most likely insufficient in detecting differences in cognitive processing. Particularly heterogeneous groups, such as CWS, may show great variation in the timing and distribution of the brain activity. Because of the temporal and spatial dispersion that follows, peak amplitude and latency based analysis may become fruitless.

6.3 Novel electrophysiological markers of atypical attentional and inhibitory control processing in CWS

6.3.1 Atypical distribution of brain activity

The brain activation pattern showed the most significant differences in right frontal areas. The CWS showed asymmetrical, intense negatively oriented, N2-related activity in this area compared to the symmetrical frontal activation in the TDC. Many alternative or simultaneous mechanisms could cause the spatial difference seen in CWS. Both the N2 and Nogo P3 component generators have been located in the frontal areas. The N2 component in inhibitory tasks is suggested to be generated in the anterior cingulate cortex (ACC) (Bekker et al., 2005; Jonkman et al., 2007; Niewenhuis et al., 2004; Van Veen & Carter, 2002). In many studies, the ACC has been associated with self-regulation processes such as conflict monitoring, response selection and outcome evaluation as well as successful inhibition of a response (Botvinick et al., 2004; Steele et al., 2013; for an overview, see Van Veen and Carter, 2002). On the other hand, the Nogo P3 component generators have usually been located in the right frontal lobe in inhibitory tasks (Enriquez-Geppert et al., 2010; Kropotov et al., 2011; Strik et al., 1998), particularly the inferior-frontal cortex and the supplementary motor cortex. In addition, in lesion and functional imaging studies the prefrontal cortex, most

often the right inferior frontal cortex, has been implicated as necessary for inhibitory control (see review by Aron et al., 2004). However, some studies have shown no effect of hemisphere (Krämer et al., 2013) or equal importance of the left inferior frontal cortex in a Go/Nogo task (Swick et al., 2008).

Therefore the asymmetric activity in CWS likely also demonstrates atypical activation of areas involved in self-regulation and inhibitory processes. The ACC may be asymmetrically overactive in CWS indexed as an enhanced right-sided N2 component activity, perhaps because of subtle left-sided hypo-activity and increased demands in the stimulus evaluation process. Increased N2-related negatively oriented activity may obscure the P3-related activity in the EEG. However, also the inhibitory control processes at the prefrontal cortex may act poorly in CWS due to the impaired functional connectivity seen in the frontal areas (Chang et al., 2017; Qiao et al., 2017). Less efficient motor deactivation would also cause reduced P3-related activity.

Even though the spatial accuracy of EEG measurements is poor compared to, for example, MRI, the findings of atypical lateralization of brain activation in this study are in harmony with the previously documented functional and structural differences. In adults there are frequent findings of left-sided hypo-activation of speech-related areas along with right-sided overactivation in vocal tasks using fMRI or PET imaging (please see meta-analysis by Belyk et al., 2015 and Budde et al., 2014). In children there are also findings of reduced gray and white matter mostly on the left (Beal et al., 2013; Chang et al., 2008). In addition, studies in CWS have shown reduced connectivity of the left-sided white matter tracts between auditory and motor cortices or between hemispheres (Chang et al., 2015; Chow & Chang, 2017; Misaghi et al., 2018). In adults, Civier et al. (2015) proposed that decreased inhibitory regulation via corpus callosum activates right-sided structures abnormally, and increased activity of the right hemisphere may thus not even represent beneficial compensation (Civier et al., 2015). However, as the structural and functional asymmetry has not been as clear in CWS as in AWS, the development of the right-sided overactivity is more likely a compensatory means (Neef et al., 2018; Sowman et al., 2014).

Considering these previous findings, the possible overactivation of right-sided structures in CWS in this study may be due to compensation for left-sided malfunctions in stimulus processing and inhibitory control and motor control. On the other hand, the decreased white matter connectivity as well as functional network integrity in CWS (Chang et al., 2015; Chang et al., 2017) likely leads to slower, less efficient cognitive processing. This could affect the synchronization

of activity between hemispheres, which is seen as altered spatial and temporal dispersion of N2 and P3-related brain activity and consequently atypical distribution and increased duration of brain activation and ERP components.

6.3.2 Atypical oscillatory activity of the brain

The time-frequency analysis of the brain oscillations demonstrated striking differences particularly in the occipital alpha activity, and especially in the Nogo condition. The wavelets of the TDC showed well-defined alpha activity over the occipital areas from around 900 ms post-stimulus. However, in the CWS this was significantly decreased and they showed very little alpha band activity. When looking at the wavelet graphs as well as the ERP waveforms, the event-related activity ends at around 600 ms. From 800 ms post-stimulus the visual stimulus had ended and only an empty black screen was present. In this way, the recorded EEG activity in the last post-stimulus time-window (900-2100 ms) resembles eyes-open resting-state EEG. Alpha rhythm in the occipital areas over the visual cortices is a routine phenomenon in eyes-closed resting-state EEG, but is also seen with smaller amplitude in eyes-open condition (Barry et al., 2007; Barry et al., 2009). If considering this time window as a resting period, the TDC would demonstrate this basic neurophysiology normally while CWS do not. However, the time period preceding the next task probably also includes anticipatory processing, and the alpha oscillation differences may thus be related to changes in the active preparatory procedures in CWS compared to the TDC.

Alpha power increase has been correlated with the inhibition of unnecessary visual information in previous EEG studies (Foxe and Snyder, 2011; Slagter et al., 2016; van Dijk et al., 2008) and also with reduced excitability of the visual cortex (Romei et al., 2007). Simultaneous fMRI-EEG studies have correlated alpha power to the blood oxygenation level-dependent (BOLD) responses to visual stimuli (Mayhew et al., 2013; Mo et al., 2013), further supporting the function of alpha synchronization in the gating of attention. Accordingly, the occipital alpha shown in TDC most likely corresponds to the suspension of visual perception and concomitant inhibition of the visual cortex when no visual processing is needed between the stimuli. In CWS, on the other hand, there is minimal occipital alpha desynchronization, indicating a highly receptive state of the visual cortex and excessive visual attention throughout the waiting period between stimuli. This suggests that the CWS may not be able to control and direct their attentional resources to significant information only. The task may force the CWS to use

more effort in, for example, visual orienting and thus demand additional attentional preparation for the upcoming task, indexed as low pre-stimulus alpha power.

In the FFT graphs the CWS showed no clear alpha peak in contrast to the TDC. Instead, among the CWS slower frequencies such as theta and delta oscillations were more prevalent, resulting in a decreased Alpha/Theta ratio. In developmental studies, EEG shows a spectral power shift to higher frequencies, decreasing theta/alpha ratio and increasing alpha peak frequency with age (Benninger et al., 1984; Clarke et al., 2001; Cragg et al., 2011; Gasser et al., 1988; Miskovic et al., 2015). Brain network development is also indexed by strengthening long-range alpha connectivity with age (Knyazev et al., 2017; Miskovic et al., 2015) along with increasing EEG variability, proceeding from the posterior to the anterior areas of the brain (Miskovic et al., 2016). Thus the domination of slower oscillatory frequencies seen in the EEG of the CWS could be due to immature development of the brain regions and/or functional brain networks when compared to the TDC.

Alpha oscillation and functional brain networks

As some brain regions show temporally connected activity in fMRI scans and/or coherent oscillation in EEG recordings they are considered functionally connected and form various functional networks. Areas activated during resting state form the default mode network (DMN) which is associated with the ongoing intrinsic activity of the brain (Laufs et al.; 2003; Raichle et al; 2001; for an extensive review, see Raichle 2015). Inhibitory and attentional tasks, on the other hand, can activate specific task-related functional networks, such as the control-related fronto-parietal network (FPN), the top-down attention regulating dorsal attentional network (DAN) and the stimulus-driven ventral attention network (VAN) (Stevens et al., 2007; see also reviews by Corbetta et al., 2008; Parks and Madden, 2013; Vogel et al. 2010). The resting state and task-related networks usually show anti-correlated activity; i.e. the DMN activation is seen with the simultaneous inhibition of task-positive networks (Chai et al., 2012; Fox et al., 2005; Fox et al., 2009). Executive control and attention rely on the balance between these networks (Fox et al., 2005; Fox et. al, 2008; Raichle, 2015; reviews by Corbetta et al., 2008; Parks and Madden, 2013).

The function of these distinct networks can be linked to brain oscillations. Knyazev et al. have coupled increased alpha range activity to the function on the

DMN (Knyazev et al., 2011). In the context of visual attention, the DMN activity has been positively correlated with high occipital alpha power in an eyes-open resting state condition in a simultaneous EEG-fMRI study (Mo et al., 2013). Mo et al. suggest that the DMN activation along with alpha enhancement acts by suppressing the external visual input in order to facilitate intrinsic mental processing. In eyes-closed condition this was not needed and therefore such activation was not seen. On the other hand, another study showed low pre-stimulus alpha-activity concurrent with the inhibition of auditory networks and the DMN leading to increased positive BOLD responses of the visual cortex (Mayhew et al., 2013). Thus the reduced alpha in the CWS could reflect weaker activity of the DMN, possibly due to imbalance between the DMN and attentional networks considering the findings of Chang et al. (Chang et al., 2017). However, the exact correlation between the alpha activity, attention and the DMN activity is still under debate. In some studies the parieto-occipital alpha power showed weak or even no correlation to the DMN (Bowman et al., 2017; Laufs et al. 2003; Neuner et al., 2014) but instead, to the dorsal attentional network (Hacker et al., 2017). Moreover, the DMN may also play a role in attentional tasks (Visintin et al., 2015; Popa et al., 2009).

Brain oscillations and attention deficit

Children who stutter have shown some similar temperament features as children with attention deficit-hyperactivity disorder (AD/HD) (Eggers et al., 2010; Eggers et al., 2012; see also review by Alm, 2014). In the study by Chang et al. (2017) nearly 15% of the children with stuttering were diagnosed with AD/HD and over 10% with some other developmental or psychiatric diagnosis during follow-up. Interestingly, studies on children with AD/HD have often shown reduced alpha and beta power with higher relative theta power compared to controls (Clarke et al., 2011; Markovska-Simoska & Pop-Jordanova, 2017; Vollebregt et al., 2015; see also review by Barry et al., 2003). Additionally, children with AD/HD lacked the posterior alpha modulation in response to cuing in a visuospatial task (Vollebregt et al., 2016) and in a cross-modality attentional task (Mazaheri et al., 2010*)*. Thus the CWS show atypicality in the alpha and theta power ratio comparable to that seen children with AD/HD implying similar abnormalities in these clinical entities. It is possible that developmental stuttering and AD/HD share some common dysfunction of attentional and cognitive control, perhaps due to brain network disturbances.

6.4 Limitations

The number of participants with stuttering is low despite continuous recruiting via various channels. The main problem was the use of such strict inclusion criteria. Many possible subjects had concurrent neurological and developmental problems, such as learning disability, developmental delay of language or diagnosed attention deficit, and were rejected for this reason. The high co-morbidity among people who stutter is a well-known fact, and some recent studies have accepted this and included also subjects with other concurrent diagnoses (see Chang et al., 2017). However, in this study problems of this kind would have caused a major confound and most likely rendered the interpretation of the results impossible. By using subjects with "pure" stuttering, we were able to demonstrate the otherwise clinically subtle defects of attention and cognitive control.

Because errors were so scarce in both groups, it could indicate a ceiling effect for inhibitory performance. Go/Nogo tasks with short inter-stimulus-interval seem to affect the inhibition process more strongly, as more automatic responses are probably in use (Benikos et al., 2013a, 2013b; Zamorano et al., 2014). Thus the task may not have induced enough pressure on the inhibitory control, leading to very few errors in both groups. The main reason to use these task parameters was to replicate the Amsterdam Neuropsychological Test as precisely as possible. Another goal was to keep the task simple and within acceptable time limits to accommodate for the youngest participants. Nevertheless, despite the relatively easy task, the EEG and ERP measures showed differences between groups and conditions, pointing towards a successful modulation of attention and inhibitory control.

In studies I and II, the control group included both boys and girls while the CWS were all boys, and the studies could therefore reflect gender differences instead of the actual condition explored. Boys who stutter have previously shown more uneven development of speech, language, cognitive and motor skills compared to girls (Choo et al., 2016). On the other hand, behavioral measures could show some sex differences based on previous literature. In 4.5- to 6-year-old children, girls have shown better performance in Go/Nogo task than boys (Liu et al., 2013) indicating better inhibitory control. When using a continuous performance task (CPT) to assess inattention and impulsivity among children with AD/HD, boys showed more impulsivity but no difference in attention (Hasson & Fine, 2012). Nevertheless, in this study the behavioral measures did not differ between the groups in study I. Developmental studies on ERPs in children during

a Go/Nogo task have not analyzed the effect of gender (Johnstone et al., 2007; Jonkman, 2006). However, in an auditory Go/Nogo task adult females showed slower N2 and P3 component latencies and higher P3 components in both conditions and were less accurate (Melynyte et al., 2017). This is contradictory to our study as the all-boys CWS group showed slower latencies. On the other hand, in developmental studies boys have shown faster maturation of the EEG by higher alpha power (Cragg et al., 2011) and increased coherence compared to girls (Barry et al., 2004). The findings in studies I and II are therefore not likely to be explained by gender.

In this task, even though studying an apparent speech problem, we used a manual task to explore non-speech related differences in inhibitory control. However, vocal and manual responding in a Stop signal task have shown similar results for the reaction time (Castro-Meneses et al., 2015) as well as ERP components (Etchell et al., 2012). Therefore it is conceivable that our findings of atypical inhibitory control in a manual task would apply to the regulation and inhibition of motor speech production as well.

Other oscillatory frequencies besides alpha and theta would be of interest due to their theoretical role in stuttering or findings in previous studies. In particular, the beta band activity may reflect the function of the basal ganglia and internal timing networks (Etchell et al., 2014). However, in this study the analysis was restricted to lower frequencies due to high risk of EMG contamination. As is typical for children, they had high frequency EMG artifact due to excess facial movements and tension despite all effort and the muscle activity mostly overlaps beta and gamma frequency brain activity. The use of independent component analysis (ICA) could have been beneficial in removing EMG artifact. On the other hand, low beta frequencies could have been useful, as in a rhythm detection task MEG has showed marked differences particularly in the lower beta range (Etchell et al., 2015). In future studies beta oscillations should be included.

On the other hand, due to the age span of less than 6 years up to almost 10 years in this study the development of the background alpha frequency is probably still ongoing (Cragg et al., 2011; Klimesch 1999; Riviello et al., 2010). Klimesch proposed the estimation of the individual alpha frequency (IAF) instead of fixed frequency bands. The IAF may vary from theta to fast alpha range, although it still represents the same cognitive function as alpha (see Klimesch, 1999; review by Neuper & Pfurtscheller, 2001). The difference in the individual alpha frequency could have provided an interesting insight into the development of background alpha in CWS compared to TDC. However, as the lower limit of

alpha in this study was as low as 7.5 Hz and the mean power of frequency bands was used, the results still show a shift towards slower frequencies in CWS regardless of whether the dominant rhythm represents alpha activity or not.

This difference in occipital alpha activity was evident in the Go condition, too, but it did not reach statistical significance. One likely explanation for this is the confounding effect of the motor response. The motor processing and the activation of motor areas in the Go condition may affect the oscillatory activity even in this later time window, obscuring the differences in the statistical analysis. Further studies of the background alpha in CWS in pure resting state as well as in an inhibitory task with longer inter-stimulus interval would be useful to separate the effect of the previous task from the preparatory or anticipatory attentional processing.

6.5 Future directions

A possible common ground behind these extensive changes in cognitive processes, ranging from attention, stimulus processing and inhibitory control to motor preparation, is abnormality in the functional networks due to white matter and cortical structural defects. It is plausible that the brain oscillation differences during the resting or preparatory state present an electrophysiological indicator of the abnormal brain network architecture in CWS compared to TDC, which is also reflected in the prolonged and excessive or, on the other hand, absent event-induced potentials.

Regarding speech in particular, fMRI has indicated disruption in the dorsal language pathway, which could specifically disturb the auditory-articulatory motor cortex interaction in AWS (Kronfeld-Duenias et al., 2016). EEG during speech tasks have also suggested weakened sensorimotor feedback activity in AWS (Jenson et al., 2018; Saltuklaroglu et al., 2017). On the other hand, simultaneous activation and bi-directional feedback of the articulatory motor and auditory systems is most likely crucial in speech perception, as proposed by Liebenthal and Möttönen (see review by Liebenthal & Möttönen, 2017) and this is modulated by attention (Möttönen et al., 2014). In CWS the central auditory discrimination of syllables was deficient (Jansson-Verkasalo et al., 2014), and other studies have also implicated problems of auditory and language processing in stuttering children (Beal et al., 2011; Weber-Fox et al., 2013).

Taken together with the current findings, it is plausible that in stuttering, the balanced interplay of multiple sensory and motor systems is disturbed, which is

possibly mediated by abnormal attentional regulation. Hence an interesting aspect for future studies would be the analysis of functional connectivity by the means of coherence analysis in CWS during an inhibitory task. Theoretically and based on the current results, the CWS would show reduced long-range connectivity between frontal and occipital areas as well as between hemispheres, perhaps over multiple frequencies.

More studies are needed, especially regarding the EEG frequency signature of the CWS, but the lack of occipital alpha and the reduced Alpha/Theta ratio were fairly consistent in this study group. Future studies should preferably investigate larger groups including younger and older subjects as well as subjects with persistent and recovered stuttering. If this finding would hold in further experiments, it could provide an easy and relatively low-cost marker for persistent stuttering. Prognostic markers of this kind could be useful in directing the therapeutic resources towards the individuals at higher risk of persistent stuttering. With the development of new plasticity-enhancing treatments, such as repetitive transcranial magnetic stimulation (rTMS) or direct current stimulation (see Chesters et al., 2018), electrophysiological markers might give insight into the optimal treatment focus as well as its efficiency.

7 Conclusion

In CWS, the processing of the given visual stimulus seems to differ from controls as indexed by the pre-stimulus brain oscillations of the visual cortices in addition to the stimulus-induced, event-related potentials. The CWS need to maintain an alert, highly receptive state throughout the simple task in order to perform equally. Despite this pre-stimulus attentional preparation, the stimulus evaluation and response selection processing is delayed and involves wider brain areas than in the controls, possibly as compensation for inefficient function. In addition to changes in ERP components related to earlier stimulus classification and evaluation processes, later and more inhibition-related electrophysiological markers were significantly different in CWS compared to TDC, indicating poorer inhibitory control and/or motor deactivation. Taken together, these findings support the idea that CWS have difficulties in more than one of the attentional subsystems; the orienting system that enables the selection of relevant information and the executive control system, including the regulation and inhibition of the motor response.

Based on this study, it is clear that stuttering cannot be defined as a pure speech dysfunction, and children who stutter present abnormalities outside speech or general motor control. Although the children with stuttering had developed normally apart from the stuttering, their brain activity revealed far more complex and profound differences than could be expected from a motor problem, and even beyond the anticipated inhibitory control defects. With the comorbidity and the similar electrophysiological markers with AD/HD, some children with stuttering and/or AD/HD may actually present one facet of a syndrome with common genetic, developmental or environmental causes, but varying phenotype.

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